PHARMACEUTICAL ENGINEERING®

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REVEALING TECHNOLOGIES FOR GAMP®

GAMP® Considerations for Open-Source Software

AI Maturity Model for GxP Applications: A Foundation for AI Validation

Quality Agreements for SaaS Solutions Intended for GxP Use

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This article aims to refresh information on open-source software (OSS) within regulated computerized systems that was first discussed in an article in May-June 2010 *Pharmaceutical Engineering®*. The adoption of OSS advanced since then, and the article explores the importance of recognizing when an organization is relying on OSS and the benefits and risks this brings from a GAMP® 5 perspective.

18 AI MATURITY MODEL FOR GXP APPLICATION: A FOUNDATION FOR AI VALIDATION

Artificial intelligence (AI) has become one of the supporting pillars for digitalization in many areas of the business world. The pharmaceutical industry and its GxP-regulated areas also want to use AI in a beneficial way. Several pharmaceutical companies are currently running digital pilots, but only a small fraction follows a systematic approach for the digitalization of their operations and validation. However, the assurance of integrity and quality of outputs via computerized system validation is essential for applications in GxP environments. If validation is not considered from the beginning, there is considerable risk for AI-based digital pilots to get stuck in the pilot phase and not move on to operations.

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As adoption of cloud technology continues to increase across the life sciences industry, so too does the need to establish a standardized and pragmatic approach for ensuring the quality of software applications used in support of GxP data and associated processes. This article focuses on the application level and the growing use of software as a service (SaaS) within the life sciences industry.

ON THE COVER The pearl in the shell represents the value of emerging and developing technologies for the global pharmaceutical industry.

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By Jörg Zimmermann


Jörg Zimmermann

Meetings, ISPE News, and More

Pandemic or no pandemic, the pharmaceutical industry is growing at an unprecedented pace, and it is very gratifying to be part of that process. COVID-19 has brought our industry to the daily news, and while the public is getting a better grasp of how we work and need to work, there are still so many misconceptions that need clarification.

You might have heard people say that "The vaccines have been developed so quickly, nobody knows what the long-term effects really are." We in the industry know that the fast development was only possible because of the foundational work that was done over the last 20 years. With a different risk profile, pharma companies and regulatory agencies worked hand in hand to move as fast as possible, working in parallel instead of sequentially, which is how the vaccines made it to conditional approval and widespread use in record time. The misconception here is the belief that development of medicines takes so long because long-term effects are being studied. That's just not true. There is still so much educational work to be done.

TOGETHER AGAIN

After the virtual ISPE Annual Meeting & Expo in 2020, the ISPE family was able to come together for a hybrid Annual Meeting that offered either in-person attendance in Boston or virtual attendance from 31 October–3 November 2021. The level of interaction in the plenary and education sessions, the exhibit hall, and the social activities was excellent. In-person attendees were so happy to be face-to-face again and to interact.

We in the industry know that the fast development was only possible because of the foundational work that was done over the last 20 years.

The ISPE Aseptic Conference is happening on 14–15 March, maybe even as you are reading this column. I am very proud to be the Chair of the program committee, and together with my Co-Chair Christa Meyers from CRB and the whole team, we have been working year-round to bring you the latest and greatest in aseptic

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Final preparations are being made for the ISPE Europe Annual Conference in Madrid, Spain, on 25–27 April 2022.

processing. We are especially proud to have very distinguished keynote speakers from regulatory agencies and industry: Paul Gustafson from Health Canada and incoming chair of Pharmaceutical Inspection Co-operation Scheme (PIC/S) will be talking about international regulatory harmonization, Alonza Cruze of the US FDA will provide insights into the FDA's learnings from remote assessments, and Joyce Hansen, SVP Sterility Assurance at Janssen Pharmaceuticals, is going to talk about the latest developments while also touching on how we can nurture our future leaders in the pharmaceutical industry. As always, another highlight of the conference will be the interactive panel discussion with the regulators, where you can get your questions answered and get into a real dialogue and discussion with FDA and other agencies. Both industry and regulators profit tremendously from this dialogue.

UPCOMING ACTIVITIES

Final preparations are being made for the ISPE Europe Annual Conference in Madrid, Spain, on 25–27 April 2022. The conference will also be virtual. We are looking forward to connecting with our members, volunteers, and sponsors for this signature conference. Speakers include representatives from European pharmaceutical companies and regulatory agencies, covering all the hot topics in the pharmaceutical industry: Annex 1 and aseptic processing, GAMP®, Pharma 4.0™, advanced therapeutic medicinal products (ATMPs), and automation and robots.

ISPE International has two major projects going on at the moment. A lot of work went into the One ISPE initiative, which redefines the relationship between ISPE International and the ISPE Chapters and Affiliates. The overarching goal of growing ISPE in all corners of the world will be achieved by next-level collaboration and support between International and Chapters and Affiliates and directly between Chapters and Affiliates. This includes the initiatives to bring students to ISPE and help them find their way in the industry. After approval of the charter regulating the relationships, we are on a good path to have this signed by all Chapters and Affiliates. What a great achievement, and a big thanks to all involved with running the project, providing input and comments, and negotiating the best way forward!

In February, the International Board of Directors conducted a two-day workshop on the Strategic Plan for ISPE for 2023–2025. Most initiatives in the existing Strategic Plan have already been implemented, and those that continue to be key topics need to be adapted to the industry's changing needs. This project is also on a good path, with the results to be officially unveiled at the 2022 ISPE Annual Meeting in Orlando. This is yet another signature event that you cannot afford to miss!

CELEBRATING GAMP®

The theme of this issue of *Pharmaceutical Engineering®* is GAMP. ISPE has been the home of the GAMP community since its early days. After celebrating GAMP's 30th anniversary in 2021, this issue continues to cover the hot topics in the field.

Open-source software has helped democratize the development of applications, but also introduces additional risks. How can open-source software be used in regulated GxP systems? The many opportunities of the technology are discussed in this issue. Also in this issue is a report on an industry-specific artificial intelligence (AI) maturity model for validation developed by the ISPE D/A/CH (Germany, Austria, and Switzerland) Affiliate Working Group on AI Validation. We also continue our exploration of software as a service (SaaS) with a look at quality agreements for SaaS solutions intended for GxP use.

As you can see, our subject matter experts provide cutting-edge insights into the latest developments.

It makes me very proud to announce the Second Edition of *GAMP® 5*, which went out for industry peer review in January. *GAMP 5 Guide–A Risk-Based Approach to Compliant GxP Computerized Systems* was published in 2008. A GAMP 5 Second Edition has been developed based on comprehensive reviews of GAMP 5 content performed in 2017 and early 2020 by the GAMP CoP Global Steering Committee and the GAMP CoP ERB (Editorial Review Board).

The primary purpose and objective of this revision is the publication of a GAMP 5 Second Edition, which will provide updates, clarify the relationship between GAMP 5 and the *GAMP® 5 Guide: Records and Data Integrity*, acknowledgment of current FDA work on computer software assurance (CSA), and an updated, dynamic, and evolving set of Appendices. *GAMP® 5* Second Edition is scheduled to be published this year, so watch for it!

I hope you will enjoy this issue of PE magazine and you can apply the learnings from the articles to your daily work.

Stay safe and see you soon at an ISPE event around the world—in person or virtual.

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

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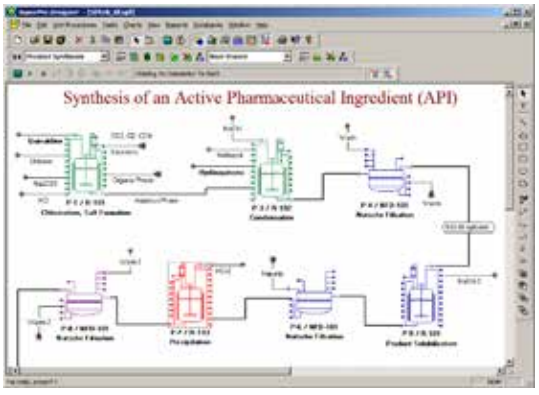

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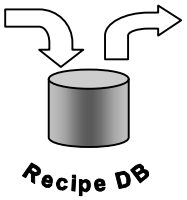

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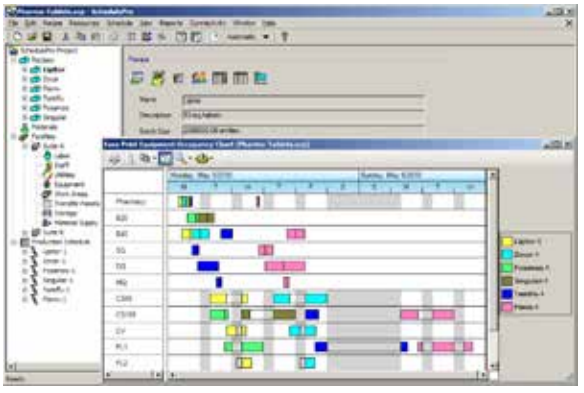

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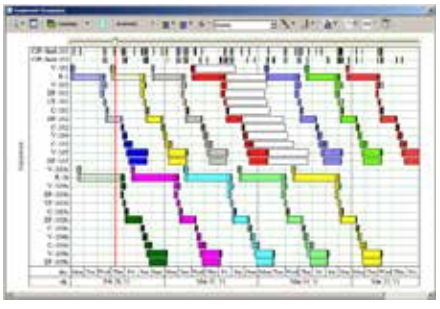

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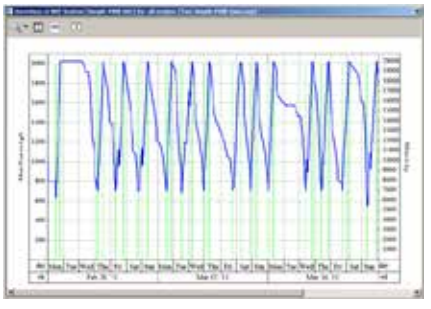

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 By Heather Bennett-Kelley


Heather Bennett-Kelley

NEW APPROACHES, NEW TOOLS

Now that the year is underway and people continue to learn how to live with COVID-19, there appear to be some areas where life and work will be changed for an extended period. Adapting and coming up with new tools and approaches will be key.

This morning when I drove to a jobsite, I thought it was a weekend morning because of how few cars were on the road. So, I couldn't help but wonder if the weekend started early or if that many people were working from home. With the pandemic, many workplaces realized that their employees can be productive at home, and maybe even more productive with a hybrid approach. My company's engineering team now has specific days when folks work from home.

This out-of-the-box approach can be applied to how we support and promote talent, as well as what happens on the manufacturing floor. The way that we did things two years ago isn't applicable anymore; if we try to live and work that way, we will have problems.

IMPACTS OF REMOTE LIFE

On the other side, some aspects of our society that help build resilience have atrophied. Personal interaction is so important to how we solve problems, find enjoyment in our work, and grow. Our young people, and those new to the industry, have been more impacted in this area than many others. Young people tend to learn by osmosis, absorbing everything that is going on around them, even if they're not directly involved in the conversation.

One of my mentors said that eavesdropping was a very important skill because you never know what you might learn: It is really just another part of situational awareness. Now that we are back in the office, at least part time, I often put my phone on speaker so that the young person I am training can hear how different conversations go (especially ones with problem-solving and those that are more difficult). By doing this, they are getting better at understanding where they can add value to a conversation, or provide fuel for follow-up questions after the call. In turn, they have started this so that I can hear their conversations. This open communication is providing a valuable and real-time tool to learn best practices in conversation and problem-solving styles.

The pandemic has really forced all of us outside the box, and forced growth where many of us (people and companies) didn't think growth was necessarily needed.

NEW APPROACHES, NEW TOOLS

The pandemic has really forced all of us outside the box, and forced growth where many of us (people and companies) didn't think growth was necessarily needed. However, because we cannot do things the way we did before COVID-19, we need to create new ways of doing things, and new tools. Young people have a unique advantage in forging new pathways because they don't have to live by being entrenched in "the way that we do things," and they don't know that something isn't broken so doesn't require fixing.

They are just asking "why" to learn and understand so they can find their place. This questioning is very valuable: we just need to listen and dig into it more. As established professionals and companies, how can we apply this style of thinking to how we run our businesses? Develop new therapies? Hire and foster talent and leadership? Does it make sense to include our younger team members in more strategy sessions, just so we can reinspire wonder or unpack unsolvable problems with a fresh eye?

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

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GAMP® CONSIDERATIONS

When Relying on Open-Source Software

By James Canterbury and Petch Ashida Druar

This article aims to refresh information on open-source software (OSS) within regulated computerized systems that was first discussed in an article in May-June 2010 *Pharmaceutical Engineering*®. The adoption of OSS advanced since then, and the article explores the importance of recognizing when an organization is relying on OSS and the benefits and risks this brings from a GAMP® 5 perspective.

Reliance on OSS has become prolific across today's information technology (IT) environments. Whether it is the use of well-known operating platforms like Linux or statistical analysis tools such as R or leveraging available JavaScript libraries to build custom applications, OSS has permeated most enterprises, including pharmaceutical/biopharmaceutical companies. When relying on OSS within a regulated computerized system, it is important to understand the method in which that software is developed and maintained so that critical thinking can be applied when determining the level of risk and mitigation strategies.

In the May-June 2010 issue of *Pharmaceutical Engineering*®, the article "Guide for Using Open Source Software (OSS) in Regulated Industries Based on GAMP" detailed the various support models for maintaining a GxP environment where OSS is used [1]. OSS is sometimes referred to as free/libre/open-source software (FLOSS) or free and open source software (FOSS), which attempts to distinguish between the values behind developing OSS and the licensing models for distributing it [2]. While important to understand, the primary concern from a GxP perspective is the development and maintenance of this software, and we will simply refer to it as OSS in this article.

This article aims to refresh *Pharmaceutical Engineering*® readers on the topic and build upon the foundation set in the 2010 article by highlighting several areas that have advanced since the publication of that article. Specifically, we will cover the importance of recognizing when an organization is relying on OSS and the benefits and risks this brings from a GAMP Category 5 perspective (see Figure 1). The large majority of OSS today would be classified as GAMP Category 1 software (i.e., embedded software components, libraries, development tools, and operating systems).

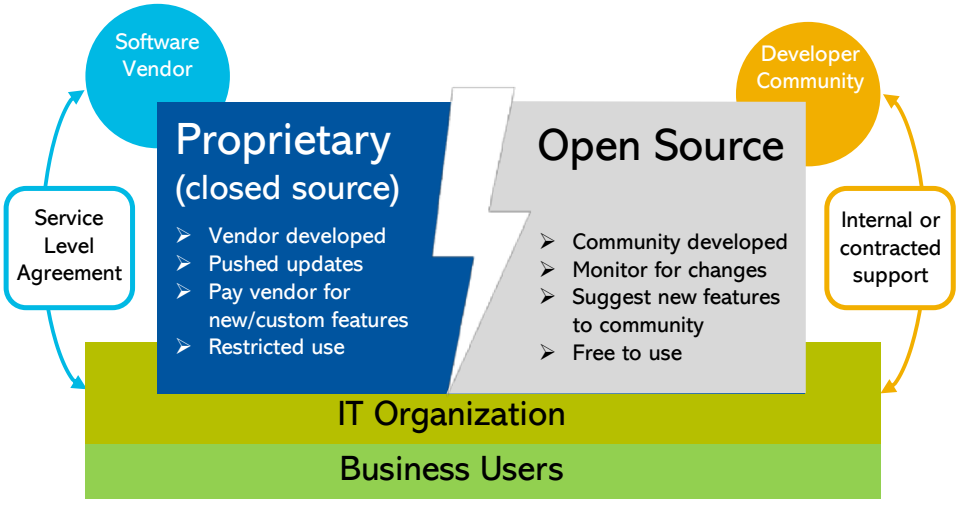
Like other infrastructure components, the inherent level of GxP risk is low; however, with increasingly connected systems and the rise in cybersecurity attacks (which often exploit vulnerabilities in GAMP Category 1 software to gain unauthorized access to networks and system resources), it is increasingly important for the GxP practitioner to have a solid understanding of what they are relying on and to plan their risk-based validation approach accordingly.

When we look toward the future, there is a strong trend for smaller fit-for-purpose applications that often run on broader, decentralized networks. In a GxP environment, these specialized systems could be GAMP Category 4 or 5 software and would carry a higher risk. Examples range from applications for managing clinical trials to post-market surveillance. These types of applications rely extensively on OSS, especially if they run on public networks.

OSS CHANGES

While a lot has recently changed in IT, the principles of GAMP set forth in the 2010 article still hold true for most companies that leverage OSS. However, there have been significant developments in the way communities organize to develop and maintain OSS. It is this collaborative development process and the freedom for anyone to access the source code to study, use, or modify it as they see fit that we must consider when using it to meet regulatory requirements.

Figure 1: Comparison of closed- vs. open-source software.



One driver for the increased adoption of OSS is its availability and reusability: developers find it easier and faster to build from a component they already know works. A software package is a collection of components that developers pull together to deliver the functionality that users need. By referencing predeveloped components, developers can develop faster and be more innovative.

For example, a few years ago, if you were building an in-house application using JavaScript and your users wanted the ability to left justify their comments in a text box (i.e., align them with the left margin), you would probably use the then-popular "left-pad" package available from the package manager company NPM (www.npmjs.com/package/left-pad) by simply including "$ npm install left-pad" in your build. Now your home-built, possibly proprietary, software is reliant on an open-source package. (Note: As of this writing, left-pad has been deprecated, but is still a relevant example).

In 2020, the Synopsys Cybersecurity Research Center (CyRC) published their annual Open Source Security and Risk Analysis report (OSSRA) [3] and found that of the 1,253 applications audited, 99% contained open-source components. In fact, as pointed out in a 2019 TechCrunch article [4], it is actually software developers, employed by companies, who often discover and integrate OSS components into their current projects. The article states,

> *Once 'infected' by open-source software, these projects work their way through the development cycles of organizations from design, to prototyping, to development, to integration and testing, to staging, and finally to production. By the time the open-source software gets to production, it is rarely, if ever, displaced.*

These references to components are often multiple layers deep, i.e., where one component refers to a library that is made up of other components that refer to libraries.

It is similar to the old anecdote of infinite regress where it was postulated that our world rested on the back of a giant turtle. When challenged to describe what the turtle stood on, the answer was an even larger turtle, with the ultimate conclusion that it was turtles all the way down. With open-source components and reference libraries, it is likewise "turtles all the way down" [5].

Software companies, realizing that this is inevitable, have begun to embrace the use of OSS. A review of the "commits" (the term used when an update to code is posted) between 2011 and 2020 shows that just behind software companies dedicated to open-source development (such as RedHat and Liferay), are familiar names such as Google and Microsoft [6]. These same corporate entities often provide the grants that support the foundations that manage the code base of large open-source projects. Even SAP, considered a highly proprietary software, has an "open source program office" as part of the Linux Foundation [7].

It is no longer a question of if your organization uses OSS; it is a question of "do you understand where it is being used?" The level of oversight and control over these software components have typically been low and should be given closer examination, especially by regulated companies.

OSS allows developers to innovate faster and deliver software with features that capitalize on the collective thinking and experience of hundreds of thousands of developers worldwide. This generally leads to more secure software, more frequent updates, and enhanced modernizations, but to reap these benefits, you need to keep it up to date.

Cultural movements aside, it is undeniable that OSS has become more prevalent, and it extends far beyond installing a Linux operating system on your server or using the Libre Office Suite because you are looking for some free software. In fact, while companies will still cite cost as a driver for choosing OSS, many are realizing that this is not the primary factor; and, as the 2010 article pointed out, "free" software is rarely free.

The decision to use OSS is not always just about cost; it can also be strategic. Because OSS does not come from a proprietary software provider, many companies select OSS so they have the option to switch to different software when needed. A 2020 survey by Tidelift showed 40% of respondents stated "avoiding vendor lock-in" as a primary driver for choosing OSS [8].

