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May-June 2021 | Volume 41, Number 3

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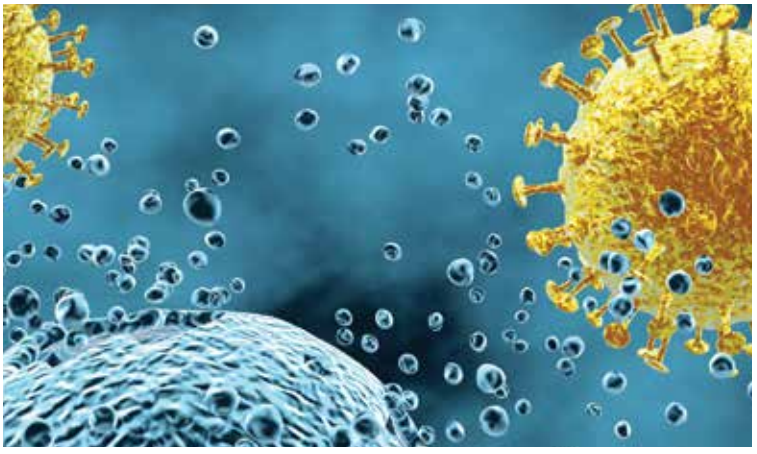

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By Joanne R. Barrick, RPh


Joanne R. Barrick, RPh

Signs of the Times

I used to think "home detention" was no punishment at all, but this last year has dramatically changed my thinking. Despite working from home for over a year, my house is a wreck! Like many of you, I feel busier than ever, despite not traveling and not driving to and from work. Disruption used to be rare and now it is common: having to adapt to new ways of doing most everything, like buying groceries, seeing a doctor, collaborating on work projects, teaching classes, and socializing.

Data accuracy and security are two areas impacted by the disruptions we are experiencing. Recently, I received three personal data breach security alerts in one day. I receive numerous phone calls telling me I owe money to the IRS, that my loan has been approved, there is suspicious activity on my credit cards, and even an email telling me $5,000 gaming systems have been purchased through my Amazon account. These events reinforce the importance of two of the many facets of our ISPE GAMP® initiatives.

CELEBRATING GAMP

We are proud that the ISPE GAMP Community of Practice (CoP) celebrates its 30th anniversary this year. The CoP now has 4,626 members, making it the third largest ISPE CoP. Throughout its 30 years, GAMP has strived to disseminate knowledge and guidance that supports a pragmatic, patient-centric approach to computerized system quality. GAMP has significantly benefited industry by driving a risk-based response to quality and regulatory requirements. The GAMP CoP has global representation from all corners of Europe to North America, Brazil, Japan, India, Asia Pacific, and most recently, Turkey.

GAMP has a philosophy of enabling innovation by adopting modern practices and advanced automation and applying critical thinking that in turn enhances operational performance and quality throughout the product life cycle. Through an extensive range of Special Interest Groups (SIGs), GAMP is currently addressing the use of Agile development frameworks, artificial intelligence, alignment with the US FDA CDRH Case for Quality, blockchain use cases, data integrity, and many other exciting avenues that will benefit the global life sciences sector.

We make decisions impacting patients every day based on data, and if the data isn't accurate, neither are our decisions. GAMP publishes invaluable guidances, and GAMP-based training classes continue to be some of ISPE's most popular offerings. My sincere appreciation and congratulations go to Heather Watson, GSK, Global Chair of the CoP, and the entire GAMP Steering Committee and organization for continually outstanding work over 30 years.

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COLLABORATION CONTINUES

Another sign of the times is that we continue to see unprecedented collaboration in the pharma industry between companies, regulators, academics, and supply chain. I recently saw an announcement from two companies that are combining their independently developed monoclonal antibodies (mAbs) into one product in an effort to provide a more effective treatment for COVID-19 and combat virus variants. I am so inspired and proud of the way our industry has quickly worked together toward ending the threat posed by this terrible disease.

Effective collaboration is also exhibited by our ISPE Chapters and Affiliates. In recent Regional Council meetings, I was amazed at the level of openness in sharing lessons learned, topics of interest, and invitations to attend each other's events. Here are just a few notable achievements/activities:

- Offerings for students and Emerging Leaders, such as hackathons, are expanding at several Chapters and Affiliates. This is a great step toward attracting young and diverse talent to our industry at a time when public awareness of the value of our industry may be at an all-time high.
- Our France Affiliate has held an event focused on distance assessment and several GAMP workshops.
- Our new Eurasia Affiliate recently held an event with over 1,000 participants.
- The Asia-Pacific Region (APAC) has established an Action Tracker and collaboration website, demonstrating impressive flexibility and adaptability.
- Many Chapters and Affiliates have their own CoPs and Women in Pharma® (WIP) activities.
- The Japan Affiliate has invited those in APAC to attend the first day of their annual meeting in May, which will be presented in English.
- The Boston Chapter has started a diversity and inclusion initiative.

I'd also like to highlight one of our newest opportunities for collaboration: the Virology SIG. I anticipate there will be very significant interest, and I am looking forward to learning more.

It won't be much longer until we are all out of "home detention," and I look forward to collaborating and celebrating face to face with many of you at future ISPE events. In the meantime, stay safe!

Joanne R. Barrick, RPh, is Advisor, Global Validation, Technical Services/Manufacturing Science, at Eli Lilly and Company, and the 2020–2021 Chair of the ISPE International Board of Directors. She has been an ISPE member since 1998.