EMERGING TECHNOLOGY AND THE ROLE OF OSS GOVERNANCE

One emerging draw to OSS is the awakening of distributed and decentralized systems that operate to form a shared network under a common set of rules. These systems are commonly known as blockchains, but blockchain is only one form of this rapidly evolving class of technology.

The heart of these shared networks are their protocols, or the core code that dictates the rules by which the network functions. A public blockchain is owned by all the members who participate in it, and it is open for anyone to join; therefore, the protocol is necessarily open source. This is not a new concept; we have been living with open-source protocols for years, but they have become entrenched in our everyday lives, even if we do not realize it.

For example, if you are reading this article online, you are leveraging the TCP/IP protocol to make sure your request to view this article in your browser made it to the right computer. The difference is that TCP/IP was created in 1973 long before there was a large internet user base, and it became established as the de facto protocol for transmission as the internet we know today was being built. Changes to TCP/IP are today governed by the Internet Engineering Task Force, a nonprofit, but arguably centralized, authority for the protocol. In a public blockchain, anyone (you do not even have to be a participant) can propose changes, and if the majority of the participants accept the change, it becomes part of the code base. This has drastic implications on how we think about system governance.

While public blockchains may take open-source governance to the extreme, most emerging technologies make heavy use of this development method, even if they later lock down their algorithms in proprietary software. For example, some of the most robust frameworks and tool sets for machine learning (ML) algorithms, which often lead to artificial intelligence (AI) applications, are built using open-source tool kits such as TensorFlow (the open-source deep learning libraries supported by Google) and the Scikit-learn library of classification, regression, and dimensionality reduction algorithms [9].

Some of these same libraries are leveraged in more established software such as R, which is a free software environment for statistical computing and graphics [10]. Even if a company is not using the R runtime environment, they are likely using it as a plug-in in their statistical reporting or visualization applications (which may be proprietary). R is governed by The R Foundation, a group of volunteers who help decide which features are needed and how to fix any bugs that are reported by the user community, which is very broad. In 2021, there were three significant version releases, each addressing multiple issues and adding/changing features, some of which your organization may rely on for making important statistical-based decisions.

In the preceding examples, there is a mix of governance models. One is used for distributed software, such as blockchain, where you may be leveraging a network in which you cannot control the changes. And another is used for locally installed applications (such as R) where you may not know that your implementation has become outdated. And in between, you have ML algorithms, where the program itself may determine when it is best to update.

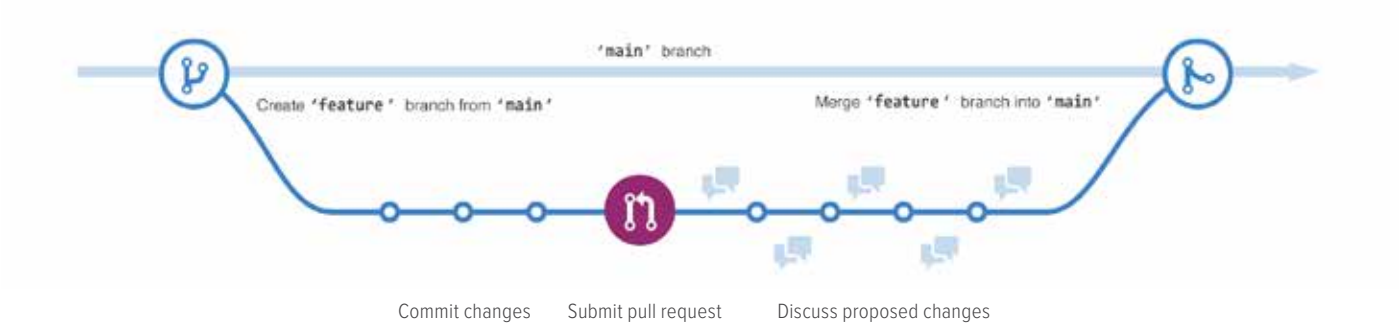
A BRIEF GLIMPSE INTO THE OSS MINDSET

It is often easiest to think of processes in an analog context. In a post on Opensource.com, Bryan Behrenshausen of Red Hat described OSS like baking a loaf of bread and sharing it with a friend [11]. But instead of just giving them the bread, you give them the recipe as well. This way, if they want to check the ingredients, they can see exactly what went into the bread, and if they noticed something did not taste quite right, they could let you know or even suggest how to fix the recipe. Or better yet, if they wanted to modify the recipe to suit their own taste, they are welcome to do so and can even share their version with others. Open source lets you blur the line between chefs, who create something new, and cooks, who follow instructions, by letting the cook talk directly to, or even become, the chef.

This communication between everyone is what fuels the "open-source community" (see Figure 2). Online collaboration tools have merged with social media to create a very responsive and adaptive approach to software development. A great example of this is GitHub, which is the most popular code-hosting platform in the world. It works by allowing a developer to create a new repository (or "repo") for a project they are working on. The repo can contain anything: folders, files, images, datasets. But most important, it should contain a README file that explains what the project is about.

This initial creation becomes the main branch of their project and is considered the definitive branch, or the source code of the project. If you, or anyone else for that matter, want to make a change, you create a branch off the main branch by creating a copy of it at that point in time. You then make your edits to the copied branch and commit your changes. If you think your changes are worthy of being incorporated into the main branch, you open a "pull request" for someone to review and pull your contribution into the main branch. This is where the collaboration begins; as soon as you submit a pull request, a side-by-side comparison of your code is created against the main branch and a

Figure 2: Visualization of collaborative development process [12].



discussion is started. Here, various developers who are interested in your project will comment on your updates (depending on the size of the community, this can take some time). If a consensus is reached that the changes should be accepted, someone with access rights to the main branch can merge the pull request to change the main branch with your updates. At this point, you can delete your branch because the main has now been updated (don't worry: GitHub keeps an extensive history of all branches, pulls, and merges). You can even require a certain number of reviews from other developers prior to allowing a branch to be merged.

Once the merge request has been completed, a new version of the main branch is available for anyone to download and use. If your project has been widely distributed, an announcement is generally made about the new version available. Occasionally a consensus cannot be reached about whether an update should be merged not. In this case a "fork" of the main branch lives on as a separate version. From an end-user standpoint, this is important because you may have to decide if you want to stay with the main branch or go with the fork. If over time, one becomes more popular than the other, or if you simply do not apply updates as new pull requests are merged, you may wind up with outdated and unsupported code. Worse yet, if you do not apply updates that addressed security weaknesses, you will be left with vulnerabilities in your applications.

What is fascinating about this process is that anyone—literally anyone with access to the internet—can view an open-source project and request changes to it. You do not have to be a developer, or even understand the source code: you can follow the community and suggest features and use cases that you think would be particularly good to include. If enough people agree with you, your request can be picked up by a developer and included in the next pull request.

This results in a strange form of user requirements, especially if you are a GxP practitioner used to seeing formal user requirements or design specifications. In an open-source community, these requirements may be captured in snippets of online dialogs or in README documents. As the previously referenced TechCrunch article puts it,

> *The community also ends up effectively being the 'product manager' for these projects. It asks for enhancements and improvements; it points out the shortcomings of the software. The feature requests are not in a product requirements document, but on GitHub, comments threads, and Hacker News. And, if an open-source project diligently responds to the community, it will shape itself to the features and capabilities that developers want [4].*

Most source code updates, especially those that are considered "components," such as the left-pad example, are handled with package managers, which let the developers bundle up their source code and push it out to anyone who is using it. Generally, developers consider it best practice to regularly install all updates before working in their environment so that they can make sure they have the latest version. Because features are added and updates are made frequently, this normally works well...until it does not. There is always the risk that the component you have been relying on might suddenly not be available. This can cause a developer's new build to fail and create disruptions while you scramble to find a replacement component.

Take the left-pad example we have been using throughout this article. In 2016, the developer who wrote and supported that code was not happy with the decisions made by management at NPM, Inc., the company that maintains the npm registry. In a fit of rage, he deleted all of his projects on NPM, including left-pad—which, according to an article on Ars Technica, "ended with JavaScript developers around the world crying out in frustration as hundreds of projects suddenly stopped working—their code failing because of broken dependencies on modules" [13].

In true open-source fashion, the community was able to rally around this and replace the repo with comparable code in about 2 hours and the software builds were able to continue. But the point is that dependencies on that one piece of code had become prolific and, in this case, a single developer was able to affect hundreds of projects with one action. It should be noted that this example is extremely rare and most OSS today repositories have redundancy built in to avoid this.

IMPACT ON PHARMA

Other than being an interesting glimpse into the world of open=source development, why does this matter for a pharmaceutical/biopharmaceutical companies? In a GxP environment, we rely on software day in and day out to perform as designed. It is always best practice to keep your company's code base running on the latest release (not the beta version, but the latest stable release). This helps ensure that any security flaws have been addressed and keeps your software compatible with future releases.

However, this comes at the risk of the code suddenly not operating as it used to (because open source can change) or it could lead to disruptions if the components being updated are no longer supported. Just like with any patch management, a good amount of due diligence needs to be taken when applying updates. But unlike commercial software, there is not always a vendor (or even documentation) to walk you through each update.

As the 2010 *Pharmaceutical Engineering*® article implied, either your IT becomes part of the open-source community, contributing to future releases, reporting bugs, and understanding the updates at a granular level, or you hire a third party to do this on your behalf. Whichever path is taken, the pharmaceutical manufacturer is responsible for maintaining the compliant and validated state of their GxP computer systems. And so GAMP plays an important role not only in the initial verification of software, but also in the ongoing verification of the environment as it is patched and updated. In the case of leveraging software as a service or vendor-hosted applications, it is important to understand their software development life cycle (SDLC) process for keeping up with the latest releases; it is often difficult (and risky) to apply a critical security patch if the codebase is already several versions behind.

RISKS AND CONSIDERATIONS FOR RELYING ON OSS IN REGULATED ENVIRONMENTS

In summary, the technical and project risks from 2010 still exist today. However, the use of OSS by pharmaceutical/biopharmaceutical manufacturers has become much more mainstream, and the level of complexity in dependencies has increased. When evaluating the overall risk to regulated systems, it is important to think like a developer. The diligence required to maintain an effective current state needs to be built into your overall IT culture. Relying on a third-party integrator to do this may alleviate some of the operational stresses, but it does not displace the risks involved. And to apply critical thinking to evaluate those risks, you need to understand what you are relying on.

This list summarizes items to consider and provides examples of good practice:

- **Understand what software you are relying on.** Even if you are purchasing commercial software, it likely has components of OSS incorporated into it. It is becoming more common to request a software bill of materials (SBOM) when evaluating new commercial software or validating in-house developed systems. Perform a risk assessment of the specific functions you are relying on.
- **Create an OSS catalog.** Build an inventory of the OSS functionality that is in use within your IT environment to help define a pragmatic governance model and to better understand where you may have risks.
- **Have confidence in the size and sustainability of the OSS community.** Newer software may be more nimble and have better features, but if the community does not have staying power, you may not have support for your system in the future.
- **Look for the use of development standards and good documentation.** Just because the source code is available for the public to review does not mean it is always developed well. Reading the documentation is usually a good indicator of the quality of the software development cycle.
- **Know what version you are using.** If you are using a local distribution of the software, you must verify that your copy does, in fact, match the version you are intending to install. Oftentimes, OSS will have several implementation options designed to accommodate a broad range of users and platforms. You also need to make sure you are downloading from a reputable source (preferably directly from the repo) and take steps to ensure the code was not altered along the way (this is often done with a checksum).
- **Understand the governance model.** Be comfortable with the governance model used by IT, or the service provider, for updates and patches. If you are implementing (or connecting to) a decentralized and distributed software (such as a public blockchain), make sure that you are comfortable with the governance model for that network and have a plan in place should that network become compromised (i.e., run your own archive node so that in the worst-case scenario, you can retrieve the transactions you have posted on-chain).
- **Keep up to date.** Make sure your SDLC process (for both you and your software vendors) requires regular patches and updates. Vulnerabilities are often exposed in software using outdated versions of OSS libraries. Unless you are compiling the program yourself, this is not always apparent.
- **Participate.** Open source works best when there is a broad community, so the best way to get new features that will make your business better is to ask for them. This requires getting involved in the forums and chats. Having this connectivity become part of your IT culture will help ensure that you stay in front of any major changes/disruptions. Regulated companies may consider putting procedures in place for employee contributions to OSS communities, to protect the regulated company from unintended risk to their intellectual property rights or conflict with business objectives.

CONCLUSION

The nature of developing software will continue to evolve as consumers ask for smaller fit-for-purpose applications and software providers push out more frequent updates to keep in front of vulnerabilities. In some cases, code is now being designed to operate privately on public networks, leading us into a world of trusted

algorithms, zero knowledge proofs, and formal verification—many of these advancements are developed under an OSS license. It's likely that reliance on OSS will continue to grow; therefore, it is beneficial to have a strategy in place for relying on OSS within GxP systems.

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AI MATURITY MODEL FOR GXP APPLICATION:

A Foundation for AI Validation

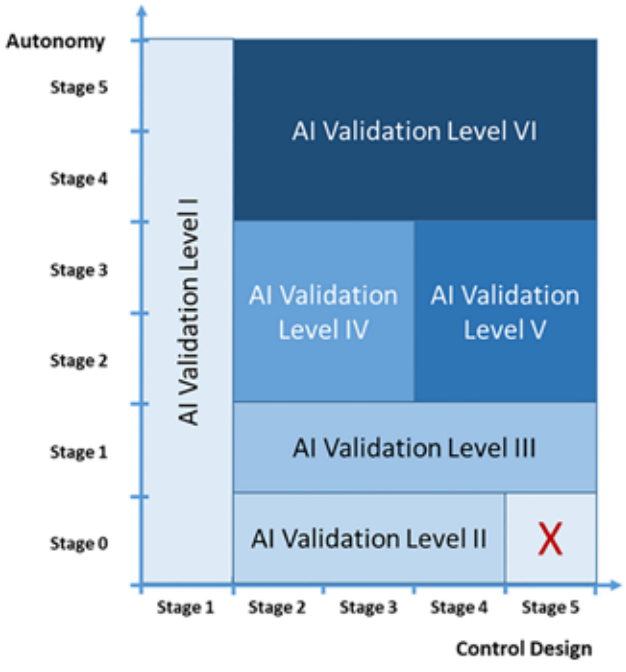
By Nico Erdmann, Rolf Blumenthal, Ingo Baumann, and Markus Kaufmann

Artificial intelligence (AI) has become one of the supporting pillars for digitalization in many areas of the business world. The pharmaceutical industry and its GxP-regulated areas also want to use AI in a beneficial way. Several pharmaceutical companies are currently running digital pilots, but only a small fraction follows a systematic approach for the digitalization of their operations [1] and validation. However, the assurance of integrity and quality of outputs via computerized system validation is essential for applications in GxP environments. If validation is not considered from the beginning, there is considerable risk for AI-based digital pilots to get stuck in the pilot phase and not move on to operations.

There is no specific regulatory guidance for the validation of AI applications that defines how to handle the specific characteristics of AI. The first milestone was the description of the importance and implications of data and data integrity on the software development life cycle and the process outcomes [2]. No life-science-specific classification is available for AI. There are currently only local, preliminary, general AI classifications that were recently published [3].

This lack of a validation concept can be seen as the greatest hurdle for successfully continuing digital products after the pilot phase. Nevertheless, AI validation concepts are being discussed by regulatory bodies, and first attempts at defining regulatory guidance have been undertaken. For example, in 2019 the US Food and Drug Administration published a draft guidance paper on the use of AI as part of software as a medical device [4], which demonstrates that the regulatory bodies have a positive attitude toward the application of AI in the regulated industries.

Figure 1: Maturity model.



INTRODUCING A MATURITY MODEL

As part of our general effort to develop industry-specific guidance for the validation of applications that consider the characteristics of AI, the ISPE D/A/CH (Germany, Austria, and Switzerland) Affiliate Working Group on AI Validation recently defined an industry-specific AI maturity model. In general, we see the maturity model as the first step and the basis for developing further risk assessment and quality assurance activities. By AI system maturity, we mean the extent to which an AI system can take control and evolve based on its own mechanisms, subject to the constraints imposed on the system in the form of user or regulatory requirements.

Table 1: Control design stages.

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
The system is used in parallel to the normal GxP processes	The system is executing a GxP process automatically but must be actively approved by the operator	The system is executing the process automatically but can be revised by the operator	The system is running automatically and controls itself	The system is running automatically and corrects itself

Table 2: Autonomy stages.

Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Fixed algorithms are used (No machine learning)	The system is used in a locked state. Updates are performed by manual retraining with new training data sets	Updates are performed after indication by the system with a manual retraining	Updates are performed by automated retraining with a manual verification step	The system is fully automated and learns independently with a quantifiable optimization goal	The system is fully automated and self-determines its task competency and strategy

Our maturity model is based on the control design, which is the capability of the system to take over controls that safeguard product quality and patient safety. It is also based on the autonomy of the system, which describes the feasibility of automatically performing updates and thereby facilitating improvements.

We think that the control design and the autonomy of an AI application cover critical dimensions in judging the application's ability to run in a GxP environment. We thus define maturity here in a two-dimensional matrix (see Figure 1) spanned by control design and autonomy, and propose that the defined AI maturity can be used to identify the extent of validation activities.

This article was developed as part of a larger initiative regarding AI validation. The maturity model is the first step. In fact, many other topics such as data management or risk assessment have to be considered in the validation of AI. The basic maturity model will have an influence on the risk assessment of the AI application.

In this article, we describe in detail which validation activities are necessary for AI systems with different control mechanisms and the varying degrees of autonomy that need to be investigated via critical thinking. The goal was to find clusters with similar validation needs across the entire area (see Figure 1) defined via the autonomy and control design dimensions.

CONTROL DESIGN

Table 1 shows the five stages of the control design.

In Stage 1, the applications run in parallel to GxP processes and have no direct influence on decisions that can impact data integrity, product quality, or patient safety. This includes applications that run in the product-critical environment with actual data. The application may display recommendations to the operators. GxP-relevant information can be collected, and pilots for proof of concept are developed in this stage.

In Stage 2, an application runs the process automatically but must be actively approved by the operator. If the application calculates more than one result, the operator should be able to select one of them. In terms of a 4-eye principle (i.e., independent suggestion for action on the one hand and check on the other hand), the system takes over one pair of eyes. It creates GxP-critical outputs that have to be accepted by a human operator. An example for a Stage 2 application would be a natural language generation application creating a report that has to be approved by an operator.

In Stage 3, the system runs the process automatically but can be interrupted and revised by the operator. In this stage, the operator should be able to influence the system output during operation, such as deciding to override an output provided by the AI application. A practical example would be to manually interrupt a process that was started automatically by an AI application.

In Stage 4, the system runs automatically and controls itself. Technically, this can be realized by a confidence area, where a system can automatically control whether the input and output parameters are within the historical data range. If the input data are clearly outside a defined range, the system stops operation and requests input from the human operator. If the output data are of low confidence, retraining with new data should be requested.

In Stage 5, the system runs automatically and corrects itself, so it not only controls the outputs but also initiates changes in the weighting of variables or by acquiring new data to generate outputs with a defined value of certainty.

To our knowledge, there are currently no systems in pharmaceutical production at level 4 or 5. Nevertheless, with more industry experience, we expect applications to evolve for applications at levels 4 and 5.

AUTONOMY

Autonomy is represented in six stages (shown in Table 2).

In stage 0, there are AI applications with complex algorithms that are not based on machine learning (ML). These applications have fixed algorithms and do not rely on training data. In terms of validation, these applications can be handled similar to conventional applications.

Table 3: Validation levels.

Level	Description	Minimum Validation Activities and Requirements
I	Parallel (AI) CS[a]	No validation required
II	Classical non-AI CS	Validation of computerized system, but no dedicated focus on AI
III	Piecewise locked state[b] AI CS	In addition to the above requirements: • Documented justification on why a model was selected • Training data verification • Model quality assurance after training • Input data monitoring in operation • Retraining procedures defined
IV	Self-triggered learning AI CS with human operation and update control at all times	In addition to the above requirements: • Monitoring of model quality in operation • Controlling quality KPIs[c] and notification process • Validation of the human factors (depending on control design) with regards to overrides, qualifications, and AI system acceptance
V	Self-triggered learning AI CS with update control, but overall or sampled operation control only	In addition to the above requirements: • Periodic re-test with defined test data set • Assurance of self-control • Control of AI system outcomes by samples for a defined, risk-oriented fraction, and adequate stratification of input/output instances
VI	AI CS with autonomous learning	Validation concept currently under development

[a]CS means computerized system.

[b]Piecewise means that the system may be regularly or irregularly manually updated to another version but provides one exact output to an instance of input data within such a version.

[c]KPI means key performance indicators.

In stage 1, the ML system is used in a so-called locked state. Updates are performed by manual retraining with new training data sets. As the system does not process any metadata of the produced results by which it could learn, the same data input always leads to the generation of the same output. This is currently by far the most common stage. The retraining of the model follows subjective assessment or is performed at a regular interval.

In stage 2, the system is still operating in a locked state, but updates are performed after indication by the system with a manual retraining. In this stage, the system is collecting metadata of the generated outputs or inputs and indicates to the system owner that a retraining is required or should be considered, e.g., in response to a certain shift in the distribution of input data.

In stage 3, the update cycles are partially or fully automated, leading to a semi-autonomous system. This can include the selection and weighting of training data. The only human input is the manual verification of the individual training data points or the approval of the training data sets.

In stage 4 and stage 5, the system is completely autonomous with reinforced ML independently based on the input data.

In stage 4, the system is fully automated and learns independently with a quantifiable optimization goal and clearly measurable metric. The goal can be defined by optimizing one variable or a set of variables. In production, the variables could be the optimization of the yield and selectivity of certain reactions.

In stage 5, the system learns independently without a clear metric, exclusively based on the input data, and can self-assess its task competency and strategy and express both in a human-understandable form. Examples could be a translation application that learns based on the feedback and correction of its user. If the user suddenly starts to correct the inputs in another language, in the long term, the system will provide translations to the new language.

VALIDATION LEVELS

The maturity levels can be clustered into six AI validation levels (see Table 3) and placed into the area defined by the dimensions of autonomy and control design (see Figure 2). The AI validation levels describe the minimum control measures necessary to achieve regulatory compliance of the systems at a high level. Detailed quality assurance requirements should be defined individually based on the categorization, given the intended use and the risk portfolio of the AI system.

Systems in AI validation level I have no influence on product quality and patient safety (and data integrity); therefore, validation is not mandatory. Nevertheless, for applications in this category, the human factor should not be underestimated. If a system is designed to provide advice and is running in parallel to the normal process for a prolonged amount of time, safeguards should be in place to ensure that the operator is handling results based on critical thinking and does not use these results to justify decisions.

Systems in AI validation level II are AI applications that are not based on ML and therefore do not require training. The results are purely code-based and deterministic and can therefore be validated using a conventional computerized system validation approach.

Systems in AI validation level III are based on mechanisms such as ML or deep learning. They rely on training with data for the generation of their outputs. Systems in this category are operating in a locked state until a retraining is performed.

For the validation, AI-specific measures have to be performed that relate to the data model and the used data, in addition to the conventional computerized system validation. The integrity of the training data has to be verified. It needs to be verified that the data used for the development are adequate for generating a certain output and are not biased or corrupted. AI validation documents should cover the following aspects:

- A risk analysis for all extract, transform, load (ETL) process steps for the data
- Assessments of the data transformation regarding the potential impact on data integrity
- The procedures on how labels have been produced and quality assured

MSD

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& Commercialization, MSD

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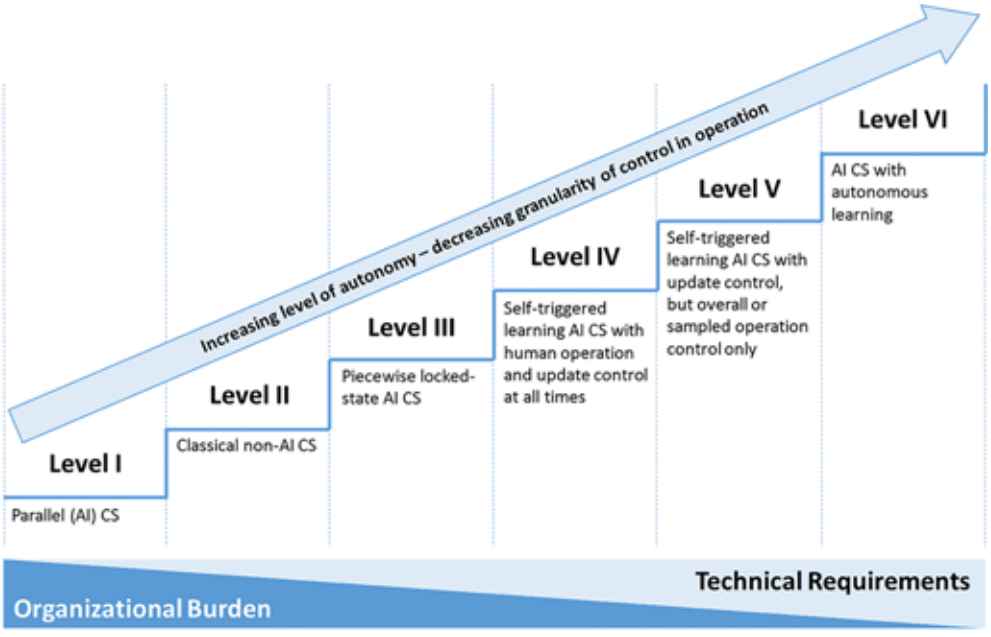
Figure 2: Representation of the validation levels with focus on business decision-making.



In addition, the model quality has to be verified during the development and operational phases. During development, it must be verified that:

- The selected algorithm is suitable for the use case
- The trained model technically provides the anticipated results based on the input data

In the operational phase, these additional aspects have to be considered and defined:

- Appropriate quality measures to monitor the model performance
- Required conditions to initiate retraining depending on model performance

For retraining, it is desirable that the input structures for the model input remain the same. Otherwise, a new assessment of the methodological setup of the development phase may be required.

To ensure that the system is only operating in a validated range, input data during operations have to be monitored. Furthermore, for systems in this category and above, transparency issues come into play, as the rationale for the generation of outputs based on different input data may not be obvious. For this reason, all available information should be visible to provide insight into the path to the outcome, and explainability studies (which aim to build trust in AI applications by describing the AI-powered decision-making process, the AI model itself, and its expected impact and potential biases) should be conducted to validate the decision-making process and provide explanations and rationales to any interested party.

Systems in AI validation level IV already inherit greater autonomy as varying aspects of the update process are automated, which can include the selection of new training data. For this reason, there is a strong need to focus on controlling key performance indicators that reflect model quality during operation. Model quality outputs should be monitored to ensure they are in the validated range. In addition, the notification process for cases, where the system requires a retraining or is operating outside of the validated range, must be confirmed.

Systems in AI validation level V have a greater process control. Therefore, stronger system controls have to be in place during the operation. This can be achieved by periodically retesting with defined test data sets. Furthermore, the self-controlling mechanism should be verified during the validation phase.

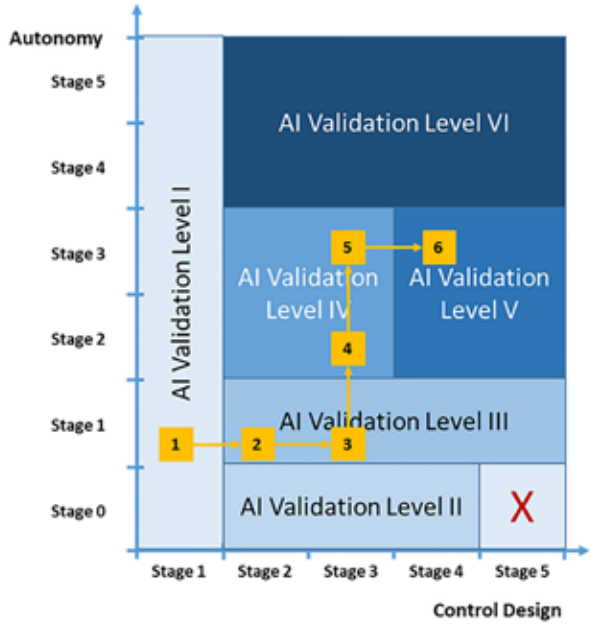
Systems in AI validation level VI are self-learning systems. It is expected that in the near future, strategies will be available for the control of continuous learning systems. There is no validation concept available now to ensure regulatory compliance for systems in this category.

In summary, the framework describes a tradeoff between the organizational burden of controlling the AI system during operation, which is more pronounced at the lower levels of the framework, and the technical requirements that facilitate increased validation activities to secure an increasingly autonomous AI system (see Figure 2).

MATURITY POSITIONING AND DYNAMIC PATH

By following the framework outlined previously, the control design of an AI system is supported with regards to the following facets:

Figure 3: Example of a dynamic AI system's path within the autonomy and control framework.



A decision has to be made about how much human control should be embedded into the operative process.

Initial design

During the initial design of the AI control mode, based on critical thinking, a decision has to be made about how much human control should be embedded into the operative process. For instance, for a first start, a mode might be chosen with less autonomy and more control, hence reducing the requirements with regard to the technical framework, yet with a higher operational burden. This decision should be critically founded on the intention of use and the risk portfolio of the specific AI system and on the company's experience with AI system design and maintenance in general. The risk assessment mechanics specific to AI are not addressed in this article.

Dynamic path

Once the AI system has been established, it should be continuously evaluated for whether the control design and the positioning in the maturity space are still appropriate, considering results from validation activities, post-market monitoring, and risk assessment updates, and from a business point of view, the balance of operational and technical burden. This evaluation may direct the design in either direction, e.g., the control design may be tightened (with more human control, less autonomy), given newly identified risks, or the AI system's autonomy may be expanded, accompanied by tighter technical control measures.

Management may consider the maturity model as a strategic instrument in order to dynamically drive the AI solution through its life cycle with regard to the system's autonomy and human control.

Example (see Figure 3):

1. The corporation decides to explore the usability of an AI system for a specific use case, parallel to an existing GxP-relevant process (AI validation level I).
2. After successful introduction of the AI system, the AI system should take over the GxP process, while still in a locked-state operation mode and controlled for all instances (AI validation level III); at the same time, stricter technical and functional validation activities are introduced.
3. Extending the AI system's value-add further, the control design is changed to a mode in which not all instances are controlled; because it's still operating in locked-state mode, AI validation level III applies. However, further controls such as sample checks of instances may be introduced, given the criticality of the GxP process.
4. After having collected sufficient experience with regard to the AI system in its specific use case, the autonomy is increased such that the system may indicate necessary retraining (AI validation level IV).
5. Extending the autonomy of the system further, the training process is now more oriented to the AI system's mechanics, i.e., in the way the retraining is performed, but the activation of such a new version is still verified by a human operator (still AI validation level IV).
6. As the final step in the solution's growth path, the control stage 4 is chosen so that the system controls itself (AI validation level V).

CONCLUSION

Because of the lack of AI/ML-specific regulations, other ways to determine the appropriate number of validation activities are required by the industry and development partners. The AI maturity model described in this article provides the rationale for the distinction among validation levels based on the AI model's stage of autonomy and control design. We consider this maturity model as the starting point for further discussions and as the basis for a comprehensive guideline for the validation of applications based on AI/ML in the pharmaceutical industry. We believe that our model has great potential for application in other life sciences industries.

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QUALITY AGREEMENTS FOR SAAS SOLUTIONS

Intended for GxP Use

By Michael Zwetkow, Kevin Wm. Roberson, and Gianna De Rubertis, ing

As adoption of cloud technology continues to increase across the life sciences industry, so too does the need to establish a standardized and pragmatic approach for ensuring the quality of software applications used in support of GxP data and associated processes. This article focuses on the application level and the growing use of software as a service (SaaS) within the life sciences industry.

Software, whether delivered as a purchased product or via a SaaS model, should be developed and managed according to a formal process, including specifications governing the software content and documented testing verifying that the software is fit for purpose. The process should be formally documented as a quality system. The quality system should align with industry best practices and standards [1–7] to help ensure quality, compliance with quality obligations, and IT security. Many regulatory requirements have a foundation in good engineering practices for IT controls.

SaaS is the capability provided to the consumer to use the provider's applications on a cloud infrastructure. The applications are accessible from various client devices through either a thin client interface such as a web browser (e.g., web-based email) or a program interface. The consumer does not manage or control the underlying cloud infrastructure, including the network, servers, operating systems, storage, or even individual application capabilities, with the possible exception of limited user-specific application configuration settings [8]. A SaaS service provider is the vendor providing the SaaS application.

QUALITY AGREEMENTS

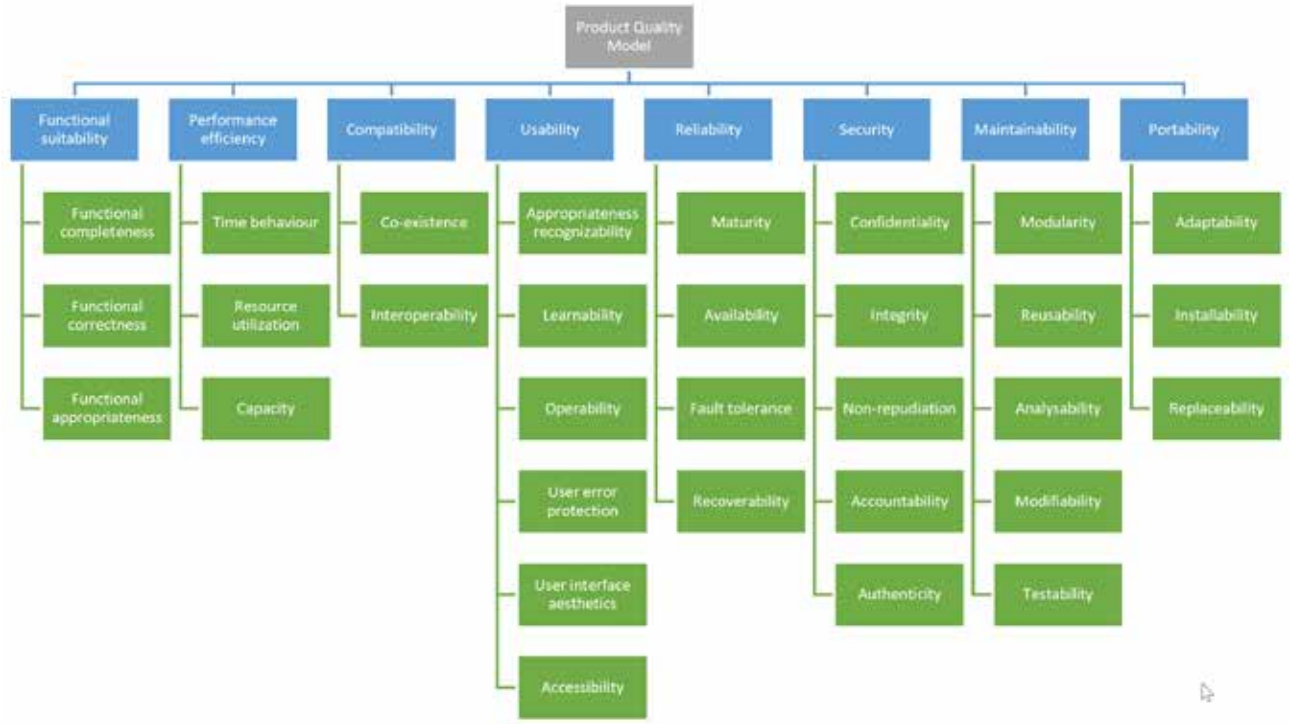
A GxP-regulated organization, referred to here throughout as a regulated company, must have clear roles and responsibilities for using an SaaS solution, interacting with the SaaS provider, and ensuring the application meets the intended GxP use. Further, a quality agreement needs to be in place to ensure that applicable requirements are met in the most pragmatic way, as this will allow the life sciences industry to use as wide an array of suppliers as possible while leveraging their services.

The regulated company must ensure that the requirements to meet the GxP intended use are understood internally, evaluated against the SaaS provider's quality system for equivalencies, and fit for purpose. The regulated company should also leverage the SaaS provider's IT services used to deliver the application to support its role in achieving GxP regulatory compliance. The regulated company should clearly document how it will leverage deliverables from the SaaS provider, the mechanism for maintaining documentation as current, and the retrieval process for the documentation (e.g., portal).

It is important to note that the SaaS provider is not subject to the same GxP regulations as the regulated company and that ultimate accountability for GxP requirements resides with the regulated company. The SaaS provider is responsible for ensuring that it has integrated quality controls and industry best practices into its software development life cycle and operational processes.

A quality agreement should define and document the key responsibilities for both the SaaS provider and the regulated company for confirming an application's intended use, fit for purpose, and associated services, including required controls and measures to ensure data integrity is maintained. The quality agreement must not delegate GxP accountabilities to the SaaS provider.

Figure 1: Key characteristics of the ISO/IEC 25010:2011 product quality model [9].



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Although it is possible that the key elements of a quality agreement are listed in other types of agreements, such as service level agreements, enterprise agreements, and master services agreements, it is important that the quality agreement is the one document that contains all of the agreed-upon quality responsibilities and defined roles of the regulated company and the SaaS provider. SaaS-appropriate terminology may be used within the quality agreement, so long as there is a common understanding of the intended meaning between the parties involved.

SAAS APPLICATION QUALITY PILLARS

Many elements contribute to the overall quality of a SaaS solution. These elements may be grouped into the following key pillars: infrastructure quality, software quality, and service quality.

Infrastructure Quality

Of the three key pillars, infrastructure quality may be the most familiar to a quality professional because of the necessity that it resembles the standard quality agreement used in the pharmaceutical development and commercialization outsourcing paradigm. The quality of physical infrastructure components including data center facilities, computer hardware, and environmental and security controls will typically be verified using normal hardware management activity following good IT practice as part of the service provider's quality system. These services should be fully leveraged in support of the regulated company's regulatory requirements.

Software Quality

From a holistic point of view, software quality is the degree to which the software meets predetermined specifications, specified requirements, and/or user needs and expectations. It implies that the software is designed and built according to best practices for software engineering, providing both functional quality and structural quality attributes to a software product.

Software users will perceive functional quality when software operates as intended, providing expected functionality without errors. Given that some performance aspects of the application will depend on the user's systems, it is important that the minimum specifications needed to connect to the application are well communicated and understood.

It can be challenging to measure software quality because different people may interpret the term differently. Software users will not perceive quality in the same way as software developers, corporate executives, legal representatives, or other stakeholders. Different perspectives will prioritize different criteria. For this reason, following existing standards and/or frameworks, which are well defined and widely accepted, is recommended.

As depicted in Figure 1, the ISO/IEC 25010 standard [9] contains a framework to evaluate software product quality, which includes a set of eight software quality characteristics, with corresponding subcharacteristics. The regulated company and SaaS provider can use this tool as part of the software development process and/or selection of the SaaS application to ensure the suitability of the product for its intended use.

Service Quality

Service quality is likely to be the most impactful of the three quality pillars because this is what users and administrators will experience from an operational perspective as they interact with the SaaS application. The critical facets of service quality include ensuring (a) security processes and tools are fit for intended use; (b) accurate, timely, and comprehensive dissemination of information that may impact the regulated company's intended use of the application (i.e., support, release management, etc.); (c) customer data are accessible only to authorized individuals (i.e., data classification, governance, etc.); (d) the accuracy and completeness of customer data and processing methods are safeguarded (i.e., security, change management, etc.) and the application and customer data remain accessible (i.e., resilience, reliability, maintenance, monitoring, capacity planning, backup, disaster recovery, etc.).