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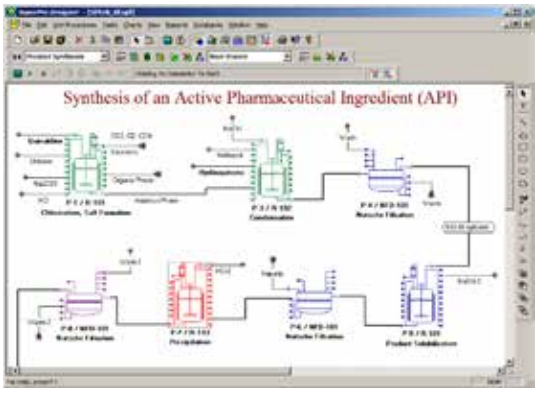

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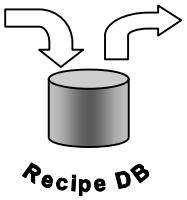

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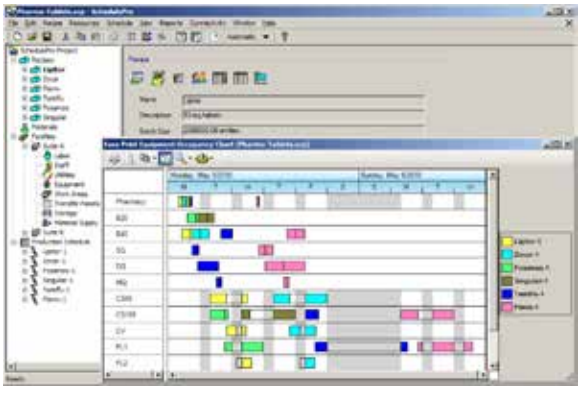

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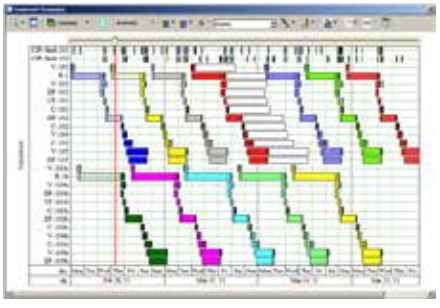

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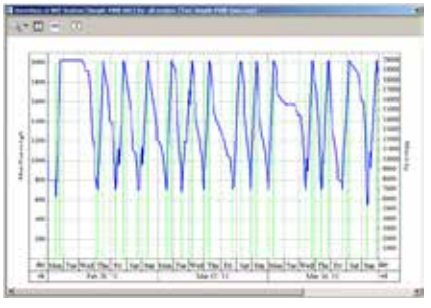

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By Vivianne Arencibia


Vivianne Arencibia

FUELING THE FIRE:
Learning to "Just Speak Up"

This year's Women in Pharma® (WIP) theme of "Fueling the Fire" harnesses the energy and passion that drive women to achieve career advancement, personal growth, and satisfaction. The 3 March webinar focused on the Diversity & Inclusion theme, where we discussed what we as leaders can do to drive greater diversity of thought and minimize the unconscious biases that limit organizations, teams, and individual growth.

Reflecting on my own career, the question was not how one can call out "group think," but rather how to be credibly perceived as providing a viable alternative approach and when/how to speak up when feeling "shut down."

SPEAKING UP

I learned that "just speaking up" effectively required a great deal of preparation and active listening to focus the argument and bring the audience along. As a young leader, I knew I had good points, creative ideas, and a lot of energy to bring forward a different perspective. However, to be able to influence and bring about change, I needed to understand the organizational culture, the history, the interests of my peers, and the drivers that prevented change. I needed to become part of the team and learn to ask questions that would prompt further dialogue. It is a life lesson, which I continue to practice with clients, peers, associates, and mentees.

Webinar participants wanted to know how to let leaders know that they do not allow diverse contributions; how and when it is appropriate to speak up; and how to be viewed as a valued contributor. I offer the following lessons learned.

Understand the perspectives of others, even if you don't agree. Prepare, listen, and don't make assumptions about why something will or will not work. The best solutions usually encompass multiple perspectives and contributions.

Assume good will. Don't assume that you are being blocked because you offer a different perspective. Many biases are unintentional, so simply state that you would like the team to consider another perspective that will build on the discussion or the solution.

Don't give up. You won't always be successful. Your ideas may be further developed to a different outcome. You will be assessed by your ability to contribute collaboratively and respond professionally, even when you disagree. Ask yourself if you can support a decision and not fixate on whether or not the decision or approach is viable because it is different than what you wanted to propose or did propose.

Don't be afraid to ask for feedback or an additional opportunity to be heard. If you feel you were not given an opportunity to contribute, speak to the team leader or manager after the meeting and let them know that you have researched a different perspective and would have liked an opportunity to contribute. This serves to help you understand how you can approach a future engagement, and allows the leader to recognize that he or she plays a role in ensuring that all team contributions are valued and diversity of thought is leveraged for the best outcome.

Treat others as you would like to be treated. As a team member, when you see someone being excluded, speak up and say, that "X has not had a chance to provide input," or "I was speaking to X, and I think she has an interesting perspective." Open the door for others to speak, and support and validate everyone's contribution.

WIP wants to continue to bring these and other discussions forward to help women in our industry work through workplace and personal challenges, whether real or self-imposed, to become our most effective, healthy, and satisfied selves. I invite you to join our community if you have not done so, get involved, and add your "fuel to the fire." Together we can bring change!

Vivianne Arencibia is President and Owner of Arencibia Quality and Compliance Associates, LLC, and Cochair of the ISPE Women in Pharma® Steering Committee. She has been an ISPE member since 1991 and is a member of the ISPE International Board of Directors.

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 By John Clarke


John Clarke

A Winning VIRTUAL HACKATHON

2020 was a year for finding new ways of working for the entire ISPE Emerging Leaders (EL) community. In February, ELs stepped up the challenge by holding the first fully virtual International Hackathon. With over 22 countries represented, the Hackathon required the participants to consider real-life challenges with working remotely and across time zones. Innovation was key to generate solutions to the problem statement provided by Bayer.

The event was planned by a task team of EL members from European Union and North American Affiliates and Chapters, along with colleagues from Bayer. At times, the organization of the event was a Hackathon in itself, requiring weekly calls and brainstorming sessions.

REAL-WORLD CHALLENGES

The Hackathon problem required the participants to work to deliver a solution for a fictional company, Pharmaceutical Universal Exports, a contract manufacturing organization for several pharmaceutical and consumer care companies. The teams were requested to expand their sites to find lean solutions without overengineering their digital journey.

The solution required transforming paper-based documentation into a digital and readable format. The solution had to innovate to avoid the retrospective digitalization of paper-based documentation and ensure (a) real-time availability of data; (b) manual processes were avoided; and (c) the solution allowed for simultaneous recording in paper and digital formats.

Each team was assigned two coaches to support and mentor them through the workshop. The coaches are industry leaders who volunteered to check in with the teams at each milestone and used their expertise to promote innovative and creative approaches to the problem. The event would not have been possible had it not been for the support and engagement provided by the coaches throughout.