NEED FOR A QUALITY AGREEMENT

As stipulated by several industry regulations and guidance documents [10–13], formal agreements should be in place when leveraging computerized systems and services managed by third-party service providers. The nature and level of risk associated with the GxP processes supported by the SaaS application should be evaluated by the regulated company to help establish the areas of the quality agreement that will require the most attention.

To establish what should be included in a quality agreement, it is important to understand the specific challenges that can affect the quality of the hosted application from the regulated company's perspective. These challenges include:

- Potential lack of visibility over the technology stack that supports the SaaS application, including other subservice providers and/or suppliers. For example, the SaaS application may be hosted by a separate infrastructure as a service (IaaS) provider.
- Functional changes made to the SaaS application that are not controlled by the regulated company.
- Delineated and defined responsibilities of the controls and processes between each party that maintain the SaaS solution in a state of control and may have a potential impact on data confidentiality, availability, and integrity.

By outlining specific activities and reporting requirements performed by the SaaS provider and the regulated company, the quality agreement can be used to mitigate the risks associated with these challenges. To accomplish this, it is necessary to understand the partition of roles and responsibilities combined with the regulated company's determination of what quality attributes are important in the context of cloud-based GxP applications.

RECOMMENDED QUALITY AGREEMENT CONTENTS

The quality agreement serves as a binding document that lists the actions and commitments that the SaaS provider agrees to accept to meet the industry standards and quality requirements deemed relevant by the regulated company. The regulated company will need to ensure the SaaS provider can fulfill the quality requirements, and both parties must agree on the responsibilities for meeting these requirements. The following sections include considerations and recommended controls that should be included in the quality agreement to ensure the SaaS solution meets the agreed-upon quality standards.

The quality agreement should also specify the key service metrics or key performance indicators (KPIs) measured. Shared dependencies should be clearly stated in the quality agreement. Examples of key metrics and measures are included where applicable in the following sections.

Roles and Responsibilities

In any contractual relationship for the provision and delivery of cloud-based services impacting GxP processes, ultimate accountability lies with the regulated company, but the roles and responsibilities are allocated between the regulated company and the SaaS provider.

The roles and responsibilities section of the quality agreement should delineate the responsible party as either the regulated company or SaaS provider, or both, for a given quality requirement. For each responsibility listed, the regulated company is establishing the controls to support the quality obligations of their GxP requirements. The SaaS provider is agreeing to fulfill these requirements by using controls to support the regulated company's quality obligations.

The responsibilities associated with managing subcontracted activities should be defined if any subcontractors or subservice providers are used for services that are critical to the quality of the SaaS application.

Quality System

The SaaS provider's quality system will direct and implement quality objectives and policies that are intended to provide a consistent level of quality and service, outlining business and management philosophies, mission, and goals. This requirement is met with any document or group of policies and/or procedures that provide the direction and expectations generally associated with the regulated company quality manual.

Standard Operating Procedures

Standard operating procedures (SOPs) should be in place to cover all critical processes and be approved according to the SaaS provider's quality system. These procedures must be current and reviewed periodically for continued relevance and accuracy. There

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must be a process in place to ensure that SOPs are updated, reviewed, approved, distributed, and trained on by the affected staff following their quality system.

Based on the intended use of the SaaS application and the applicable regulations, the following is a list of recommended topics that should be included in the service provider's processes:

- Physical and environmental security
- Logical security
- System monitoring and maintenance
- Data retention
- Data classification
- Data access policy (ensure data are not deleted or altered by the service provider without permission)
- Data protection and confidentiality
- Software development
- Computer system verification
- Change management
- Incident management
- Risk management
- Documentation management
- Asset/inventory management
- Training management
- Data backup
- Disaster recovery
- Business continuity
- Vendor management

The SaaS provider should have a system in place to ensure training on internal policies, procedures, and technical aspects of the respective roles within the company. Examples of key training metrics include:

- Number of training gaps (incomplete training)
- Frequency of refresher training and training review

Software Development Life Cycle

The SaaS provider should follow well-defined processes and industry best practices for software development. Use of quality-driven coding and design practices generally results in software that is fit for the intended use and easy to maintain and update, which will be reflected in how well the software complies with or conforms to a given design (based on functional requirements or specifications) and aligns with user expectations. Failure to meet functional requirements or specifications would be managed as deficiencies or bugs, which can be prioritized and classified based on risk and impact. The risk must be addressed with an appropriate mitigation strategy.

The SaaS provider's development process should follow good engineering practices using a software development life cycle (SDLC) process, incorporating the appropriate controls for software development and testing. The accountability for GxP compliance and validation remains with the regulated company and thus must be verified. This verification may include monitoring of key quality metrics and measures and adherence to activities specified within the quality agreement. Examples of key metrics and measures include:

The SaaS provider should have a system in place to ensure training on internal policies, procedures, and technical aspects of the respective roles within the company.

- Number of critical feature or user requirement gaps or errors
- Number of critical bugs

Security

Security measures should be implemented to minimize the risk of potential security breaches and unauthorized penetration of the software that results in stolen information, altered records, or other forms of accidental or malicious behavior. Security arrangements should comply with all local legislative requirements for data privacy, for example, General Data Protection Regulation (GDPR) in the EU. One example of an industry standard in the area of cloud security is The Consensus Assessment Initiative Questionnaire (CAIQ) v3.1 [14].

These measures may be broken down in terms of the people, processes, and technology aspects of security. From a technical perspective, the quality agreement should specify expectations surrounding the conduct of periodic vulnerability analysis and evidence of penetration testing. In terms of processes, the SaaS provider must implement the necessary controls that describe how access to the backend of the system is provided and how privileged access is managed. With respect to people, the SaaS provider and regulated company should maintain vetting processes for any personnel with privileged access, ensuring there is a limited number of personnel with administrative access supporting the application.

A strategy for communicating and escalating security incidents must be defined. The SaaS provider must notify the regulated company of any known security breaches within a specified, agreed-to timeframe. The quantity and severity of vulnerabilities found in the software system need to be reported. Additional consideration may be required if parts of the system are managed by a third party. Examples of key metrics and measures include:

- Frequency of periodic penetration testing and vulnerability scanning
- Number of known security breaches
- Time taken to investigate and resolve security incidents
- Maximum time before a security breach is reported

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Figure 2: Key responsibilities for data integrity shared between the SaaS provider and regulated user.

SaaS Provider	Regulated User
• Establish security controls to support confidentiality, integrity, and availability of customer data. • Implement robust risk and quality management processes to ensure quality of delivered products and services. • Follow industry best practices for infrastructure control, software development, and service delivery to ensure all components of the cloud remain in a controlled state. This includes implementing proper governance controls for service management, update management, and review of access controls. • Implement robust data encryption technology to encrypt customer data at rest and in transit.	• Establish governance controls and operational processes covering data integrity, system administration, and proper operational use of the application. • Implement logical security controls and processes to protect against unauthorized access to the cloud application. • Conduct end-user training on proper system use. • Manage data inputs, processing, storage, and outputs for completeness, accuracy, and timeliness, while adhering to the principles of attributable, legible, contemporaneous, original, accurate (ALCOA). • Perform system user acceptance testing to verify fitness for intended use and regulatory compliance. • Perform periodic review with SaaS provider input.

Data Integrity and Record Management

For SaaS applications that manage GxP electronic records under the definition of 21 CFR Part 11 [15] and EudraLex Volume 4 Chapter 4 [16], the quality agreement should identify the expected technical and procedural control objectives that should be in place to ensure the integrity of data stored within the application. The SaaS provider should identify how these control objectives are met with a balance of technical, procedural, and behavioral controls.

Given that several of the controls for ensuring data integrity are shared between the SaaS provider and the regulated company, it is important to identify each party's responsibilities.

Shared Data Integrity Responsibilities

Activities should be clearly delineated and specified in a roles and responsibilities table; see the Appendix available online at https://ispe.org/example_responsibilities_quality_agreement_appendix that covers all generation, processing, review, reporting, archiving, and retrieval of GxP data in a process that ensures data integrity at all steps.

The quality agreement should also indicate whether there are any specific technical dependencies or assumptions with regard to how the regulated company can generate accurate and complete copies of the records contained within the application, including the corresponding audit trails for each record.

Audit Trail Considerations

For applications that manage electronic records under the definition of US FDA 21 CFR Part 11 [15] and EudraLex Volume 4 Chapter 4 [16] and that are required to maintain audit trails, the quality agreement should identify the expected technical and procedural controls that should be in place to ensure the data integrity requirements of the audit trail data.

The main purpose of the audit trail is to provide assurance concerning the integrity of the electronic record; therefore, a properly implemented audit trail should have the following key characteristics:

- Technical: The audit trail entries are generated by the computer system when an electronic record is created, modified, or deleted by a user.
- Secure: Audit trail data must be stored in a secure manner and must not be editable by any user.
- Contemporaneous: Each audit trail entry must be time-stamped according to a controlled clock that cannot be altered by users once the time has been set. The time should be based on either central server time or local time, so long as it is clear in which time zone the entry was performed.
- Traceable: Updates made to records must not obscure previous values and where required by regulations, the reason for changing the data and the person making the change must also be recorded.
- Archived: The audit trail must be retained as long as the electronic record is required to be stored.
- Available: The audit trail must be available for review and copying.

Software Release Cycle

In most cases where significant customer configuration of the SaaS application is needed, the SaaS provider will be expected to provide the SaaS application users access to a preproduction environment where they can assess the impact of upcoming changes, perform any necessary regression testing, and train users before these releases are pushed to the production environment.

The quality agreement should indicate the types of environments the users will have access to and provide as much clarity regarding the release process as possible, including (a) agreed-upon release frequency; (b) publication and extent of associated release notes; (c) impact assessments identifying the key features/functions of the system that were updated; and (d) time allotted for the regulated company to have access to a new release in a preproduction environment where they can perform impact evaluation, testing, and/or user training on upcoming features/functionality prior to release into the production environment. Examples of key metrics and measures include:

- Frequency of updates
- Time taken to deploy updates
- Number of bugs found in new releases
- Maintenance downtime

Testing

The SaaS provider should be able to document and present the methods used to ensure that the processes/systems are operating as intended and that the output is valid. The SaaS provider should also provide documented evidence to demonstrate that their processes/systems have met agreed/specified user requirements.

The testing and verification by the regulated company should be commensurate with the risk to the GxP data, patient, and processes covered. This testing must provide evidence demonstrating data integrity and security and strict confidentiality of all data. The regulated company needs to evaluate the SaaS provider's documentation package in view of their own risks. If additional controls or extended testing is in order, it is documented in the quality agreement. Examples of key metrics and measures include the following:

- Number of incidents, problems, and changes aligned to failures
- Percentage of requirements/test coverage

Documentation

It is acceptable practice for a service provider to maintain their system documentation within a tool providing traceability to the components within their software development life cycle. System documentation including requirements specifications, configuration and design specifications, and architecture and data flow diagrams should be developed and maintained. The specifications should be current such that they demonstrate control and reflect the current version of the application and are readily retrievable, if required. Changes to system specifications and requirements should be implemented in a controlled manner following the service provider's internal change management processes.

Change Control

The SaaS provider will ensure quality and the contractually agreed-upon level of service regarding release management and the cadence for delivery. Releases must be implemented by a formal change control process ensuring a state of control through management of changes to prevent unintended consequences.

All changes are executed per internal procedures in a controlled manner to evaluate and mitigate any potential negative impact to the regulated company's data. In the unlikely event that a planned change cannot eliminate a negative impact or there are any changes that could impact regulated company data, the regulated company should be notified prior to the change. Example of key metrics and measures include:

- Number of major (customer-impacting) changes
- Number of emergency changes
- Time taken to perform changes
- Number of times a change has caused issues in the system

Service Support and Communications

The quality agreement should also specify the key information to be provided by the SaaS provider. This could include but is not limited to:

- Release notes with functional impact assessments
- Public-facing product roadmap with enough detail to allow the customer to evaluate new functionality and impact of potential changes to existing functionality
- Third-party audit reports, attestations, and/or certifications (e.g., SOC 2 Type II, ISO 9001, ISO 27001, FedRAMP)
- Statement or policy affirming commitment with respect to maintaining a quality-controlled environment through which the service is delivered, including a description of SOPs and verification methods used to establish that the service functions in the manner intended
- Statement or policy governing customer data destruction upon contract termination and how data will be transferred back to the customer upon contract termination and/or an interruption in service

Examples of key metrics and measures include:

- Time taken to resolve critical bugs
- Notification lead time for planned system maintenance that could impact system availability
- Notification lead time for addition of new functionality and change or removal of existing system functionality (e.g., release notes)
- Notification of a change in services including mergers, acquisitions, and divestitures
- Allotted time for data repatriation in case of contract termination

Monitoring

Monitoring processes and tools should be deployed to identify issues that affect the performance, reliability, and security of the application. Metrics or KPIs used to measure performance and reliability should be defined and used to identify issues in real time and as a predictive indicator of potential issues that could

The SaaS provider is responsible for delivering a quality solution following industry and good engineering best practices.

then be resolved before user experience is affected. How and when these metrics and indicators need to be communicated to impacted users should be included in the quality agreement. Examples of key metrics and measures include:

- At a minimum, quarterly application availability/up time percentage commitment levels
- Performance and reliability monitoring
- Vulnerability management of access to customer data
- Process capacity and usage monitoring
- Network connectivity issues

Service/Application Review

Service review and/or equivalent process by the SaaS provider of the SaaS application/process should be conducted and documented following an IT industry standard. This approach will ensure continued quality and the ability to meet the requirements for the contracted services. The goal of this documented review is to provide evidence of the continuing controlled state for the product/process and continuous improvement. Examples of key metrics and measures include:

- Frequency of service and application reviews
- Incidents and problems
- Component failures
- Database performance

Supplier Assessment

Depending on the intended use and the outcome of the risk assessment, the structure of the assessment could consist of an on-site audit, remote audit, postal audit, or a review of available documentation and certifications such as SOC 2 Type 2 reports, ISO 9001, and ISO 27001 [1, 5, 6].

Independent assessments of the groups, systems, and processes must be conducted to ensure conformance with the quality and regulatory items listed in the quality agreement. The type and depth of the assessment would be directed by the quality unit of the regulated company using risk management to determine how to structure the assessment commensurate with the risk associated with the intended use.

For additional information and guidance regarding the potential use of SOC 2 Type 2 to support the assessment process, please refer to the *Pharmaceutical Engineering*® article, "Application of SOC 2+ Process to Assessment of GxP Suppliers of Services" [17]. Examples of key metrics and measures include:

- Number of audit observations
- Responsiveness to address observations

System Retirement/Contract Termination

The quality agreement should include provisions for transfer of data back to the regulated company upon system retirement and/or contract termination. In this context, it is important to ensure there is a commonly understood definition of the term "user data." For example, does it include audit trails, electronic signature manifestations, and previous versions of records?

It may also be important to specify the format of the extracted data to be provided and to identify the facilities and services that will be available to extract the data at the end of the contract. For example, some SaaS vendors may provide an application programming interface that allows users to retrieve their data programmatically.

CONCLUSION

The accountability for GxP requirements, including the integrity and use of the data, resides with the regulated company. The SaaS provider is responsible for delivering a quality solution following industry and good engineering best practices. Many tools are available to the regulated company to assist with the decision to use a specific SaaS provider. ISO certifications and SOC2 reports are just a few examples. The SaaS provider should have established processes and documentation following industry standards in place that can be utilized by the regulated company.

Automated IT services and monitoring tools provide services that can be directly leveraged by the regulated user in a proactive approach. Security vulnerabilities, database performance, component failures, application, and platform errors can be routinely monitored to provide real-time feedback on the status of the IT services and supporting infrastructure. These items should be outlined in a detailed quality agreement that delineates the specifics between the companies' management of the quality product life cycle considerations.

By implementing a quality agreement, both parties acknowledge and accept their responsibilities and commit to meeting quality objectives that can be measured via agreed-upon quality metrics and KPIs. The appendix identifies and considers the responsibilities shared between the regulated company and the SaaS provider when establishing the quality agreement. The specific activities and acceptance criteria may differ from case to case and are based on who is responsible for each activity, the regulated company or the SaaS provider.

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Additional Resources

- Object Management Group. Practical Guide to Cloud Service Agreements v3.0. https://www.omg.org/cloud/deliverables/practical-guide-to-cloud-service-agreements.htm
- Object Management Group. Cloud Service Level Agreement Standardization Guidelines. https://www.omg.org/index.htm
- US Food and Drug Administration. "Data Integrity and Compliance with cGMP–Guidance for Industry." December 2016. https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf

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SUPPLIER QUALIFICATION PROGRAM

for Key Raw Materials

by Elizabeth Rivera

With the publication of recent guidance, specifically the US FDA Quality Systems Approach to Pharmaceutical cGMP Regulations [1] and the PIC/S guide on Good Manufacturing Practice for Medicinal Products [2], the pharmaceutical industry has been scrutinizing raw material suppliers with more rigorous qualification programs to determine if they can provide the necessary goods and services to the standards required by companies meeting GMP.

The supplier qualification program is an evaluation of raw material suppliers. The requirements for supplier qualification are wide-ranging and complex, and a qualification process should identify and mitigate the associated supply risks of raw materials and services. Different regulations and guidance for medicinal drug products for human or veterinary use and investigational medicinal drug products must be followed, and various European directives and GMP guidelines also define requirements and expectations [3, 4]. For this article, "raw material" is considered any material that is somehow employed in a GMP-regulated process, and "supplier" is used in this discussion as a general term to encompass source manufacturers, vendors, re-packagers, and distributors.

Supplier qualification can also be considered a risk assessment tool because it produces an acceptable level of assurance that suppliers, vendors, and contractors can supply consistent quality of raw materials and services in compliance with applicable requirements. The quality system approach calls for periodic auditing of suppliers either by paper or on-site, and the approval process may include proof or completion of some activities and documentation.

Auditing suppliers is an expensive task that requires a serious commitment of time and resources. However, from a business perspective, it makes good sense to evaluate suppliers at a frequency and level of requirements appropriate to their impact on the final drug product. Several papers have been published about supplier qualification strategies for active pharmaceutical ingredients (APIs), excipients, and primary packaging components [5–9]. This article focuses on non-GMP-regulated raw materials such as detergents, disinfectants, gowning, and other consumables for life sciences applications.

RISK-BASED MATERIAL EVALUATION

A wide range of raw materials can affect product quality or process performance. Raw materials include APIs, process aids, materials, contacting process fluids, excipients, devices, and primary and secondary packaging. Raw materials may be further classified by their use in the manufacturing process and their subsequent effect on quality.

For simplification purposes, in this article, the categories are defined as follows:

- Starting raw materials: These materials are known to significantly affect product quality, are well characterized, and may be part of the medicinal products or in direct contact with them. Examples include APIs, excipients, USP-grade reagents, and primary packaging components.
- Key raw materials: These materials impact process consistency, but do not significantly affect product quality. They may be characterized as thoroughly as needed based on risk. Some examples are detergents, disinfectants, and food-grade lubricants. Also, they may include cleanroom gowning, commodity chemicals, secondary packaging components, and other processing aids.
- Non-starting or non-key raw materials: These materials do not meet the other categories.

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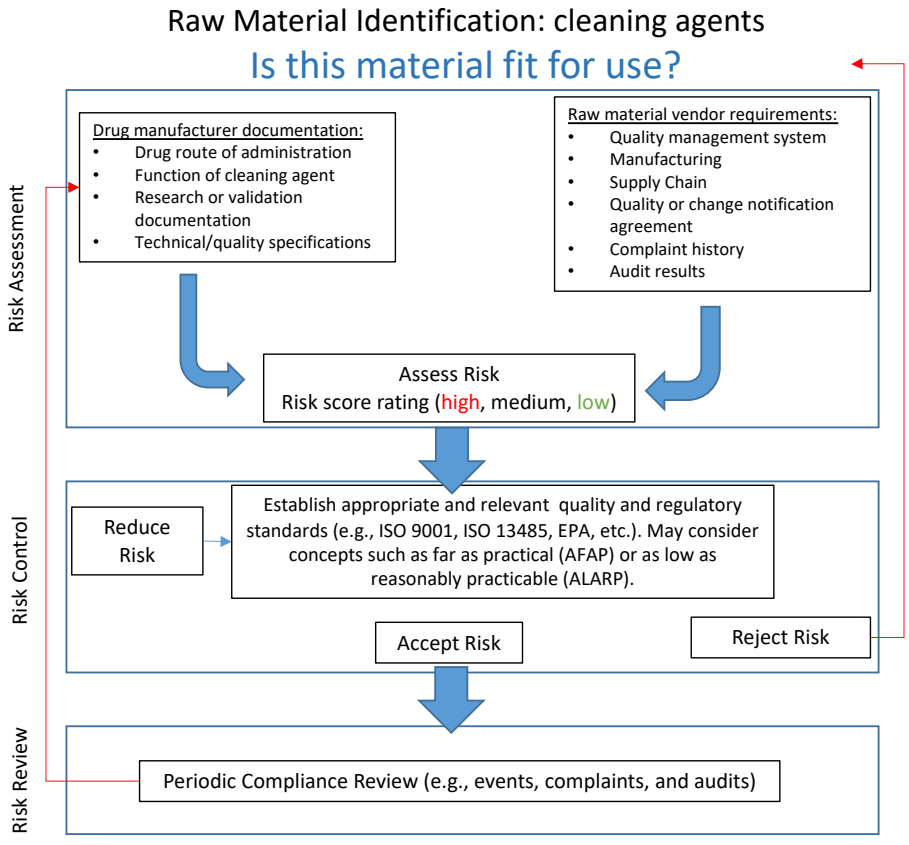
Figure 1: Example of a risk management flowchart for evaluation of a cleaning agent.



Regulatory guidelines focus on manufacturing practices for the starting raw materials intended to be parts of the medicinal product, such as APIs, excipients, and primary packaging components. The guidelines for starting raw materials define similar GMP requirements for drug products [10–12], which is reasonable because APIs and excipients are recognized as primary materials for medicinal products, and are therefore a potentially higher risk to final product quality.

Key raw materials used in the facility are considered important due to their role in a validated process (e.g., cleaning validation, sterilization processes, and disinfectant qualification), but they are not regulated by the FDA or any other GMP authorities. Virtually no industry standards have been established for most key raw materials. Further, guidance that specifically addresses supplier qualification has not been formally established, especially for key raw materials, which makes establishing supplier qualification processes even more challenging and reliant upon each company's requirements.

The supplier auditing program should be based on the risk associated with the material being provided [13]. Raw materials should be classified as high, medium, or low risk depending on the criticality of the medicinal product or process. If the pharmaceutical manufacturer has many suppliers, then these suppliers should also be assessed by classifying them into different levels based on their impact on the medicinal product.

The ICH Q9 Quality Risk Management guidelines offers principles and tools applicable to different aspects of pharmaceutical quality [14]. As shown in Figure 1, risk assessment becomes a critical aspect in the qualification and management of raw material suppliers. Therefore, the ICH Q9 guideline can be a useful reference when creating a supplier qualification program. The example in Figure 1 relates to cleaning agents used for cleaning validation of processing equipment. The risk management process could be implemented retrospectively for currently used cleaning agents and prospectively during cleaning process development.

The following questions may be used to guide the risk assessment process:

- In what part of the product manufacturing process is the material used?
- What role does the supplier play in the supply chain?
- Has the validation or product development team determined the classification of this raw material? Why or why not?
- Is this supplier the sole source of the raw material?
- To what industries does the supplier provide materials?

Table 1: Assessment to justify selection of cleaning agent supplier.*

Risk Level / Parameter Description	High = 3	Medium = 2	Low = 1
Effect on critical cleaning parameters	Increases cleaning parameters (per lab studies)	No lab data available only history	Reduces cleaning parameters (per lab studies)
Ability to detect residue on surface	Requires sophisticated analytical equipment not available on site	Only one testing method possible	At least three popular test methods available easy to implement
Ability to quantify residue on surface	No testing method available	Requires sophisticated analytical equipment not available on site	At least three popular test methods available easy to implement
Ease of removal from surfaces	Requires solvent other than water	Increases water consumption	Reduces current water consumption
Overall product toxicity	Residue limit < X	No data available but generally recognized as safe.	Residue limit > Y
Personnel safety	Full body personal protective equipment (PPE)	Requires standard PPE.	Minimal to no PPE
Supplier reputation and quality certification	Poor or no quality system	No certification/registration	ISO 9001 or FDA registered site
Supply chain	Locally produced	unknown	Globally available
Technical support/expertise	None	unknown	Available

*Risk priority number (RPN) is a numeric assessment of risk assigned to a process, or steps in a process. In this example: lowest = 9, threshold = 18, highest = 27.

The need for supplier qualification may be misinterpreted during the early stages of product or process development, such as clinical trials and prevalidation work [15]. For example, it is expected that the raw material used in the development phase, not the supplier, will be qualified during stage 1 of the life cycle model, as discussed in the FDA Process Validation Guidance [16]. Raw material qualification differs in that the focus is on demonstrating that the material is adequate for the process (e.g., manufacturing, cleaning, and sterilization). However, the raw material supplier will subsequently be qualified should the development or validation groups determine that the material or components will be used in the commercial-scale process. Table 1 is a good example of how the ICH Q9–recommended risk assessment tools can be valuable when evaluating multiple suppliers of the same raw material type.

Table 1 depicts the foundations of such a risk assessment to determine the appropriate level of quality and technical requirements by including the two primary principles issued by ICH Q9 : (a) that the evaluation of the risk to quality could be based on scientific knowledge and ultimately link to the protection of the patient, and (b) that the level of effort, formality, and documentation of the quality risk management process could be commensurate with the level of risk [14].

INDUSTRY TRENDS

Supplier qualification should be completed before the pharmaceutical manufacturer reviews. The qualification relies on approval of the test results reported on the certificate of analysis or conformance and on at least one on-site identity test.

The general supplier approval procedure for key raw materials starts with the buyer, purchasing, or procurement department contacting the preselected supplier. An internal specification sheet is created and sent to the supplier for review and approval. Supplier assessment surveys, also known as paper audits, may also be sent to the supplier at this point. The supplier-completed questionnaire is then received by the company's procurement and then quality departments. Suppliers may be required to provide samples (if first qualified), and the quality control lab tests those samples. The samples provided will be analyzed by quality control (QC) and reported to quality assurance (QA). If the results comply with the established specification, then QA may plan for an on-site supplier audit. An on-site supplier audit is planned and scheduled. If the on-site audit results are satisfactory, then the supplier is considered approved.

It is important to note that all steps mentioned may not apply to all key raw materials and may vary per company. As previously

mentioned, the supplier qualification requirement should consider the risk classification of the material. Over the years, global companies have established minimum supplier qualification requirements including quality surveys, quality agreements, on-site audits, and technical support.

Quality Surveys

To determine if a supplier can meet expected quality requirements when supplying raw materials, a questionnaire may be used to gain information about the quality standards, regulations, certifications, or best practices applicable to the type of key raw material being supplied. Surveys should contain questions applicable to the approval of a particular supplier. While it is important to know that a supplier of key raw materials has appropriate quality systems and best practices while manufacturing key raw materials, the materials are not GMP regulated, and full adherence to the GMP regulations established for drugs, medical devices, or other GMP-regulated materials is not realistic. The best that can be expected is a key raw material being manufactured "at an FDA registered site" or "manufactured under a quality system that models a GMP-compliant quality system."

Quality surveys are intended to provide a basic understanding of the supplier's quality management system. Questions should be straight to the point and clear, and companies should be cautious about including questions unrelated to quality systems such as pricing, environmental health and safety practices, or product technical questions. Instead, other survey forms that focus on those business aspects can be sent separately. Because of proprietary and company confidential restrictions, many key raw suppliers may omit details when responding to survey questions that ask to "describe," "explain," or "attach a copy." For the same reasons, a supplier may deny some information (e.g., highest education level achieved by an individual in a certain position) if irrelevant to quality systems.

Quality Agreements

In November 2016, the FDA published the guidance Contract Manufacturing Arrangements for Drugs: Quality Agreements, which describes the agency's current expectations for firms that outsource the production of drugs subject to current GMP regulations [17]. This guidance has been the basis for quality agreements in the industry, even though it is focused on contract manufacturers instead of raw material suppliers. Nevertheless, the concepts in the guidance document could be applied in the quality agreement to establish the expectations between the contract giver (company) and contract acceptor (supplier). Several important aspects for quality agreements are discussed or recommended in the literature [18–21].

The following aspects must be clearly stated and agreed upon:

- The roles and responsibilities of the company and the supplier
- How deviations and out-of-specification results will be investigated, documented, and resolved
- How changes that may need to be made to the manufacturing process, equipment, analytical methods, or specifications are managed and communicated
- How complaints are handled and resolved
- What rights the company has for on-site audits and management of audit observations

Common issues with quality agreements about key raw materials are that they often prohibit all changes without first obtaining the company's consent. First, this type of broad prohibition exceeds the legal requirements applicable to medicinal drugs, which permit routine, non-major changes to be made without first notifying the FDA. By unduly restricting non-major process improvements, companies may substantially undermine the suppliers' ability to implement quality-improving, efficiency-generating, and cost-saving measures that, in the long run, benefit both parties.

Additionally, it is not logistically possible for suppliers of non-customized globally available key raw materials to contact every end user and request consent to proceed with a change. For example, if a key raw material supplier accepts a contract with excessive change notification requirements without review, this could eventually compromise the supplier's ability to maintain compliance with the established quality agreement between both

Table 2: Common concerns related to cleaning agents and other non-GMP-regulated key raw materials.

Compliance Topic*	Reference Guidance	Pertinent Question(s) for Supplier
Transmissible spongiform encephalopathies (TSE) and bovine spongiformencephalopathy (BSE)	[27, 28]	Is the material produced with animal-derived ingredients? If so, what can you tell us about the animal-derived ingredient(s)?
Residual solvents	[24]	Is the material produced with class 1, 2, or 3 solvents? If so, what can you tell us about the solvent ingredient(s)?
Elementary impurities	[25, 26]	Is the material tested for elementary impurities? If so, what can you tell us about the impurity(ies)? Or Are metals or metal catalysts used to produce the material? If so, what can you tell us about the metal ingredient(s)?
Pallet treatment	[29–31]	What type of pallet is used to ship the materials: plastic or wood? If wood pallets, are they chemically or heat-treated?
Nitrosamines	[32, 33]	Is the material produced with any known N-nitrosamine or nitrosating agents?
Melamine	[34]	Is melamine used to produce the material? Or Is the material produced with components that are at risk for melamine contamination?
Jatropha	[35]	Is the material produced with components derived from jatropha plant?
Phthalates	[36]	Is the material produced with dibutyl phthalate (DBP) or di(2- ethylhexyl) phthalate (DEHP)?

*This is not an all-inclusive list.

parties. On the other hand, suppliers must acknowledge the needs of GMP-regulated companies and avoid significant changes that affect product quality, fit, form, and function, which may impact the use of the key raw material by companies in validated manufacturing. When unavoidable, all efforts should be made to ensure that the company is notified in a timely fashion and provided sufficient information and product supply to address their validation concerns.

Quality agreements vary in their level of procedural specificity, and often the requirements are inconsistent with the supplier's standard procedures. Some quality agreements may merely state that the supplier "has procedures" governing a particular area. Other companies may set forth detailed procedures that the supplier must implement for a particular area and these detailed requirements may create issues for key raw material suppliers. For example, the quality agreement may provide a three-year retention period for batch records, but the supplier's normal procedure may call for a two-year retention period. In this example, although there may be nothing inherently unreasonable about retaining batch records for an additional year, the supplier may want to follow current policies instead of assuming the long-term cost of tailoring its procedures to accommodate a single customer.

On-Site Audits

Pharmaceutical manufacturers are responsible for auditing high- and moderate-risk suppliers, and these audits should be determined on a case-by-case basis. Where an audit is not deemed necessary, this should be justified appropriately, including with a formal risk assessment. When a supplier audit is indicated, it should be conducted by staff with adequate knowledge and training. A written plan for the audit should be prepared before the audit. After the audit, an audit report should record what was reviewed and any observations identified. The supplier should be expected to deliver a written response to any deficiencies, and these responses should be reviewed before the audit is closed. The resulting audit report can form the basis for the approval of the supplier.

The supplier should be re-audited at a specified frequency to verify ongoing performance. A rationale for the minimum audit frequencies for each supplier should be documented. The standard industry practice is every 3–5 years for non-GMP-regulated key raw materials. Even if the initial audit was on site, a desktop and/or questionnaire audit might be acceptable for re-audits if there have been no quality issues and the supplier has a good quality and compliance history.

The COVID-19 pandemic resulted in governments imposing temporary measures such as confinement, quarantine orders, and

travel restrictions that are impacting GMP manufacturers in their capacities to perform on-site supplier inspections. Consequently, many drug manufacturers have adopted temporary measures such as performing virtual supplier audits to maintain compliance and supply of medicines to patients. The term "virtual audit" applies to inspections performed off-site using enhanced communication and information technology to fulfill a legal requirement of an on-site inspection. The only difference is that the inspector is not physically present. These audits may also be described as "remote" or as "distant inspections."

Technical Support

The supplier's ability to provide technical support is critical for the design, qualification, and monitoring stages of the process life cycle approach. For example, for cleaning agents used in validated cleaning applications, technical support could include laboratory testing for selecting the best cleaning agent and cleaning parameters, which saves time and resources during start-up or when trouble-shooting existing cleaning issues. Technical support should be available via phone calls, emails, teleconferences, webinars, and on-site support if needed. Technical literature may include the following, as applicable: material safety data sheet, certificate of manufacture/analysis, technical data sheets, technical tips, and laboratory reports.

COMMON ISSUES WITH GUIDANCE DOCUMENTS

A series of supply chain disasters—such as heparin, melamine, and nitrosamines contamination—has resulted in more pressure than ever for pharmaceutical manufacturers to develop better supplier qualification practices [22]. Material management and supplier evaluation are key processes to avoid batch failures and adverse effects on patients. As a result, pharmaceutical manufacturers are demanding quality system compliance with adequate standards and increased information transparency from their suppliers [23]. Some raw material suppliers require more provenance information from their suppliers, such as source, origin, and other essential information for traceability purposes.

Most FDA (or equivalent agency) guidance documents related to the subjects mentioned previously are applicable to medicinal products and their starting raw materials. However, key raw materials that are not purposely added to or in direct contact with the medicinal product may be beyond the scope of those documents. For that reason, requesting suppliers of key raw materials to make the product fully compliant with such guidance documents is not realistic. In some cases, compliance may not even be feasible due to the type of material.

The USP <467> Residual Solvents and USP <232> Elemental Impurities guidances are good examples to illustrate this issue. The first is a standard for the testing and potential reporting of residual solvents in pharmaceutical products. Residual solvent is defined as organic volatile chemicals that are used or produced in the manufacture of drug substances, excipients, or in the preparation of drug products [24]. Similarly, elemental impurities specify limits for the number of elemental impurities in drug products [25, 26]. These impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently.

These USP documents do not apply to key raw materials such as cleaning and germicidal agents used in drug manufacturing facilities because these types of items are intended to clean and disinfect surfaces. Some surfaces on which these cleaning agents are applied may also be in direct contact with drug products; however, residues are generally removed before the equipment is used. An effective and validated cleaning procedure will ensure that any potential for residuals from cleaning agents is not transferred over from the cleaning process into the next batch of drug product.

Even though key raw materials may be excluded from USP <467>, USP <232>, and other similar guidance documents, assessing the risk for potential contamination into the manufacturing process is still recommended. A better approach is to ask suppliers more pertinent questions as applicable to the material instead of requesting a declaration of compliance with these standards or guidance documents. Table 2 provides a list of common compliance topics and reference guidance documents with a suggested question for non-GMP-regulated key raw material suppliers.

CONCLUSION

Considering the regulatory challenges, it is important to have a deep understanding of key raw material suppliers when sourcing materials worldwide. Suppliers must be willing to provide the information needed for regulatory filings or other regulatory requirements, including materials not governed by GMP regulations. Favoring suppliers that can supply reliable and high-quality products ensures safe and effective drugs and makes good business sense.

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About the author

Elizabeth Rivera is a Technical Service Manager for the Scientific Division of STERIS Corporation in Mentor, Ohio. She provides technical assistance for life sciences consumables such as detergents, disinfectants, and sterilization assurance products. She is responsible for assisting companies with supplier qualification requirements including paper surveys, on-site audits, quality agreements, and others. Elizabeth has 20 years of experience and has bachelor's and master's degrees in chemical engineering from the University of Puerto Rico. She has been an ISPE member since 2010.

MEMBER OF THE YEAR 2020

An Inspirational Leader in Industry Service

By Marcy Sanford

Eamon Judge

Eamon Judge, the 2020 recipient of the Max Seales Yonker Member of the Year award, exemplifies the values behind the award: service to the industry and inspiring ISPE members to volunteer.

ISPE's 2020 Annual Meeting was a virtual event due to the COVID-19 pandemic and did not include a Member Breakfast or member awards. Instead, ISPE bestowed the 2020 Max Seales Yonker Member of the Year Award at the 2021 Annual Meeting in Boston, Massachusetts, to Eamon Judge, Global Engineering Advisor/European FM Lead and Chair of the Industry Engagement Subcommittee of the ISPE Ireland Affiliate. The award was announced at the Annual Meeting, with Eamon accepting it virtually.

While introducing the award, 2020–2021 ISPE International Board Chair Joanne Barrick told online and in-person attendees that "this award honors members who dedicated themselves to excellence and service to our industry and to ISPE. Max Seales Yonker was an active member, Society leader, and a relentless contributor to ISPE and to our industry. When her family, and her ISPE family, lost her to cancer in 2005, it seemed only fitting that her memory be honored with an award that recognizes that same commitment to Society service. The memory of Maxine Yonker reminds us that we are all patients, and it reminds me of the vital work that each one of you do to advance the development, production, and delivery of a safe and reliable drug supply.

"Eamon Judge has been an active member and leader within the ISPE Ireland Affiliate for more than 17 years," Barrick said. "He has made a particularly significant contribution to the Society by leveraging his position as ISPE Ireland Affiliate President to form and lead the Irish COVID Alliance, which has been nothing short of remarkable. From April 2020 to date, Eamon led the COVID Alliance, a group of 50 private and public sector organizations who mobilized to assist the Irish Health Service during the COVID-19 pandemic. Among others, the Alliance addressed assuring adequate oxygen supply for ventilators, acquiring surge capacity equipment for the healthcare system, organizing volunteer maintenance and utility workers to support hospitals, and developed and implemented a process to manufacture a critical short supply reagent for COVID-19 testing, supporting over 5 million PCR tests. Midway through 2020, after sharing the activities of the Alliance with the ISPE European Affiliate Committee, the Ireland Affiliate joined with the ISPE UK Affiliate to share experiences as they partnered with the Institution of Chemical Engineers (IChemE) to develop a 'knowledge exchange' among companies in the UK. Eamon inspires others to engage in volunteer activity and truly exemplifies the value of ISPE Membership to the industry."

ROOTS IN SCIENCE AND SERVICE

Eamon Judge grew up in a family with strong scientific interests. "My interest and background in science goes back to my father, who originally was an engineer with our electric utility and was a very curious man," Eamon said. During World War II, he was a telecommunication technician in the civilian workforce that accompanied the Allies. He wired up telecom in the caves in Gibraltar before the invasion of North Africa."