VIRTUAL HACKATHON

The Hackathon ran four weeks. The first week allowed the newly formed teams a chance to establish a schedule for the workshop, assign roles, and do some preliminary research on the problem statement. Week 2 was for incubation and development of the solutions, and week 3 was devoted to maturation of the proposal and generation of a video presentation for judging. Each team submitted a 15-minute video presentation, and it was apparent that the format supported the teams in pushing the boundaries of their creativity to present an optimal solution to the problem.

The virtual format of the Hackathon allowed a different approach from past ISPE EL Hackathons, especially when it came to the judging. A panel of eight judges with representatives from the ISPE International Board of Directors and Bayer assessed and scored submissions from each team in a preliminary judging round.

The fourth week culminated in a Grand Finale, where the two finalist teams presented their solutions live to the panel of judges. The Digi-Engineers and Optimus Prime teams were the finalists, and these teams blew everyone away with the quality and creativity of their solutions. The Digi-Engineers were ultimately named the winners.

THE WINNING SOLUTION

The Digi-Engineers successfully identified a system innovation solution, Digitalization, a single-user interface that provides automation, advanced analytics, and continuous process verification (CPV). Real-time collaboration, interactive dashboards and reports, automation, advanced analytics, and CPV equal increased productivity and profitability in the solution.

The Digi-Engineers team was Prudence Edwards, Pablo Benitez, Giuseppina Elena Dragonetti, Stephan Huelber, Domiziana Piili, Nadin Osman, Andrew Svetozarov, and Andrea Tanzini. The coaches were Stuart Hall and Jean-François Duliere.

Team Lemniscate was recognized for the Best Video Presentation. Team members were Moneem Ahmed, Veneshia Alison, Teri Del Rosario, G. P. Wahyunanda, Joanne Patricia, Firena Setyanti, Charlotte Gallardo, Tania Hamdhani, and Fenny Mulyo. The coaches were Jesus del Valle Rosales and Cy Rodriguez.

Congratulations to the Digi-Engineers and all the teams who took part in this year's Hackathon. Their engagement and effort really showed in the solutions presented!

John Clarke is a Process Lead with Pfizer in Dublin, Ireland, and the 2020–2021 ISPE International Emerging Leaders Chair. He has been an ISPE member since 2014.

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IT SERVICES:
Applying Good IT Practice and Automation

By Christopher John Reid and Siôn Wyn

This article focuses on pragmatic quality- and risk-based approaches to IT infrastructure. It covers recommendations made by a US FDA/industry team linked to the US FDA Center for Devices and Radiological Health (CDRH) Case for Quality initiative [1]—which is promoting a risk-based, product quality, and patient-centric approach to computerized systems assurance—as well as the GAMP® reexamination of approaches to IT infrastructure control and compliance.

The ISPE *GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* [2] defines typical IT infrastructure components and processes that form the IT quality management system (Figure 1).

Traditionally, IT infrastructure qualification practices have been employed to ensure that IT infrastructure is appropriately specified, designed, configured, and deployed. Now, advances in IT practices, service models, service management tools, and automation provide an opportunity to establish and maintain the qualified state of IT infrastructure in a robust and efficient manner that minimizes the risk of IT infrastructure failure affecting regulated business applications and data.

EMBRACING INFRASTRUCTURE AUTOMATION

As reported in a panel discussion, "FDA and Industry Collaboration on Computer Software Assurance (CSA)" [3], at the Institute of Validation Technology's 20th annual Computer and IT Systems Validation conference, 23 April 2019, the FDA and industry team's recommendations are to:

- Embrace automation in the management of IT infrastructure
- Use electronic means rather than paper documentation
- Leverage continuous data and information for monitoring and assurance

This approach improves quality and process control while lowering quality, security, and integrity risks.

The team reported case studies on replacing manual, paper-based, and error-prone test evidence and specification maintenance with an automated, error-free approach based on standard tools. In these case studies, the time savings were ten-fold (i.e., the automated approach takes only a tenth of the time of the manual method).

RISK PROFILE OF IT INFRASTRUCTURE

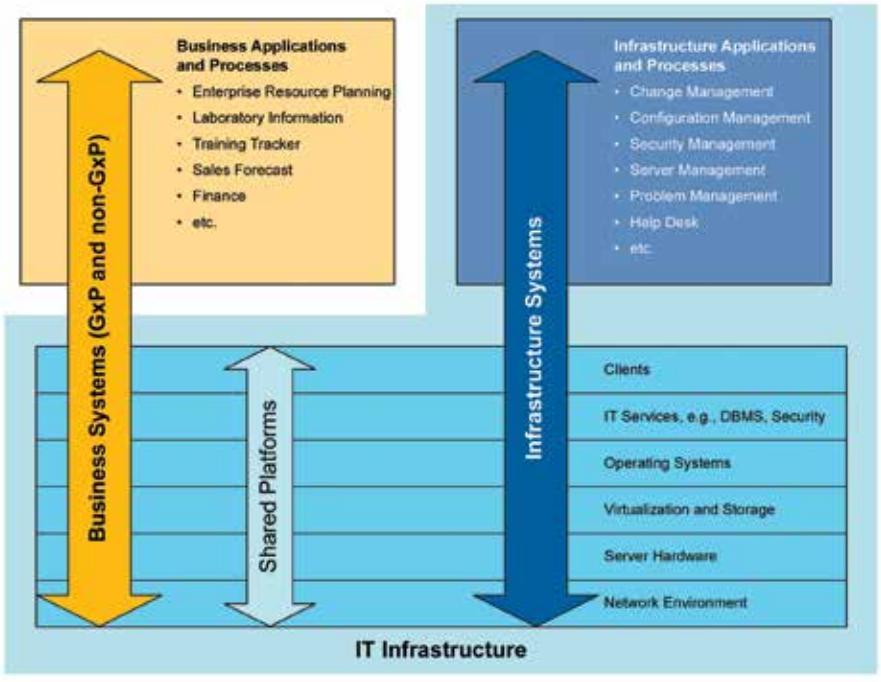
The primary risks resulting from a failure of an IT infrastructure environment relate to:

- Data protection and data integrity
- Business application availability and performance

IT infrastructure architectures incorporate widely used industry standard components (GAMP® Category 1 hardware and software) that typically include error detection and self-correction features, leading to a low failure rate and a high probability of threat and error detection.