While Eamon's family encouraged his interest in STEM, they were unsure of his career path at first. "When I picked chemical engineering as my course of study, my parents scratched their heads and said, 'What's that?' They had no idea what a chemical engineer was at the time. Being an engineer meant building bridges."

After earning his bachelor's degree in chemical engineering with First Honours from the University College Dublin, Eamon started reviewing his employment opportunities. When he decided which company he wanted to work for, his parents were once again scratching their heads. "When I decided to join Eli Lilly in 1980, the company had just arrived in Ireland and was setting up a new plant. My parents had never heard of them. I was offered other job opportunities from companies that were well known in Ireland, including the electrical company that my father worked for. But I decided to try Lilly because what struck me during my interview, which is also the reason I am still with Lilly 41 years later, was Lilly's values and because when I was doing my round of

interviews, they were the only company where everyone was on a first-name basis. They looked at you as a person. Now most companies are like that, but in the late 1970s and early 1980s, most companies were much more formal. Lilly was quite different and that was appealing to me."

Throughout the 1980s, Eamon held operations management roles and took on director-level responsibility for small molecule active pharmaceutical ingredient (API) operations and engineering/health, safety, and environment (HSE) supply chain functional leadership at Lilly's API site in Kinsale, Ireland. "We were a very small site at the time, like a child compared to the major US sites. We started producing APIs using chemical synthesis and within four to five years had established ourselves to the point that we became recognized as a final API production site, had been regulatory approved for the same, and were supplying to markets all over the world."

During the mid-1990s, he and his wife and children relocated to Lilly's corporate headquarters in Indianapolis, Indiana, where he held several leadership roles in corporate strategic facilities planning and technology and facilities design. He returned to Ireland to lead the operation of Lilly's bulk aseptic manufacturing facilities. In the 2000s, Eamon had senior management responsibility for engineering, IT/process control, and HSE during the addition of two large mammalian cell culture API facilities. He was recently EMEA (Europe, the Middle East, and Asia) Leader in Lilly's global engineering function with project planning responsibility for significant capital investments in Europe and Asia. Eamon has had a long interest in sustainability and in 2020, he proposed and led the construction of Ireland's largest private solar farm at the Lilly Kinsale API site. He has since been contacted by five other pharmaceutical companies to advise them on the development of similar projects.

PANDEMIC HELP

Throughout his career, Eamon has faced various challenges. His determination to help when the COVID-19 pandemic first started affecting Europe certainly saved lives. "My first moment of realization of how bad COVID-19 was going to be was on 4 March 2020 while I was watching a BBC program and they were showing some scenes from Northern Italy, footage of a collapsing ER unit where people couldn't get oxygen and couldn't get into intensive care, and you saw the trucks taking the bodies away. I thought if this is coming our way, it is going to be terrible. It's going to need a response; our health service is going to be swamped by this. They are in the business of treating and saving people; they are not in the business of logistics and engineering.

"Ireland has companies in the pharma sector and service companies that all work together and are also connected through ISPE. So, the following morning, I rang the principals of four of the major engineering firms and I said, 'Look, I don't know what we'll need to do, I don't know what they'll need, but we'll need to respond fast. There'll be no purchase orders, there'll be no payment, it'll all be pro bono,' and they all said, 'We're here, tell us what you need.'"

The group, which became known as the COVID Alliance, grew to 50 private and public sector organizations that all mobilized to help the Irish Health Service by formulating testing reagents, producing PPE, upgrading hospital oxygen systems, staffing nursing homes, and more. Many of the members are long-time supporters of ISPE activities. Eamon went on to partner with the ISPE UK Affiliate to coordinate a similar initiative. Eamon said ISPE connections proved fruitful throughout developing COVID Alliance responses.

ISPE AND "COMRADESHIP"

Eamon's roots in ISPE are strong. Eamon joined ISPE in 2004 and was the President of the ISPE Ireland Affiliate for six years. He said he initially joined ISPE after returning to Ireland from the US as a way to stay connected, but has found he gets much more than networking opportunities from his membership. "People talk about ISPE being good for networking, but it is more than that. It's a sense of comradeship. ISPE provides a forum for connection with each other, and while members realize that some of their information is proprietary, there is a lot of other information that is appropriate to share for the benefit of patients, the community, or the environment and it is very positive that people are willing to help each other out."

During his tenure as ISPE Ireland Affiliate President, the Affiliate hosted the ISPE European Biotechnology Conference in Dublin in 2017 and the ISPE European Annual Conference in 2019, which had the largest attendance at any ISPE European Annual Conference to date. Eamon established a foundation for the subsequent development of student chapters, is an advocate for Women in Pharma® and Emerging Leaders (EL), and has established the Irish Pharma Manufacturing Leadership Forum. "I've taken part in some of the EL Hackathons both in Las Vegas and Dublin and also virtual ones and I'm blown away by their ideas. We think we are being mentors to help them but more often than not it is the ELs who are helping us to look at the world differently."

In addition to his mentoring work with ISPE's ELs, Eamon promotes STEM to students of all ages at local schools, has been involved in Scouting Ireland as a member and leader, and has been involved for over 20 years with the Young Scientist Exhibition, an annual Irish science competition for elementary through high school students. His passion for connecting with and helping others is evident in everything he does. "Over the years, three groups of students from the local high school I work with have gone on to be overall winners. It is great to see the students grow as they develop their projects and many of them have gone on to STEM careers locally with Lilly and other companies."

In his spare free time, Eamon enjoys doing DIY projects, listening to podcasts, and spending time with his wife, Maureen, and three children, two of whom are engineers, while the other has a genetics and computational biology background.

And while the past few years have been challenging for everyone, Eamon see some positive outcomes from the pandemic for the pharmaceutical sector. "I think we'll be able to use what we've learned during the pandemic to bring medicines to patients quicker. I think it's made us able to focus more on what is critical and what is not, and helped us identify supply chain issues that would have come up eventually as the use of single-use materials has exploded. It's shown us where there are opportunities to partner with regulators more effectively and make progress more efficiently. It's shown that things can be done quickly and safely when necessary to meet the needs of patients."

About the author

Marcy Sanford is ISPE Publications Coordinator.

ISPE BRIEFS

ISPE Foundation Participation at the 2021 ISPE Annual Meeting

By Bill Mojica

The ISPE Annual Meeting & Expo is our signature event, uniting the pharmaceutical industry's best and brightest to share their expertise, showcase their brands, and network. The 2021 Annual Meeting was no different but added a hybrid component. For the first time, the ISPE Foundation had a strong presence at the meeting in Boston. The Foundation utilized a Virtual Golf Experience Lounge to share its mission and initiatives with attendees.

The Foundation continues to support education, training, and research as it builds its impact on the industry. As part of its mission, the Foundation provides travel grants annually to current students, Emerging Leaders, and Women in Pharma® to attend the ISPE Annual Meeting. In 2021, the Foundation awarded 11 grants totaling $14,000 to attendees from Bangladesh, Denmark, the Philippines, and the United Kingdom. In the US, individuals from California, Massachusetts, Pennsylvania, and Texas received funding as well. Of those who received grants, four attended virtually and the other seven traveled to Boston to attend in person. Attendees went to sessions including regulatory affairs, Pharma 4.0™, cell and gene therapy, and new approaches to process agility and reliability.

Z.A.M. Shabeer Thahir, Process Validation Engineer with Thermo Fisher Scientific, and Chair of ISPE Emerging Leaders UK, attended the conference. He said, "I had an absolutely fantastic time at the ISPE Annual Meeting. I learned about polyvinylidene fluoride as a viable alternative to stainless-steel piping and new software solutions for paperless validation." Thahir had a chance to connect with several of the ISPE Foundation travel grant recipients and said, "I really enjoyed the networking aspect."

Carolina Serrano Martinez, Incoming Process Engineer at Eli Lilly and Co., and Founder of the Student Chapter at Texas A&M University, was one grant recipient. "The 2021 ISPE Annual Meeting was an incredible experience that opened my eyes even more to what ISPE has to offer," she said. "As my first time attending, I connected with a variety of professionals eager to support young professionals and students like me."

Amanda Schumacher, Market Sector Leader at Borton Lawson, another grant recipient, commented, "This was my first time attending the ISPE annual conference and it was a great experience. The technical sessions were so relevant and informative, and the networking resulted in many new productive relationships. I especially enjoyed the Women in Pharma session and the opportunity to connect with leaders and partners in the industry."

The Foundation continues to strive to help shape the future of the pharmaceutical industry. Thabir observed, "this was all made possible by the grants provided by the ISPE Foundation and ISPE UK. I'm grateful for their support." Martinez added, "My attendance was only possible thanks to the support from the ISPE Foundation, and I am so grateful for that opportunity."Schumaker said, "I'd recommend this conference to anyone, from industry leaders to those just beginning in pharma. It is a well-rounded and thoughtfully inclusive conference that will leave you with new perspective and relationships."

About the Author

Bill Mojica is ISPE Director, Development & Foundation Operations.

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at **ISPEFoundation.org**.

ISPE® FOUNDATION

ISPE Japan Affiliate's Emerging Leaders Make a Strong Start

In 2021, the ISPE Japan Affiliate established the Emerging Leaders (EL) Team to provide a variety of technical training sessions in addition to networking opportunities. The training sessions will include seminars, workshops, and plant tours for ELs in Japan, as a part of activities contributing to development of the pharmaceutical industry. ISPE members under the age of 40 are eligible to join the EL Team; currently the Team has nine members.

On 27 October 2021, the EL Team hosted a webinar format on continuous manufacturing (CM). Since the ICH Q13 draft Guideline "Continuous Manufacturing of Drug Substances and Drug Products" was released in July 2021, CM has become a prominent topic of discussion but knowledge and experience in Japan remain limited, so the webinar offered ELs an opportunity to further their knowledge of the subject.

Experts from F. Hoffmann-La Roche, Ltd. presented an introduction to CM and showed examples of the company's projects in small molecule drug substances and drug products. The presentations were provided in English with a moderated question and answer session on a chat platform.

This was the first English-only webinar provided by the ISPE Japan Affiliate. Approximately 40 ELs from various business sectors attended and asked questions. Follow-up questionnaires revealed that approximately 90% of the participants reacted positively to the webinar.

The EL Team will make its utmost efforts to continue to offer opportunities for the ELs to participate in wide-ranging activities. The Japan Affiliate would highly appreciate your support for their activities.

—Yuya Nomoto

New ISPE GAMP® GPG Supports Innovation in Life Sciences

The drive within life sciences to improve patient safety and product quality, and provide value to society, while reducing costs, requires constant and effective innovation. However, because the pharmaceutical industry operates in a highly regulated sector, some practitioners may apply unthinking, prescriptive, and rigid approaches that are not commensurate with the needs of the process, the nature of the system, and the real risk to the product and the patient.

The new *ISPE GAMP® Good Practice Guide: Enabling Innovation–Critical Thinking, Agile, IT Service Management* discusses three key topic areas where regulated companies can apply innovation to meet rapidly changing industry needs. "The application of critical thinking, adoption of incremental and iterative (Agile) software development models and methods, and utilization of modern IT service delivery options enables the life sciences industry to provide innovative solutions to support the development and advancement of patient health," explained Guide Co-Lead Chris Clark, Director, TenTenTen Consulting.

Guide Co-Lead Heather Watson, Director, TenTenTen Consulting Limited, added, "This new GAMP Good Practice Guide shows how these concepts are interwoven: applying critical thinking when leveraging iterative software development practices and using both to underpin the delivery of IT service through appropriate management of IT Service providers."

"This GAMP Good Practice Guide provides information to support the adoption of current best practices in software engineering, data management, and 'as a Service' offerings (XaaS)," said Guide Co-Lead Siôn Wyn, Director, Conformity Ltd., "including encouraging the use of supporting tools and automation, thus facilitating the best use of resources and the application of appropriate, up-to-date, and proportionate approaches." The Guide is available at https://ispe.org/publications/guidance-documents

—Marcy Sanford, ISPE Publications Coordinator

MEET THE ISPE STAFF

SUSAN OBARSKI

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Susan Obarski, Senior Director, Project Management Office.

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

My role has a dual nature of leading ISPE projects as well as helping the organization look at its body of work holistically. For example, this year, I am serving as the project lead on the One ISPE Initiative. This initiative is modernizing and improving the ISPE Affiliate and Chapter structure to help ISPE achieve its mission and vision. Projects like these are transformative for the organization as they will improve the member experience around the globe. I also work with the ISPE Leadership Team to collect and evaluate metrics to assess overall organizational health.

What do you love about your job?

I love that I am a part of the work that ISPE delivers through its staff and volunteers worldwide. This work directly impacts patients—all of us—and that is something I am grateful for daily. I also love how dedicated ISPE staff and volunteers are to ISPE's mission.

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

I love to enjoy the outdoors and living in Florida makes this easier to do year-round. I am also a huge Star Trek fan and always enjoy watching any Star Trek episodes and movies to relax!

PE Magazine Wants Your P+E!

Tell us about your Chapter and Affiliate events and conferences, trainings and Women in Pharma® meetings, Emerging Leaders activities, and Communities of Practice and Special Interest Group work, and we'll share it with all of ISPE in *Pharmaceutical Engineering's* People+Events (P+E) section. Be the reporter, and we'll be the editor, helping you share your information.

Have you recently attended an ISPE conference session or webinar and would like to share highlights from the conference? We are always interested in subject matter expertise in sharing highlights of sessions and webinars with PE readers who may not have been able to attend the events. Please contact ssandler@ispe.org for more information.

Please submit articles and short items for ISPE Briefs to ssandler@ispe.org—ISPE Briefs can be up to 400 words, articles can be up to 1,000 words. Photos are welcome: at least 300 dpi or >1 MB.

VALIDATION OF ASEPTIC PROCESSES

Using Media Fill

By Richard Chai and David J. W. Barber, PhD, CBiol, MRSB, PCQI

Aseptic process simulation (APS) is essential for validation of an aseptic manufacturing process and is required by regulators to demonstrate the aseptic capability of such processes. A successful program of APS and aseptic manufacturing requires significant operator training, skills, and supervision; thorough maintenance; effective cleaning and disinfection; significant oversight of every aspect of the operation by quality assurance; and microbiological monitoring by quality control.

An overall validation of aseptic processing (as distinct from manufacturing process validation [PV]) is used to assess the contamination risk of an aseptic production process by simulating the manufacturing process using microbiological growth media instead of the drug solution. This is necessary in part because the sterility test used to release batches of sterile products has inherent limitations in detecting contaminated units in batches with low levels of microbial contamination, due to the limited number of samples that can be removed for destructive testing; this relationship has been evaluated statistically [1].

Sterility assurance in aseptic processing requires contributing elements—such as the heating, ventilation, and air conditioning (HVAC) system, cleanroom environment, material transfer, equipment, and manufacturing process steps, including sterilization processes and sterilizing filtration—to be qualified and validated as applicable and for personnel to be trained and qualified. Simulation of aseptic manufacturing processes using liquid microbiological growth medium (also referred to as media simulation or APS) is required by regulators to demonstrate the aseptic capability of these processes.

APS consists of three consecutive media simulations with designated personnel in the specific cleanroom environment, followed by repeat media simulations at six monthly intervals. Any media fill failures require thorough investigation and root cause analysis, and further media simulations may be required to complete the validation.

Aseptic processes are typically carried out in conventional cleanrooms with vial filling and stoppering in Grade A laminar airflow (LAF) in a Grade B background environment. The filling environment may be further protected within a restricted-access barrier system (RABS) with glove ports for access to the filling line. Alternatively, processing equipment for the critical steps may be enclosed in a glove box or isolator. Each of these systems enhances the filling environment's sterility assurance but also presents challenges for material transfer, operator access, environmental monitoring, and APS.

REGULATORY EXPECTATIONS

Aseptic manufacturing and validation follow current GMPs and related GMP Annexes and Guidance. These pertain to the manufacture, validation (APS), and control of sterile products for injection (as well as eye drops and advanced therapy medicinal products). Current guidelines come from the European Union/Pharmaceutical Inspection Convention (EU/PICS), China (2010) GMP (NMPA), United States Food & Drug Administration (US FDA), and World Health Organization (WHO) [2–13]. They may reference related International Organization for Standardization (ISO) and Parenteral Drug Association (PDA) standards [14–17], such as those relating to cleanroom air-cleanliness classification and particle monitoring [17].

Because of the high safety risk profile for parenteral drug products, the protocols, results, and reports for APS form an integral part of regulatory submissions for such products, meaning they are included in investigational new drug (IND) applications, new drug applications (NDAs), and marketing authorizations (MAs). Ancillary documents such as training records, environmental monitoring reports, deviations, and investigations are key topics of scrutiny during facility inspections, as well as the qualification of facility, the equipment and utilities, and the process validation.

The expectation in APS is twofold. First, it must achieve three consecutive media batches that meet target acceptance criteria. Second, the solution filtration process must be validated against a

microbial challenge with 10^7 colony-forming units per square centimeter of filter medium (using Brevundimonas diminuta, a small-celled Gram-negative bacterium suspended in the drug solution).

Examples of media fill run sizes and acceptance criteria for APS that have been incorporated in GMP Annex [6] and Guidance [10, 11] include:

- When filling less than 5,000 units, zero contaminated units should be detected. A contaminated unit is considered cause for revalidation following an investigation.
- When filling 5,000 to 10,000 units, one contaminated unit should lead to an investigation, including consideration of a repeat media fill. Following investigation, two or more contaminated units are cause for revalidation.
- When filling more than 10,000 units, one contaminated unit should lead to an investigation, and two or more contaminated units are cause for revalidation.

APS CONSIDERATIONS

The following is an overview of points to consider when designing the media fill study for an aseptic manufacturing process.

Worst-Case Challenge

APS should mimic, as closely as possible, all aspects of the aseptic manufacturing process and should involve a "worst-case" approach as a challenge to the robustness of the aseptic operations. The "worst-case" should be defined with supporting rationale.

Risk assessment principles should be used to determine the worst-case challenges related to line speed, container size, batch size, hold time, configurations, and operating conditions.

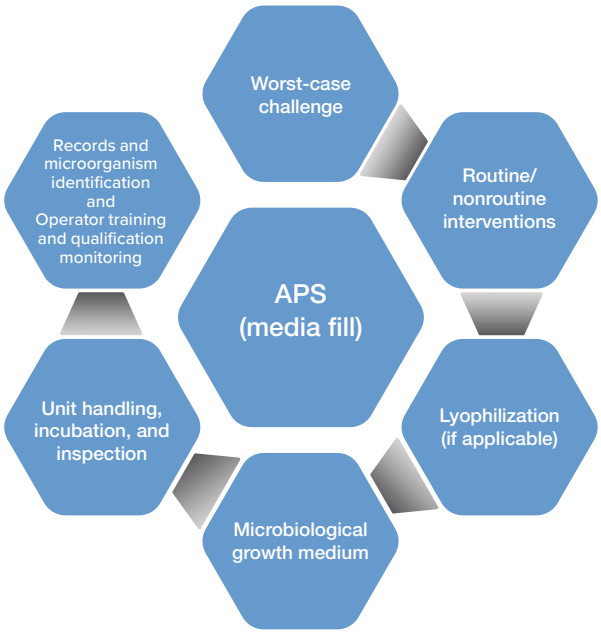
Some examples of worst-case challenges :

- Filling process
  - Aseptic assembly of equipment and aseptic connections prior to commencement of filling
  - Slowest filling speed with widest opening vials/containers
  - Maximum filling volume for small vials/containers, due to handling difficulty that can result in more interventions
  - Maximum batch filling duration (may include lyophilizer loading and door opening duration)
  - Operator fatigue as contamination risk
- Operating conditions
  - Maximum number of personnel in aseptic area
  - Shift changes, personnel changes, and operator breaks
- Hold time
  - Equipment/room clean hold time
  - Equipment sterilization hold time

Routine and Nonroutine Interventions

Interventions to be included for simulation in the media fill protocol include routine and nonroutine manipulations by operators. The regulatory expectation is that interventions included in APS should be compliant with current GMPs, and APS must not be used to justify poor aseptic practice or equipment design.

Figure 1: Points to consider when designing the media fill study.



Routine interventions include charging stopper and seal hoppers, removing jammed stoppers or toppled vials, taking environmental monitoring samples (settle plates, active air samples, and contact plates), and checking in-process control samples (e.g., manual weight checks). Routine interventions should be performed as described in the production standard operating procedure (SOP) or the batch record or environmental monitoring SOP. Procedures to be followed in the event of machine jams and spills may include partial line clearances, including removal of exposed units.

Nonroutine interventions may include changing the filling nozzles or handling unexpected events, such as breakdown maintenance, line stoppages, machine adjustments, and material transfers. Interventions can also be grouped by access point, and their risk assessed so that worst-case (highest risk) interventions are included in the study.

Lyophilization

EudraLex Annex 1 (2009) [6] states, "The process simulation test should imitate as closely as possible the routine aseptic manufacturing process...." It is unlikely that the exact lyophilization cycle for the product can be replicated during media simulations due to the constraint of maintaining the media to support microbial growth. Deviation from the production cycle must be justified. For example, if the recommended temperature range for media is 5°C to 25°C, the chamber pressure, normally 100 to 200 mbar, should

not be lower than the equilibrium vapor pressure of the media at the loading temperature to avoid boiling away the media and to avoid overconcentration of media, which could adversely affect the recovery and growth of microorganisms.

The chamber dwell time during APS does not impact risk because the higher chamber pressure required to avoid boiling of media does not require the use of a pressure control (gas injection) system. In the absence of airflow transport mechanism and turbulence, the chamber dwell time becomes immaterial during APS. Based on risk analysis, the aeration or vacuum-break step in the lyophilization cycle may have higher risk of contamination because it involves air turbulence [18] and the possibility of entrained particles entering the containers. Because the application of full vacuum is not possible during APS, multiple partial vacuum steps should be considered to simulate the worst-case aeration. The media volume in the vials before lyophilization must ensure the wetted surface of the container mimics the production case.

Media simulation of the lyophilization step could involve loading the required number of media-filled vials as per the routine commercial production procedures, while assuring the time that the door is open to the cleanroom environment is at least as long as the maximum time incurred when loading a commercial batch of product.

Once the modified media lyophilization cycle has been completed, the chamber vacuum should be broken using sterile-filtered compressed air so that all units are stoppered under pressure to avoid inhibiting microbial recovery and growth. (Sterile-filtered nitrogen gas should not be used to break the vacuum unless a specific anaerobic media simulation is undertaken.)

MICROBIOLOGICAL GROWTH MEDIUM

Media for microbiological recovery and growth are defined in pharmacopoeia—such as the United States (USP), European (Ph. Eur.), Chinese (ChP), and Japanese (JP) Pharmacopoeia—and should be made and sterilized according to the manufacturer's instructions. The media used in APS for filling sterile, depyrogenated containers is generally tryptone soya broth (TSB), or soybean casein digest medium (SCM), which supports recovery and growth of viable aerobic microorganisms. Anaerobic growth medium such as fluid thioglycolate medium (FTM), which supports recovery and growth of obligate or facultative anaerobic bacteria, may be considered under special circumstances (e.g., where the product solution is to be filled into nitrogen-flushed vials).

The growth medium, supplied as a dry powder, is a critical material for APS. It is recommended that the manufacturer is qualified and monitored as an approved supplier; a growth promotion certificate may be obtained with every batch. Prior to release for use, batches of the media to be used for APS should be reconstituted and sterilized; then samples should be subjected to quality control testing for growth promotion by inoculating with ≤ 100 colony-forming units of representative compendial strains of microorganisms. Microorganism strains from environmental monitoring may be included in the growth promotion test.

Unit Handling, Incubation, and Inspection

After filling, stoppering, and sealing, 100% visual inspection is performed for defects such as the presence of visible foreign matter, high or low fill volumes, and damaged vials, stoppers, or seals. Such defective units would be normally removed (rejected) from product batches, but in the case of APS batches, such defective integral units must be retained and all such containers must be incubated. If filled containers are broken or otherwise damaged so that they are nonintegral and potentially contaminated, they must be recorded and reconciled with the batch record quantities. All appropriate media fill container units must be incubated.

The incubation conditions selected are optimal for recovery and to allow for detection of both slow-growing and normal contaminating organisms, i.e., adequate to detect microorganisms that might otherwise be difficult to culture. The incubation conditions used generally are 20°C to 25°C for seven days (lower temperature first) followed by 30°C to 35°C for a further seven days.

Containers are typically incubated on their sides, and while subjected to each incubation temperature, turned at least once to ensure that the entire interior surfaces of the vials and the stoppers are contacted by the growth medium.

Records (chart printouts or electronic records) of the incubation conditions must be maintained, including the date and time of incubation commencement, turning of vials, transfer to the second incubator, and further turning and completion of incubation. Incubated vials must be inspected by operators qualified to distinguish sterile vials ("no growth") from vials showing microbial growth (surface pellicle or turbidity in the solution). A small number of sterile ("no growth") vials should be selected from the incubated vials for use as after-test growth controls; these vials are then inoculated with ≤ 100 colony-forming units of the compendial microorganism strains mentioned previously, and incubated, followed by inspection for positive microbial growth.

Environmental Monitoring

During APS, all routine and normal processes (such as cleaning, disinfection, and maintenance) should be continued to maintain the cleanroom environment in qualified status. This includes particulate and microbiological environmental monitoring, which can demonstrate that the specified cleanroom environment conditions are maintained. These monitoring results may provide key information for the investigation of a failed media run.

Particulate monitoring during aseptic product filling and APS consists of continuous monitoring for particulates in the < 0.5 μm and < 5.0 μm ranges, using a particle sampler attached to an isokinetic probe located near to the point of fill in the Grade A area. A permanent record of the particle counter's printout (or certified true copy if the printout is on thermal paper) must be attached to the batch record for the product fill or APS batch. The regulatory/action limits for the monitoring, per m^3 air volume, are not more than 3,520 particles in the < 0.5 μm particle size range and not more than 20 particles in the < 5.0 μm range.

The microbiological methods used should be described in an SOP, including a map of the locations at which the samples are to be taken or plates exposed. Each batch of environmental sampling plates must be tested for sterility and growth promotion capability against the recommended compendial strains of microorganisms before release for use.

The methods used for environmental monitoring are stated in China GMP [3] and EudraLex, current Annex 1 [6]: active air sampling (1 m^3 sample volume) onto 90 mm agar plates; settling plates 90 mm in diameter, with exposure up to 4 hours (if the APS or production filling lasts longer, new settling plates must be exposed for each subsequent 4-hour period); surface contact plates 55 mm in diameter (in which the plates are contacted against machine surfaces or cleanroom walls, floors, or operator gowns); gloved-finger samples performed by cleanroom operators during the filling period and upon leaving the cleanroom, taken by contacting four fingers and thumb onto the surface of a 90 mm tryptone soya agar (TSA) settle plate.

Media is usually TSA for viable aerobes or sabaroud dextrose agar (SDA) for fungi (molds) and yeasts. Surface contact plates may be TSA, usually incorporating a neutralizing agent to counter detergent residues from the sampled surfaces. Agar residues are removed from the sampling locations by wiping with 70% alcohol.

The expected (regulatory) action limits for the microbiological monitoring results of the Grade A cleanroom areas (Grade A LAF in Grade B background; RABS; isolator), including during APS, in colony-forming units are tabulated in China GMP [3] and EudraLex, current Annex 1 [6]. Adjacent Grade B, C, or D cleanrooms through which operator gowning and material transfer for the APS occur should also be monitored; the stated regulatory (action) limits for these cleanroom grades are also included in the China GMP [3] and EudraLex, current Annex 1 [6]. The frequency of monitoring Grade C and D cleanrooms is to be determined based on quality risk assessment because such monitoring at the time of an APS may help investigate any discrepancy or failure.

Records and Microorganism Identification

In APS batches, the numbers of colony-forming units recorded on the environmental monitoring plates in Grade A (LAF, RABS, or isolator) and Grade B areas should be recorded. An isolate should be taken from each visually distinct microbial colony and identified by species using available biochemical and/or nucleic acid identification methods so it can be compared with organisms in contaminated units that arise during the APS. This information will be critical in investigating and determining corrective actions in the event of an APS media fill that exceeds acceptance criteria. Environmental samples (those with colonies) from Grade C and D cleanrooms should be enumerated and preferably also identified, as the information regarding the numbers, species, and locations of contaminating microorganisms may prove crucial in the investigation and resolution of a failed media fill.

APS consists of three consecutive media simulations with designated personnel in the specific cleanroom environment, followed by repeat media simulations at six monthly intervals.

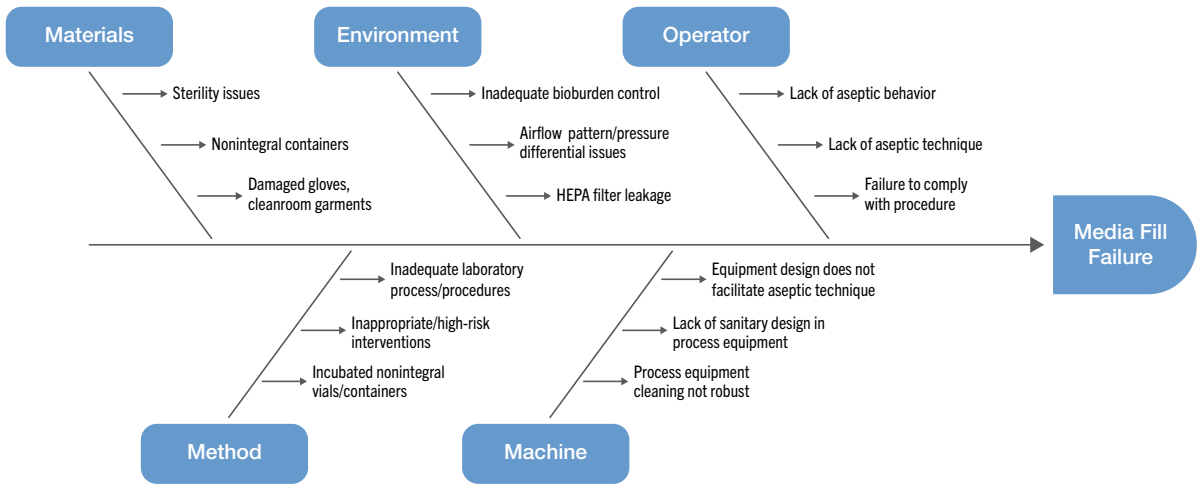
Operator Training and Qualification

Prior to APS batch manufacture, operators performing APS must be trained in relevant procedures, including cleanroom gowning, aseptic connections, and correct cleanroom behavior, as well as in product-specific manufacturing procedures. All staff qualified to work in the area, including maintenance personnel, need to be included in APS.

Relevant training points:

- Sterile materials and equipment should be handled only with sterile instruments, such as forceps. Between uses, instruments should be protected from contamination.
- After initial gowning, sterile gloves should be regularly sanitized by spraying with a qualified sanitizing agent such as sterile 70% isopropyl alcohol (IPA) to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, components, or critical surfaces.
- Rapid movements create turbulence in the critical environment, disturbing LAF and the integrity of sterile environments, and entraining particles. Operator movements should be slow and deliberate.
- Aseptic operators should not disrupt LAF designed to protect critical surfaces. When performing aseptic manipulations (such as making aseptic connections, removing samples, or retrieving fallen or jammed components from a filling line), operators should be trained to approach the location slowly and deliberately from the side whenever possible.
- After initial theoretical training, aseptic training operators should be allowed to practice their movements in a mock-up or nonsterile practice environment before being permitted to participate in operations in the cleanroom environment.

Figure 2: Media fill failure root cause investigation and identification using an Ishikawa diagram.



MEDIA FILL FAILURES AND ROOT CAUSE DETERMINATION

A key step in the investigation is identifying microorganism(s) species in positive media vials and any colonies appearing on environmental monitoring plates, particularly those from the Grade A/B environments, including from RABS/isolator monitoring. Identification of species from colonies on plates exposed in the lower-grade adjacent cleanrooms, through which materials or personnel have accessed the filling rooms, may also be crucial.

The review of the deviation should encompass the preparation and manufacturing processes—including cleanroom cleaning and disinfection, components and materials sanitization/sterilization and transfer processes, HVAC and cleanroom operating parameters during the filling period, filtration process and integrity tests, filling operation, stoppering and capping equipment, and taking and transferring in-process or environmental samples. The review should focus on documentation, including any deviations or atypical events, but may also include a review of CCTV records of the filling rooms and operations and documented interviews with operators. Review should also include recent engineering work or prior media fill batches.

An Ishikawa diagram showing cause-and-effect links to a specific failure is a useful tool that can be used to investigate and identify the root cause of a media fill failure (see Figure 2).

Based on the potential root cause interactions identified in Figure 2, investigating the possible failure modes and corresponding risk mitigation measures will be necessary (Table 1).

In the investigation, different possibilities may provide the evidence to support root cause determination, such as the ability to match the identification of an environmental isolate from the current (or recent) batch with the identity of the contaminating organism in the failed media units, or a significant processing discrepancy or error or equipment failure.

Case Study

In a sterile injectables manufacturing plant, a routine media fill showed growth in one vial. The microorganism was a micrococcus, typically associated with human skin, attributed to an engineering intervention using an unsterilized tool and not reflective of normal practice. A repeat media fill was done, which also showed growth in one vial with no obvious root cause. Manufacturing of product was put on hold. Following an investigation, it was noted that the APS included approximately 80 interventions to simulate any possible activities that might be required in normal production. However, in normal production, far fewer (< 20) interventions occur routinely. Therefore, it was concluded that the process may have been excessively stressed and was not representative of the commercial process being simulated. Three further media fills were initiated, of which the first media fill showed growth in one vial.

The investigation using RNA ribotyping identified that the microorganism in all three media fills showing growth was the same—a *micrococcus*. Microbial testing showed that one operator tended to shed greater numbers of skin particles than other operators, including this microorganism. The investigation also identified variability in how materials were passed into the sterile core, potentially providing a route of ingress.

A risk assessment was carried out to determine any safety issues arising from the sporadic low-level contamination in the process. It was concluded that based on the nature of the microorganism, the sterility assurance levels achieved by the process, and

Table 1: Potential causes of media fill failures.

	Description	Possible Failure Mode	Risk Mitigation
Operator	Aseptic behavior	• Excessive and unnecessary touching of surfaces • Talking unnecessarily in critical areas	• Periodic aseptic behavior and aseptic technique training • Periodic audit on aseptic behavior and technique
	Aseptic technique	• Inadequate sanitization of gloved hands/surfaces after high-risk activities • Rapid movement in critical areas • Activities that may compromise sterility, such as actions above sterile open vials/containers	
	Compliance to procedure	Tasks not performed according to procedure	Periodic audit to ensure strict adherence to procedure
Machine	Equipment design	Equipment design not facilitating aseptic interventions, and increased risk of contamination during intervention	Design qualification; modifications may be required to mitigate the risk
	Sanitary design	Inadequate sanitary design in process equipment leading to cleanability issues	
	Process equipment cleaning	Process equipment cleaning procedure not robust	Design a robust cleaning procedure considering the type of soil, cleaning parameters, and the use of appropriate cleaning detergent, if required
		Reduced cleanability of stainless-steel surfaces due to corrosion, which could lead to formation of biofilm	Periodic maintenance of stainless-steel surfaces to minimize risk of corrosion
Environment	Bioburden control	Inadequate cleaning and disinfection program for cleanroom surfaces	Design a robust cleaning and disinfection program using sanitizers, disinfectants, and sporicides
	Airflow pattern/pressure differential	• Inappropriate airflow pattern in critical area • Differential pressure excursions in critical room/area	• Remediate airflow pattern to minimize risk of contamination to products • Ensure interlocking of doors
	Leakage	Leakage in HEPA filter	Periodic maintenance and leak tests
Method	Laboratory process/procedures	Laboratory process/procedures inadequate	Review and remediate laboratory procedures to minimize errors
	Inappropriate/high-risk interventions	High-risk interventions disrupt unidirectional (laminar) airflow, and thus increase the risk of contamination	Smoke studies to be conducted and evaluated for risk of contamination (turbulence) for each intervention
	Incubated nonintegral vials/containers	Failure to spot nonintegral vials/containers	Training of inspectors on nonintegral vials/containers
Material	Sterility issues	Parts/packaging components not sterile due to sterilization process issues	Verify sterilization processes meet acceptance criteria and assess impact of any excursions
		Sterility of parts/packaging components compromised after sterilization, prior to usage	Ensure sterile parts/packaging components are protected from contamination through the use of appropriate protective barrier
	Nonintegral containers	Nonintegral vials/containers not segregated	Training on inspection of nonintegral vials/containers prior to incubation
	Damaged gloves, cleanroom garments	Damaged gowns and gloves can increase risk of contamination	Confirm the integrity of the gowns and gloves visually

the regulatory guidelines, the safety risk was low. However, it was now obvious that the process was not operating in a validated state. No further batches of the product were manufactured until the process was shown to be in a validated state, as evidenced by three successful media fills. Members of a sterility assurance expert group from the wider company assisted during the investigation. The plant ensured that the necessary remediations identified during the investigation—reallocation to other duties of the "shedding" operator and reduction in number of interventions simulated per media fill (the interventions were divided into three groups, one group to be included in each of three media simulations)—and the potential contributory aseptic practices were revised and operators retrained before conducting three successful media simulations to revalidate the process.

Table 2: Typical media fill regulatory observations.

No.	Area	Observations
1	APS design	Failure to: • Carry out adequate growth promotion testing of media batches • Use correct incubation conditions or duration • Qualify all manufacturing personnel by participating in APS, and subsequently exceeding the maximum number of persons the room is qualified for • Fill and incubate sufficient vials in the APS • Simulate the lyophilization process cycle adequately • Justify the difference between growth media makeup and pharmaceutical solution makeup • Perform smoke studies of interventions to evaluate the effects on unidirectional (laminar) airflow • Include representative process interventions by operators in the filling machine LAF cabinet, RABS or isolator, in the APS runs
2	Operational	Failure to: • Reconcile and incubate *all* integral media-filled vials • Perform media fills after major facility shutdowns that include significant activities that may compromise cleanroom control • Specify procedures that all personnel authorized to enter the aseptic processing rooms during manufacturing should participate in a media fill at least once a year
3	Root cause analysis	Failure to: • Determine the root cause in the investigation of APS batches exceeding the acceptance criteria for contaminated units • Identify contaminating microorganisms to species in contaminated media units • Properly investigate alert or action limit exceedances in environmental monitoring, or identify contaminating microorganisms to species (such that they can be related to microorganisms found in contaminated APS vials) • Conduct thorough investigation on the cause of contaminated APS prior to repeating APS runs
4	Personnel	Poor aseptic technique and practices: • Failure to sanitize gloved hands after touching nonsterile surfaces • Rapid movements in critical areas where the product is exposed to the environment • Removing a jammed stopper by reaching over exposed sterile stoppers in the stopper bowl • Inadequate training of media vial inspectors to examine media-filled units following incubation

Potential GMP Discrepancies During Media Simulations

Given the enhanced frequency of regulatory inspections in companies where aseptic manufacturing is used and the growth of monoclonal antibody and other biological products requiring aseptic filling, there are many examples of GMP failures and APS issues. Some typical examples that have appeared in warning letters and summaries by regulators are provided in Table 2.