Threats to the IT Infrastructure environment largely come from cyberattacks, unauthorized access, system and component failure, or inadequate resource provisioning (storage capacity, processing capacity). These risks are continuous, and it is therefore imperative that the currency of IT infrastructure controls is

Figure 1: The IT infrastructure provides a controlled environment within which business applications operate in support of regulated business processes. (DBMS = database management system.)



maintained (e.g., through security patching) and monitoring is in place to provide early detection of any threat. IT infrastructure design incorporates a high degree of resilience that mitigates both single-point and complete failure.

Further, IT infrastructure supports business applications that hold, process, and transmit regulated records. The completeness and accuracy of these regulated records are largely governed by the business processes supported by these business applications. IT infrastructure is a secure platform that hosts these applications and data and does not directly impact regulated records. This ensures that the risk to patient safety, product quality, and regulated data integrity resulting from an IT Infrastructure failure is low.

IT infrastructure also supports nonregulated business applications and data. Therefore, the IT infrastructure cannot effectively be partitioned into GxP and non-GxP. As such, common IT practices and controls are used to manage IT infrastructure supporting both GxP and non-GxP operations.

Industry-standard IT management practices, electronic service management tools, modern IT service models, automation, and continuous monitoring are essential for ensuring the performance, security, and integrity of the IT infrastructure environment.

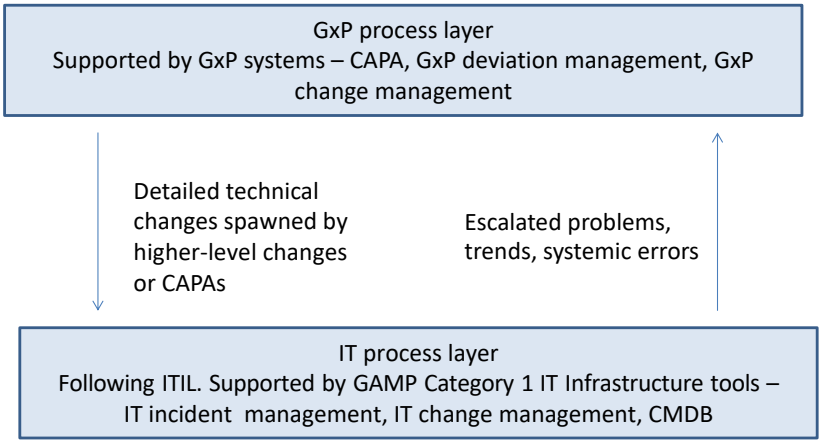
IT QUALITY MANAGEMENT SYSTEM

An IT quality management system based on well-established, cross-industry IT governance standards such as IT Infrastructure Library (ITIL) [4] is essential to the effective management of the IT infrastructure environment. The IT quality management system establishes robust processes, technologies, and subject matter expertise to effectively manage the IT infrastructure environment in accordance with risk. Further, such IT quality management systems use metric-driven continuous improvements to enhance IT controls maturity. Examples of IT practices include the following.

- General management practices:
  - Strategy management
  - Portfolio management
  - Architecture management
  - Workforce and talent management
  - Continual improvement
  - Measurement and reporting
  - Risk management
  - Information security management
  - Knowledge management
  - Organizational change management
  - Project management
  - Relationship management
  - Supplier management

- Service management practices:
  - Business analysis
  - Service catalog management
  - Service design
  - Service level management
  - Availability management

Figure 2: Relationship between product life-cycle quality system and IT quality system.



- Capacity and performance management
- Service continuity management
- Monitoring and event management
- Service desk
- Incident management
- Service request management
- Problem management
- Release management
- Change management
- Service validation and testing
- Service configuration management
- IT asset management

- Technical management practices:
  - Deployment management
  - Infrastructure and platform management
  - Software development and management

These IT practices are consistent with the expectations of the ISPE *GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* [2].

Service Management Tools

Electronic service management tools that incorporate configuration management databases (CMDBs) and electronic workflows supporting change management, configuration management, and incident and problem management are integral to the IT quality management system.

The CMDB supports effective management of the configuration status of IT infrastructure components and business applications. Electronic workflows ensure adherence to processes and collaboration of IT subject matter experts across global organizations.

IT Qualification vs. IT Quality Management

Traditional qualification activities can be integrated into the IT quality management system and service management tools, avoiding the need for one-off protocols and paper records management. For example, if we consider a backup service, work instructions can be created within the service management tool to define how a new server or storage device is added to the backup solution. Backup scheduling is configured within the backup tool to ensure backups are scheduled at the right frequency. Alerts are configured to automatically notify of failures. Evidence of backup logs and backup restoration tests can be captured in a secure repository. This can all be achieved without the need to create and execute standalone protocols. In essence, the backup deployment, configuration, and monitoring become part of the operational processes of the IT quality management system.

Product Quality Management vs. IT Quality Management

There are fundamental differences between the quality management system directly supporting the regulated product life cycle, and the IT quality management system supporting information technology and infrastructure.

Quality management systems supporting the product life cycle include risk management processes such as deviation management, corrective and preventive action (CAPA), and change management. The processes engage business and quality assurance subject matter experts to effectively evaluate and manage risks impacting patient safety and product quality.

Similar processes are included in the IT quality management system, but they are focused on IT risks relating to availability, performance, and information security. These processes include incident and problem management and change management that engage IT subject matter experts in the evaluation and management of IT risks.

Interfaces may be established between the IT quality management system and the product life-cycle quality management system (Figure 2) to hand off potential risks relating to patient safety and product quality. For example, an IT incident may potentially

impact GxP data (e.g., data loss or corruption). Such incidents should be communicated to business and quality assurance functions so that the business and regulatory impacts can be assessed and mitigated. The CMDB will support IT in identifying IT incidents that could potentially impact GxP.

IT INFRASTRUCTURE LIFE CYCLE AND AUTOMATION

The IT infrastructure life cycle comprises:

- Resource provisioning
- Configuration management
- Monitoring
- Compliance
- Optimization

Resource provisioning utilizes Infrastructure as Code (IaC) and virtual machine templates to provision new servers and services that are configured in accordance with IT standards. Infrastructure code and templates are subject to version control using code management tools. Changes to code and templates are fully auditable in the event of an inadvertent or unauthorized change.

Configuration management ensures that infrastructure code and templates automatically provision a standard configuration. Thus, code and templates can be verified once and used many times when provisioning like resources.