CONCLUSION

APS with microbial growth media is an integral part of an aseptic manufacturing operation. The design of the APS must take into consideration various operating parameters to avert a worst-case scenario for the media fill challenge. Such parameters can be determined by risk assessment, and typically include the container-closure configuration, batch size, operating conditions, and interventions. The risks involved with individual interventions need to be identified, assessed, and mitigated to minimize contamination risk. Equally important is a team of highly trained and competent operators that have knowledge of microbiology and aseptic technique and practices; a sound and effective cleaning and disinfection program for cleanrooms; regular equipment cleaning and maintenance; and cleaning and sterilization processes. Attention to such considerations ensures a robust and successful APS program.

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LESSONS LEARNED in Global CQV

By Gráinne Ryan and Paul Ryan

Global commissioning, qualification, and validation (CQV) project delivery has in recent years been required to push the boundaries on delivery methodologies and techniques to ensure sufficient production capacity is available to meet ever-expanding patient needs. This article focuses on lessons captured in the execution and resource management of large-scale global CQV projects in an environment of change and compressed project timelines.

Recent years have witnessed increased challenges from global pharmaceutical manufacturers to reduce the standard timelines for the completion of major capital development programs [1]. The initial challenges were driven by a need to meet increasing patient demands, with timelines subsequently accelerated even further in the global response to the COVID-19 pandemic.

In response to these challenges, well-established and long-used CQV methodologies and management practices were reevaluated to determine how project scope could be adjusted to not only meet pharmaceutical regulations and industry standards, but to do so in highly compressed timelines. Established ideologies were challenged and new ways of working were championed to ensure client facilities delivered on schedule.

Additionally, as the number and scale of major CQV projects being executed in parallel increase globally, resource recruitment, onboarding, and retention are becoming ever more important for the successful completion of projects. Companies must be able to not only source and rapidly mobilize experienced teams, but also ensure that key personnel are retained for the full duration of projects.

This article focuses on selected lessons captured during the execution of large-scale global CQV projects. Areas of focus include CQV delivery methodologies, including the one-test approach and implementation of an electronic evaluation platform (EVal); use of virtual factory acceptance tests (FATs); and enhanced/improved CQV project resource management, including recruitment, retention, and onboarding using a competency assessment and tracking tool (CATT). The projects on which these lessons were captured were delivered while maintaining the highest possible pharmaceutical standards to achieve and exceed regulatory requirements.

CQV DELIVERY METHODOLOGIES

Project delivery schedules for a "qualified" plant have received significant focus in recent years in an effort to reduce overall project timelines. These efforts have escalated even further in response to the pandemic, with the need to produce hundreds of millions of vaccine doses in an expedited timeline [2].

This reality has pushed the pharmaceutical industry to reassess standard practices and project delivery methodologies that have been used for years [1]. Accelerated project timelines have pushed the boundaries and, some might say, helped the development of new project delivery approaches.

Identifying and eliminating non-value-adding, or wasteful, activities in the preparation and execution of CQV tasks has been a primary focus. Recognizing potentially wasteful activities can be a challenge, as the pharmaceutical industry is rooted in predefined and agreed-upon methods of working that are informed by compliance and regulatory guidance. The implementation of a one-test approach and the introduction of EVal platforms were identified in conjunction with client project execution resources in discussion at the outset of projects as two potential enablers for a reduction in non-value-adding activities.

One-Test Approach

The one-test approach aims to ensure that each test is executed only once and is not repeated in subsequent CQV phases. It attempts to maximize the value of all tests conducted across each project phase. The challenge is embedding the one-test approach at the start of the project, which would ensure that all requirements are identified in the user requirements and are then cascaded through the design, procurement FAT, and on-site testing phases. To successfully implement the one-test approach, all project personnel who support the design and FAT phases must be suitably trained to ensure that the output from the FAT can be used to support subsequent phases.

For equipment packages, the one-test approach seeks to complete as much testing as possible offsite in the FAT phase. This leads to a reduction in the level of on-site testing and thus

the potential for repeat testing. Repeat on-site testing is a consistent source of adverse cost and schedule impacts on CQV projects of all sizes. The one-test approach also ensures that the equipment is shipped only after robust testing and that confidence is established that the equipment is functioning as per design and user requirements before it leaves the vendor facility.

Lessons learned from implementing the one-test approach:

- Embed the approach at project kickoff, before detailed design or vendor discussions.
- Establish vendor capabilities prior to any purchase order placement either through a preinquiry assessment process or by performing a quality audit during the package inquiry stage.
- Detail, track, and document the required training for FAT execution personnel to avoid the risk that the FAT testing may not be considered acceptable to support subsequent phases.
- Do *not* modify design or equipment after completion of the FAT phase. There should be no further design development or equipment modification other than the close out of the agreed-upon FAT punch list.

EVal Platform Implementation

EVal is a digital platform that enables the electronic generation and execution of CQV activities. It is generally used for life-cycle or good manufacturing practice (GMP)-critical documents such as strategy, traceability, and protocols. Templates are drafted, reviewed, and approved within the platform. It also enables full electronic execution. EVal can also be used for non-life-cycle documents, but this will require the team to extend platform access outside the direct project/CQV team to equipment vendors. Some pharmaceutical companies are already extending this access to support a full electronic delivery target to address commonly repeated wastes across the CQV project life cycle.

The implementation and use of EVal can significantly help improve CQV timelines and eliminate waste throughout the documentation preparation and execution phases, but they require a cultural change within organizations to support right first-time delivery. Value is extracted by implementing the appropriate digital technologies throughout the project life cycle to maintain the flow of data, documents, and models to support CQV requirements. The use of digital technologies for CQV is still in relative infancy, in part due to lack of platforms suitably compliant with 21 CFR 11. This is starting to change. Other strategies in use include the partial adoption of some elements of EV such as use of site/company documentation management systems for pre- and postexecution approval of protocols, use of databases to gather equipment, instrumentation and other information during design and construction stages, and subsequently transfer to a site master database. Content of the databases would be verified during CQ activities either at the FAT in the vendor facility or on site during the initial start-up and commissioning stages.

CQV documentation preparation

Document preparation is labor intensive, with documentation preparation waste repeatedly contributing to higher-than-anticipated CQV labor costs. Examples of this type of waste include inconsistent approaches to document formats, inconsistent documentation quality, and poor management of information repeated across multiple documents.

EVal platforms work to address these quality issues in a number of ways, providing for a centralized control of templates throughout the project life cycle and automatically generating protocols and complete systems test packs. Digital implementation also provides for the seamless transfer of design data from the digital design platform to the EVal platform. This reduces the time wasted in the population of data in CQV protocols. It also assists in data accuracy and can eliminate time spent in quality control checking.

CQV protocol execution

CQV execution schedules frequently have multiple critical paths, and a delay in one path potentially impacts multiple other paths. Electronic execution can help reduce project schedule risk by decreasing the potential for execution completion errors, providing real-time progress completion tracking, and offering a platform for rapid deviation assessment and resolution. Using preapproved protocols, electronic execution is enabled via the use of digital handsets, which can be used in the field to support paperless execution and recording.

Implementing digital delivery structures such as EVal requires careful planning to ensure that all parties are aligned on the deliverables, are suitably trained, and have the correct access to the digital platform. EVal can be scaled according to project size and the appetite for its usage, which will be determined by the project team as part of the overall project delivery strategy. Considerations such as the size of the project, schedule demands, cost of implementation, and training requirements must be reviewed to determine the scope of EVal implementation. The overall EVal strategy will be documented as part of the project and CQV strategy.

Important lessons gathered around the use of digital platforms in support of CQV delivery to date:

- Select the platform as early as possible.
- Get buy-in on the project templates up front and then build on the electronic platform.
- Determine the full extent of digital implementation (for example, will all CQV documents be generated or just the project life-cycle document?).
- Determine the level of access to the digital platform (will the platform be solely for CQV team use to generate and execute protocols, or will other project partners such as equipment vendors be provided with access to upload and execute their documentation, such as FATs and site acceptance tests?).

VIRTUAL FATS

The onset of the COVID-19 pandemic in early 2020 impacted major pharmaceutical investment projects worldwide. One of the most

significant impediments to project completion was the prevention of process equipment deliveries due to the inability of project teams to attend FATs at vendor facilities [3].

Traditionally, significant numbers of core engineering design team representatives and client end user personnel traveled to vendor facilities worldwide to inspect equipment and witness test protocol execution as part of FATs. In the pandemic, innovative solutions were required to facilitate FAT testing and ensure the release of equipment for delivery to site. Virtual FATs were conceived as a format where the vendor would execute the FAT at their facility while being observed virtually by core engineering design team representatives and client end user personnel.

When virtual FATs were introduced, there were a number of initial obstacles. Foremost among those obstacles was the need for an industry mindset change, which required engineering firms, clients, and vendors to agree that new ways of working for FATs were possible, that the new ways of working could be implemented quickly, and most important, that these ways met the requirements of all parties.

Another significant challenge was identifying suitable technology, equipment, and applications to facilitate the execution of virtual testing to a level that would meet the requirements of all FAT stakeholders. The required technology needed to facilitate both desk activities (such as reviewing vendor documentation) and field activities (such as piping and instrumentation diagram [P&ID] walkdowns and witnessing live testing). Additionally, vendor facilities needed to have sufficient wifi connectivity, particularly on the factory floor, to ensure good quality, uninterrupted streaming of test execution.

Once these initial connection challenges were overcome, practical structures had to be developed to ensure that the FATs could be run efficiently. Project-specific procedures for FAT testing had to be updated to detail the additional requirements introduced by virtual testing. Training was completed on the updated procedures by all parties involved in the FAT, including vendor resources. Microschedules were developed by the FAT lead for all testing, structured around half-day blocks, which ensured each team member knew when they needed to be available to attend test execution.

Where necessary, vendors' capabilities had to be upgraded to support the virtual FAT concept by investing in technology upgrades (hardware and software) in workplaces and by ensuring staff were trained to meet the requirements for virtual FAT execution. Additionally, the approval of the use of electronic signatures (e-signatures) was a key enabler for recording virtual testing.

The initial FATs took place at a steady, controlled pace as all parties came up to speed on the processes. Several important lessons were identified during these initial FATs. First, it was key to designate the FAT lead as the single point of contact for all requests—design changes, additional testing—as this ensured that the vendor's focus remained on executing the FAT and not on addressing questions from multiple different team members. Meeting ground rules ensured etiquette was maintained, particularly where multiple attendees were observing the same sequence of testing. The need to allow adequate time in the daily schedule for the vendor to get set up and address issues was also identified.

When the lessons captured on the initial FATs were implemented, subsequent FATs ran much smoother. The technology was proven to work, quality was not compromised, and the benefits of virtual FATs became evident to all involved. Implementing virtual FATs was also found to be an enabler for the execution of concurrent FATs in multiple locations. Before COVID-19, the availability of specialist resources (e.g., quality assurance, electrical, and instrumentation) would have prevented simultaneous FATs in multiple locations due to the travel time required between locations.

Virtual FAT benefits

The virtual FAT had a number of benefits, one of the most significant of which was safety: Personnel were not required to travel to a vendor facility during the COVID-19 pandemic. Companies also experience a reduction in costs associated with FAT travel and accommodation. The reduced travel also led to carbon dioxide reduction. On one major capital project in 2021, an estimated 250 metric tons of carbon dioxide was offset by reduced FAT travel.

Virtual FATs also showed an increase in quality and productivity. Several FATs were attended on the same day in different locations. Virtual FATs provide for the right people being available at the right time. FATs were recorded with all-party agreement. Teams were focused on what was on the monitor.

Although virtual FATs have facilitated a new way of working on capital projects, they have not fully removed the need for the core engineering design team to attend vendor facilities. Engineering design team representatives are still advised to regularly visit vendor sites pre-FAT to ensure the vendor is on target for FAT. Additionally, there should be a provision for core engineering design team representation at the FAT itself. This core engineering design team will support coordination at the vendor facility, witness specific testing (such as vessel drainability and pump range), and assist with the setup and operation of the audio-visual equipment required for the FAT to run successfully.

CQV PROJECT RESOURCING

Resourcing has taken on a new significance in an environment of increasingly compressed project schedules and newly emerging execution approaches, such as those discussed previously. The recruitment, retention, and onboarding of resources are key activities in support of successful CQV project delivery.

Personnel Recruitment and Retention

There are four elements that have been found to significantly contribute to a successful recruitment and retention program for CQV projects: a dedicated global CQV resourcing manager, an in-house talent acquisition team, referral rewards, and reward and recognition programs.

Dedicated global CQV resourcing manager

A coordinated, centralized approach to personnel management is crucial where companies are executing multiple major CQV projects in parallel for different clients. Having a designated global CQV resourcing manager has been found to provide a coordinated CQV resourcing effort.

One of the resourcing manager's primary goals is to ensure that the needs of all major projects are met equally. Weekly meetings should be held with individual CQV project managers to ensure all resourcing requirements (e.g., number of roles, experience level, need date) are tracked. The information should be collated on a centralized database and used to prioritise project resourcing needs.

The resourcing manager should coordinate daily with the Talent Acquisition (TA) team to review progress on candidate searches, plan candidate interviews, and align on commercial negotiations. Where relevant, the resourcing manager can also communicate across internal company departments to identify resources from other sectors or departments (e.g., design, construction) who are qualified for and interested in a CQV execution role.

Talent retention is a key activity for the CQV resourcing manager. The establishment of a long-term relationship between an employer and a capable CQV resource is beneficial to both parties. The CQV resource is provided with long-term continuity of employment, and the employer can plan across multiple projects and mitigate against the risk of personnel leaving a project before completion. Building the long-term relationship requires regular contact between the CQV resourcing manager and individual CQV resources, particularly in the last four to six months of a project, when resources are naturally beginning to consider the next steps in their career paths.

Talent acquisition team

An experienced in-house CQV talent acquisition (TA) team will play a key role in identifying and bringing suitable candidates through the recruitment process. The dedicated TA team will support candidate recruitment by working with the CQV resourcing manager to (a) ensure the resourcing effort remains continually focused on the prioritized open roles as identified in the resourcing database, and (b) identify opportunities for talent sourcing such as global projects nearing completion and recruitment platforms search profiles.

Beyond actively supporting resourcing, the TA team will positively represent the company and client projects to candidates throughout the recruitment progress, develop multimedia content for use on company media platforms and external recruitment, and maintain roles on the company career portal and recruitment websites.

Referral rewards

Referral rewards allow employers the opportunity to use the contact networks of their employees to source new talent to join their organizations. Experienced CQV team members are often the best recruiters, as they have built up a network of similarly knowledgeable contacts and will be driven to refer suitable candidates by the desire to be part of the strongest possible CQV team. Companies need to ensure that the terms of the referral rewards are sufficiently generous to make it worthwhile for existing team members to recommend candidates, with minimal administration requirements for employees to obtain their reward when a recommended candidate is hired.

> The recruitment, retention, and onboarding of resources are key activities in support of successful CQV project delivery.

Reward and recognition programs

Reward and recognition programs provide a platform to support project safety, quality, and schedule objectives while also supporting personnel retention. The majority of major capital projects in the pharmaceutical industry now have safety recognition initiatives in which the performance of individuals or companies is audited on an ongoing basis, with weekly and monthly rewards for excellence.

Companies are also implementing programs where individual team members are rewarded for the overall project safety performance, project quality (right first-time execution), and long-term commitment to the project. Retention bonuses pay team members a lump sum at project end if they remain until completion. The lump sum must be large enough to entice an individual to stay on until the end of their contract. Such programs also assist with the long-term retention of key personnel.

Resource Onboarding

Once hired, CQV resources need to be appropriately mobilized and onboarded on site in a timely fashion, without impacting existing project progress. Effective onboarding of new resources is challenging in any work environment, and especially so in live CQV environments.

New project resources need to be brought up to speed on all applicable aspects of the project (plant layout, P&IDs, automation interfaces, safety procedures, ways of working) as quickly as

New project resources need to be brought up to speed on all applicable aspects of the project as quickly as possible while ensuring ongoing CQV activities are not adversely impacted.

possible while ensuring ongoing CQV activities are not adversely impacted. Upon completing the onboarding process, CQV execution resources should be sufficiently competent to execute live commissioning activities in the field, either on their own or in teams with minimal direction and supervision.

Standard onboarding structures are normally designed to handle a small number of new hires (one to three resources) per month on a project. When onboarding numbers increase in excess of five resources per month, onboarding programs stop functioning efficiently, resulting in delays in new hires becoming effective additions to the existing team.

Onboarding case study

The challenge of onboarding a larger number of resources presented itself on a major capital CQV project in 2020, which required over 20 CQV execution resources to be onboarded onto a schedule-critical project within a three-month period while ensuring (a) the safety of both new and existing personnel was not impacted, (b) new hire onboarding was completed as per in-house project and client site procedures, and (c) planned project execution progress in the three-month period was not impacted.

Utilizing experienced team members to mentor new hires on field execution activities during their initial six weeks on site was a key part of the existing onboarding process and needed to be retained. The increased number of new hires to be mentored required the workload of experienced team members to be balanced between achieving planned project execution progress and supporting the mentoring process.

While training on the CQV procedures (documentation, classroom lock out/tag out [LOTO] training) was possible for the new hires within the required six-week timeframe, successful completion of field training in this period was a major coordination issue for existing team members.

A competency assessment and tracking tool (CATT) was developed to plan, coordinate, track, and record all aspects of the onboarding program of all new hires while maintaining project safety, quality and schedule targets.

CATT

The CATT compiled the details of all hiring and training into a single database. Each new hire was assigned their own tab in the database dedicated to recording their training progress. Template pages were developed that captured the specific CQV area training programs (upstream, downstream, CIP) with the new hire assigned to the training program for their CQV work area. The page also contained the assigned mentor, duration of mentor period, and a list of the activities the new hire could and could not carry out during their initial mentoring period. Confirming what tasks new hires were not to complete was regarded as a key safety benefit of the CATT implementation.

The CATT database was managed by a CQV project engineer responsible for all aspects of the database, including coordinating with new hires, managing day-to-day issues with the training programs, and ensuring regular updates were provided to all stakeholders. One of the primary responsibilities of the CQV project engineer was to hold weekly meetings with CQV management representatives (project, technical, and safety) to ensure proactive management of the training progress of each new hire.

In advance of the weekly meetings, the project engineer updated the individual pages of the CATT database with training progress information gathered from the assigned mentors and CQV area leads. The meeting provided for additional training supports to be put in place if deemed necessary based on constructive feedback or allowed for the acceleration of the initial mentoring period based on suitable positive feedback. The weekly meeting also allowed for regular review of mentor workloads to ensure a balance was being maintained between mentoring and execution tasks.

When new hires were deemed to have successfully completed the initial mentoring phase, the CATT was signed off by the CQV manager and the relevant CQV area lead. A "close out" section confirmed the specific tasks the new hire was deemed competent to perform. Where relevant, it recorded any remaining specialist training that the new hire may yet have to complete (such as vessel entry).

The initial implementation of the CATT provided some key early lessons, which were subsequently incorporated into the program.

- Early engagement and alignment on the information in the CATT: Ensure the new hire, their assigned mentor, and the area CQV lead meet to review the CATT and align on the content at the outset of onboarding.
- Mentor selection: Mentor suitability can be influenced by many factors, such as mentor workload, new hire experience, and any previous time spent working together.
- Regular communication on progress during the mentoring phase: Feedback to the new hire from management is key, especially in cases where resources are struggling to meet the

initial assessment progress expectations. This feedback should include the development of an agreed-upon support plan.

- Implementation of tools such as the CATT: Use of a CATT can assist in rapidly deploying competent resources to meet peak loading demand in fast-track project timelines while maintaining safe working environments.

CONCLUSION

The timelines required to deliver projects to meet patient needs will continue to challenge the CQV sector. The execution of CQV practices will continue to need reassessment to identify more efficient ways of working. The lessons outlined in this article represent a small cross-section of steps taken on recent large-scale capital projects in support of accelerated timelines. The new ways of working identified here must be embraced and implemented in a structured, regulatory-compliant manner to fully realize the benefits for project execution and, ultimately the benefits for the patient.

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