Monitoring uses tools that monitor IT availability, performance, incidents, and security vulnerabilities. Automated alerts are directly sent to support teams to enable a timely response. Self-correcting technologies allow for adjustments in configuration to address performance and other issues. Security log monitoring identifies and reports potential unauthorized access attempts.

Compliance is monitored to minimize the risk of deviation from standard configurations. Environments are automatically audited against configuration standards configurations, and deviations are self-corrected following inadvertent or unauthorized change.

Optimization is enabled through metrics provided by monitoring tools. IT infrastructure resources such as processing capacity, storage capacity, database capacity, network routing, and load balancing can be adjusted based on feedback to maintain system availability and performance.

IT INFRASTRUCTURE MONITORING

Monitoring technologies provide real-time feedback on the status of the IT infrastructure environment. Such monitoring includes, but is not limited to:

- Information security vulnerabilities
- IT environment availability
- Database performance
- Infrastructure component failure
- Network connectivity issues
- Application and platform errors
- Virtual environment performance

Machine learning is now being deployed to evaluate data sets (events and logs) generated by monitoring tools. Data trends are analyzed to predict potential IT infrastructure incidents and proactively act to minimize the risk of IT infrastructure failures.

CONCLUSION

Historical IT infrastructure qualification processes based on paper records can be inefficient. Such approaches often only confirm the correct operation of the IT infrastructure at a point in time and seldom provide assurance that IT controls continue to operate effectively.

Advances in IT infrastructure service models, virtual technologies, automation, monitoring, and self-correction technologies have led to significant improvements in IT governance. Implementation of an IT quality management system based on industry standards, electronic service management tools, and automation is fundamental to managing IT risks.

GAMP Global Leadership strongly supports and endorses the application of these approaches as an effective way of achieving the controls principles defied in the ISPE *GAMP® Good Practice Guide: Infrastructure Control and Compliance* [2].

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BEST PRACTICES for Deploying Real-World Evidence Solutions

By Frank Henrichmann and Oliver Herrmann

Real-world evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD) relating to patient health status and the healthcare delivery [1]. RWE helps healthcare companies better understand and establish stronger evidence of products' performance, clinical value, and cost-effectiveness outside the controlled environment of clinical trials. Outcome-based studies are increasingly depending on RWD and RWE to speed up drug development and approvals, and ultimately reduce development costs.

Furthermore, when derived from RWD such as medical data generated in hospitals, RWE can provide additional insights into epidemiology, compliance, and costs, and therefore can help to satisfy the rising demand for information from payers, regulatory bodies, and healthcare providers regarding drug safety. In September 2020, former US FDA Commissioner Scott Gottlieb, MD, outlined RWE's impact on the clinical development, regulatory decision-making, and postmarket data collection of COVID-19 vaccines and treatments [2]. He noted that RWE provides flexibility for postmarket safety and effectiveness data collection, supports decision-making about patient care, is used to augment data sets already being accrued, and enables substantial improvements in the clinical care of COVID-19 patients in a relatively short period of time.

The RWE market is expected to be worth $1.6 billion by 2024 [3], and its value may possibly be greater than that due to effects from the COVID-19 pandemic. RWE solutions are available for drug development and approvals, market access and reimbursement/coverage decisions, clinical decision-making, medical device development and approvals, and other applications of relevance in the life sciences industry.

But how exactly is RWE generated from RWD? Are there specific quality aspects to be considered in the validation of RWD and the tools utilized to generate RWE used for regulated purposes? And how can GAMP® principles be used to validate the components and deliverables?

FROM RWD TO RWE

RWD are routinely collected from a variety of sources [4–6], including:

- Electronic health records (EHRs) and electronic medical records
- Claims and billing data
- Product and disease registries
- Patient-generated data, including in home-use settings
- Health-related apps and mobile devices
- Health surveys
- Observational studies
- Social media

Studies/analyses conducted on RWD lead to RWE. Such studies may complement the information collected and analyzed through a traditional clinical trial [7]. For example, in 2018, blinatumomab was approved for the indication minimal residual disease (MRD)–positive acute lymphoblastic leukemia using data from a single-arm clinical trial that included a historical comparison group of retrospective data on patients collected from clinical sites [8].

CURRENT CHALLENGES

If RWE is used in a regulated context, the processes and tools used to generate the RWE should be validated.

Operational challenges in RWE generation include feasibility, governance, and sustainability issues. Among the key issues are the complexities of accessing and using multiple data sources that have different legal requirements for sharing data. Data anonymization is required to meet data privacy regulations, and efficient and timely delivery of data must be ensured [9].

Technological challenges include differences in terminologies, data formats, quality, and content that exist across multiple databases, leading to heterogeneous data. Heterogeneity may cause significant problems when pooling multiple data sets from various populations to explore diseases, events, or outcomes [9].

PROCESS OVERVIEW

Because RWE might be generated to answer a variety of questions, ranging from non-GxP-relevant market research to GxP-relevant clinical trial or pharmacovigilance support, the associated processes must have adequate controls in place for GxP-relevant RWE generation while at the same time enabling flexible and efficient processing of all analysis requests. Examples of adequate control may include validation/qualification of platforms and computerized systems and independent double programming (multiple programmers using the same specifications and raw data to assess whether they achieve the same results) [10].

As the general process of generating RWE cannot be exclusively associated with a single business process, it is essential to establish a robust product and process understanding for each project that generates RWE. The risks associated with the usage of RWE within the GxP-regulated busines process are key to scaling life-cycle activities as part of the life-cycle approach and defining the required controls during the analysis. The general process of generating RWE typically provides a framework and workflow to ensure only qualified/validated tools are used and project-specific risk assessments are performed.

The process to generate GxP-relevant RWE from RWD can generally be described in the following phases: analysis, build, and execution and reporting.

Analysis Phase

During the analysis phase, the following aspects must be documented and approved in, for example, a RWE study/analysis protocol:

- Definition of the business question to be answered for intended use of the RWE (e.g., for clinical trials, reimbursement, drug safety)
- Selection of the research approach (e.g., noninterventional study, analysis of social media), data source (e.g., EHR systems, product and disease registries) and methodology (e.g., population, exposure, and outcomes of interest)
- Approach to identify and minimize bias

During this phase, the required technology and the development and execution activities as well as potential challenges should be assessed at a high level. For example, a long-term study involving continuous monitoring of social media using artificial intelligence (AI) requires radically different approaches and controls than a one-time analysis of product registry data using traditional statistics. As stated previously, a risk assessment considering the supported business process should be performed and documented at this phase. Aspects such as audit trails of data changes or change control for continuously trained AI to ensure the results can be reproduced in cases of need should be considered in this phase.

Build Phase

During the build phase, the following aspects must be documented and approved in, for example, an RWE study/analysis plan:

- Description of the sample size considerations for the study data source
- Formal definitions of exposure, outcomes, and other variables included in the analysis, including any manipulations/transformations that will be conducted
- Methods for dealing with bias, missing data, and other data issues
- Methods for analyzing and documenting the study outcomes

RWD analysis usually involves development of statistical programs and algorithms; therefore, all statistical programming deliverables should be developed according to processes established for statistical analysis in other GxP-regulated areas, such as clinical trial data analysis. Depending on the associated risks, practices such as peer reviews of code/algorithms and independent double programming may need to be developed and tested in the build phase.

Execution and Reporting Phase

After the successful build and testing of the RWD analysis, the RWE is generated. Depending on the intended use of the RWE, the RWE might be produced only once or repeatedly. The outcome and a summary of the build phase should be documented in an RWE-study/analysis report. If the RWD analysis is executed repeatedly, a maintenance plan might be required.

Responsibilities

The generation of RWE requires a cross-functional team capable of critical thinking to identify and adequately address all risks to patient safety, product quality and data integrity. Table 1 identifies roles and responsibilities for members of this team.

DATA SOURCES

Just like in a traditional clinical trial, data quality in an RWE analysis is of critical importance. A risk-based approach considering the specific regulatory use of the evidence, the overall data integrity of the entire regulatory-relevant data set, and, ultimately, the safety of the patient should be used to determine the necessary level of RWD quality. The FDA has provided the following example in their guidance to illustrate this point [1]:

A specific registry might be leveraged for post market surveillance, but not be adequate to support a premarket determination of reasonable assurance of safety and effectiveness or substantial equivalence.

RWD are typically collected and aggregated for specific, nonregulated purposes, so an understanding of the strengths and limitations of the RWD, and how these qualities potentially impact the relevance and reliability of the data in the context of the intended use, is critical. It should be noted that RWD could be biased—for example, data from premium healthcare providers may not be representative of the entire population. Additionally, the qualification and the intentions of the people recording the data (patient, physician, clinical investigator, etc.) may introduce bias and/or affect the overall quality of the data. Recently, a COVID-19 hydroxychloroquine study published in *Lancet* had to be retracted because the findings were based on EHR data from inconsistent sources, compromising the overall quality of the combined data set [11, 12].

If RWD are used to generate RWE intended to support regulatory decision-making, the following aspects might be considered in the selection of RWD sources:

- Appropriate scope for the intended use
- Data integrity (primarily accuracy and completeness)
- Ability to verify data against source documentation
- Definitional framework (i.e., data dictionary)
- Whether the data are representative and generalizable to the relevant population

RWD may be provided directly by organizations that collect and process them, or they may be obtained from specialized RWD providers that curate, aggregate, and clean or transform data received from healthcare providers or other sources. The following areas should be covered when auditing RWD providers.

- Coverage/quantity: For example, patient coverage, sample size, representativeness, completeness
- Granularity/depth: For example, types of patient-level data, such as diagnoses, procedures, laboratory tests, quality of life, observations, and outcomes
- Accessibility: Data access and usage limitations, raw data sharing, data privacy
- Quality: Richness of the data, origins of the data, data-entry quality standards
- Legal issues: For example, permission to use data for secondary purposes
- Timeliness: Data-refresh frequency, historical coverage
- Technical quality: For example, system validation/qualification, IT processes, data cleaning and transformation processes

Table 1: The RWE-generation team.

Role	Responsibilities
Business representative	• Definition of requirements and risk assessment • Review of the RWE deliverable • Usage and further processing of the RWE within the business process, including archiving
Data science representative	• Controlled data transformation and storage • Adherence to the RWE-generation process • Development and testing of algorithms • Documentation of the development process
IT	• Provisioning of qualified computing environment
Quality assurance	• Auditing of data providers, storage providers, and tool suppliers

It should be noted that it may not be possible to verify all data integrity aspects for RWD sources because these sources are often anonymized. For example, it may not be possible to identify the patient or the reporter of the data, or data may not be "original" anymore because data are copied and transformed to be suitable for RWD analysis. All data transformations should be clearly documented, and adequate controls should be in place to ensure the ALCOA+ (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available) [13, 14] aspects of data integrity are not violated in the process.

As data sources can only be assessed against known intended data usages, documentation of the RWD and RWD vendor evaluation is important to enable further future usage of the data for new purposes. This documentation must be controlled by robust data governance processes that assess and document the appropriateness of the RWD for each intended use, and control the access to the data.

DATA PROCESSING PLATFORMS

Organizations often establish complex IT platforms to store and analyze RWD. These platforms must establish data availability, provide tools for the development of analysis algorithms, and have adequate processing power that can be flexibly allocated to an individual analysis.

Data governance processes should be in place to define data availability aspects and requirements for each source of RWD, such as:

- Need for data transfers, including requirements for transfer frequency and mode (incremental or full)
- Need for audit-trail data changes
- Type of database model (relational, object, graph, flat files, etc.)
- Type of data (structured, unstructured, semistructured, etc.)
- License and access model

Furthermore, the analysis of RWD often requires a large amount of processing power; therefore, the RWD/RWE platform must provide functionality to flexibly assign processing power (e.g., as provided by graphics processing units [GPUs]). The processing

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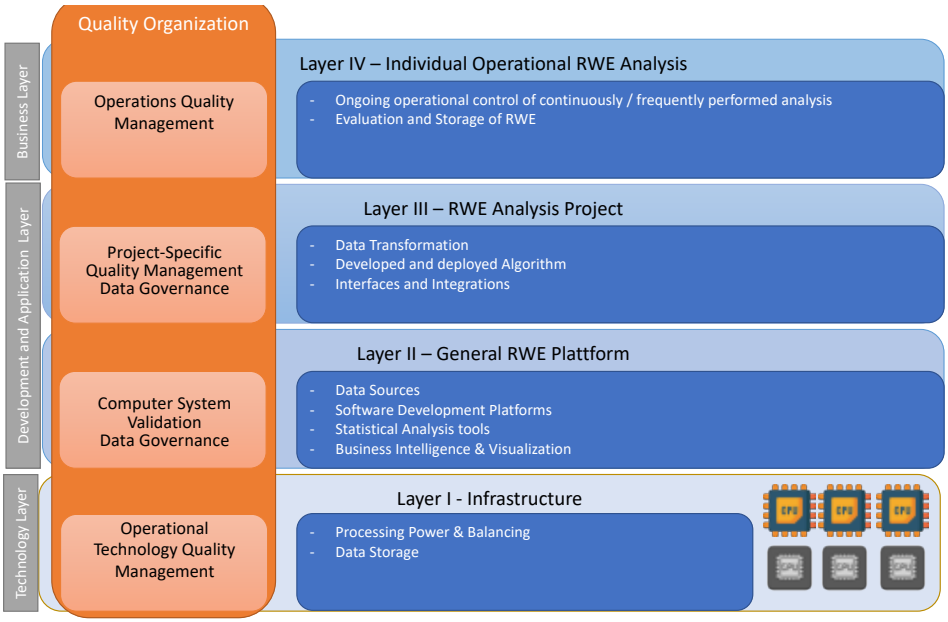
Figure 1: RWE platform layer model.



power must be usable for a potentially large set of development tools ranging from statistics software such as R and SAS to programing environments used in AI development such as Python, to "self-service" analysis tools intended for nontechnical end users. Often, specific additional libraries must be acquired and integrated in the analysis. In addition, visualization tools may be required to provide the RWE in a format that facilitates decision-making or further processing.

The underlying infrastructure and supporting vendors for these platforms must be qualified following the principles as laid out in the ISPE *GAMP® Good Practice Guide: IT Infrastructure Control and Compliance* [15].

QUALITY OVERSIGHT

From a computerized system validation perspective, RWE platforms are similar to platforms used in clinical trials, where a set of tools and systems supports an individual clinical trial. Therefore, a similar approach could be used as described in the *GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data* (*Good eClinical Practice*) [16]. Figure 1 presents a four-layer model for the RWE platform.

Layer I provides qualified infrastructure with a special focus on supplying the required processing power for individual RWE activities as well as adequate data storage for RWD and RWE. Processing power might be provided by central processing units (CPUs) or GPUs. The qualification and process for provisioning GPUs are especially important, as they are often the only areas where GPUs might be used for GxP-relevant data processing.

Layer II establishes a tool set for the development of analysis algorithms using reliable data sources. The tool set also encompasses all tools required for data ingestion, as well as reporting and visualization tools required to provide the RWE in the required format. This tool set should be validated/qualified to ensure these tools are fit for the development of the algorithms to analyze RWD. The aspect of change control is of critical importance because most of these development tools are improved constantly or could be modified with additional functionality or libraries. As noted previously, reliable data sources are needed; furthermore, all performed qualification and evaluation activities should be recorded as part of the platform qualification/validation. Risk assessment of the data sources, the tool set, and the development process should always consider that RWD analyses with direct and significant impact on patient safety and/or product quality could be developed and implemented.

Layer III uses the underlying layers to develop and deploy the algorithms, including all necessary data transformations for an individual analysis, following defined processes for software development and project management as applicable. The algorithms may be interfaced with other systems. Algorithms or solutions should be validated following the principles outlined in the *GAMP® 5 Guide* [17] but also build upon the validation activities performed in Layer II. The primary focus of algorithm validation should be the correctness and reliability of the developed algorithm and the associated risks derived from the supported business process. The GxP risk of the business process should drive the extent of the controls that are required. For example, while an algorithm for a GxP critical area might require double programming and additional independent review, an algorithm for an area with low GxP risks might just be independently reviewed. Similar controls that have been implemented in other areas, such as

statistical analysis of clinical trial data, can be adapted to RWD analysis. The risk and the complexity of the analysis are also the key drivers for determining the required evidence and documentation that need to be established.

Layer VI includes RWE use by business function, including adequate storage. For algorithms that are executed continuously or frequently, adequate operational controls must be established as for other computerized systems. These controls may address topics such as backup and restore, business continuity, training, and so on.

Throughout all layers, adequate control of data and tools (e.g., user access and user rights) must be established and maintained to ensure data integrity is maintained throughout the entire process.

RISK ASSESSMENT

Organizations often establish a central data science department that provides RWD/RWE services for the entire organization, including GxP- and non-GxP-relevant requests for RWD analysis. As with any other software or computerized system, algorithm- and code-based RWE systems require risk assessments to appropriately identify and design the required controls, and to scale and justify the validation efforts. Because RWD analysis can be done in various ways using statistics and/or AI, and because the resulting RWE can support all business processes regardless of their regulatory relevance or relation to product quality or patient safety, every RDE analysis project must receive a careful risk assessment. The vast majority of these projects should be classified as bespoke software (GMPS Cat. 5) because they include the development of custom code. A clear definition of the intended use of the RWE and sufficient, documented user requirements, including the required data sources, form the basis for the risk assessment.

Risk assessments need to be performed for:

- All platforms and tools
- All data sources and providers
- All analysis projects and their support of business processes (intended use)
- Data transfers and data flows (including interfaces)

The risk assessment for platforms and tools should be performed as part of computerized system validation processes and activities. It should be noted that a significant number of tools are open source or are provided by vendors that are not familiar with GxP requirements. The tools used in RWE generation are also used in a number of other industries that are not as regulated as our industry. GAMP 5 provides robust guidance for such risk assessments and can also be applied to open source software (see "Guide for Using Open Source Software [OSS] in Regulated Industries Based on GAMP" in *Pharmaceutical Engineering,* May/June 2010 [18]).

As outlined earlier, the quality of the RWD is of key importance. Risk assessments must determine the level of qualification required for the data providers and determine the reliability of the data itself. These risk assessments should be based on data integrity aspects, such as ALCOA+, and data privacy aspects; and issues with biased data must be included. Further guidance on data life cycles and data governance can be found in the *GAMP® Guide: Records and Data Integrity* [14].

Often, extraordinary large amounts of data must be collected, transferred, and stored for the generation of RWE. The security and integrity of the data during these activities must be ensured. Access control and possibly encryption in transit, as well as encryption at rest, may be required. A robust data governance framework is therefore advisable.

Obviously, not all RWD analysis projects have that same risks, and each should be evaluated individually. In particular, analyses resulting in data for regulatory submissions and analyses related to patient safety or product quality must be reliable and trustworthy, and the generation of the RWE should be traceable and/or repeatable.

CONCLUSION

As the use of RWE for regulated purposes grows, the need to validate the tools and processes used to generate RWE also increases. The validation approach outlined in this article, which adopts concepts from the validation of statistical analysis, AI, and clinical trials, and is based on GAMP guidance in combination with a robust data governance framework, will facilitate regulatory compliance and, even more important, reliable and trustworthy RWE.

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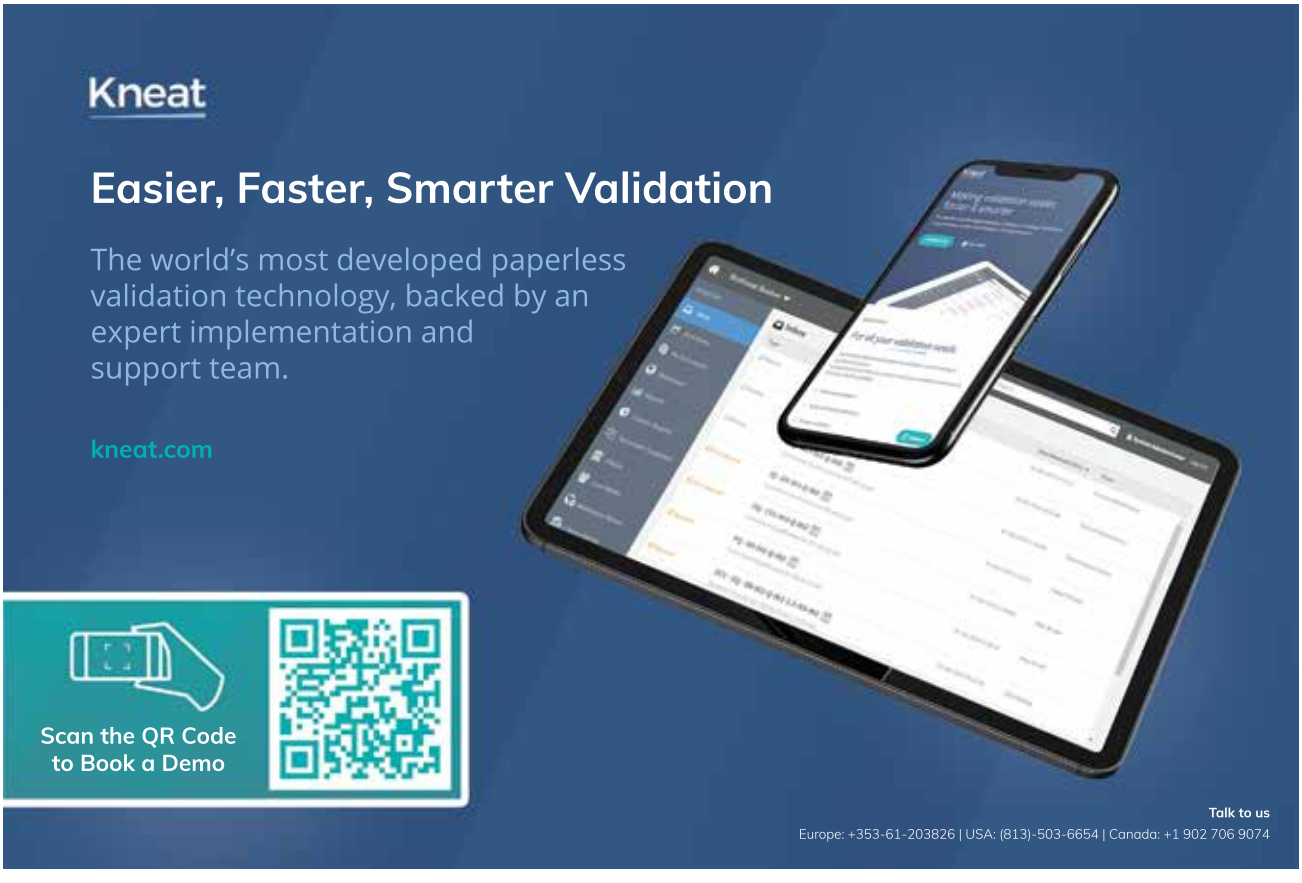
Oliver Herrmann, Founder, CEO, and Senior Executive Consultant at Q-FINITY Quality Management, is an expert in quality management, computer system validation, data integrity, and compliance. In 2004, Oliver founded Q-FINITY to combine process management with the requirements for the validation of computerized systems and sharing this experience via an integrated service portfolio. Over the last 16 years, he has gained extensive experience in planning, development, execution, documentation, and auditing of strategies, projects, and measures for GxP-regulated environments. He has supported projects focusing on chromatography LIMS, PCS and MES through ERP, pharmacovigilance, EDC, efficacy, DMS, and more. An ISPE member since 2005, Oliver has served as a co-lead of the GAMP SIG for the validation of clinical systems and coauthored the ISPE *GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data*. He is Cochair of the GAMP D/A/CH Steering Committee and a member of the GAMP EU and Global Steering Committees.



HAPPY 30TH ANNIVERSARY

to the GAMP® Community of Practice!

By Siôn Wyn

GAMP founders (from left): Tony Margetts, Guy Wingate, and David Selby.

In 2021, the ISPE GAMP® Community of Practice (CoP) is celebrating 30 years of promoting industry good practice for computerized systems and encouraging technical innovation and progress, while protecting patient safety, product quality, and data integrity.

The ISPE GAMP CoP promotes the understanding of the regulation and use of computerized systems within the pharmaceutical, biopharmaceutical, and medical device industries, as well as other regulated organizations, and works with other ISPE CoPs to ensure a consistent ISPE message.

The GAMP CoP forms relationships, coordinated through ISPE, with like-minded industry associations and competent regulatory authorities aimed at creating globally harmonized quality approaches to implementation and operation of computerized systems. The GAMP CoP also involves many suppliers and service providers, aiming to identify and share best practices, with the goal of having a positive influence on the quality of computerized systems used in the industry.

OBJECTIVES

GAMP's objectives have progressed from a focus on compliance to include encouragement and support for innovation and technical progress that benefits both the patient and the public.

The scope of GAMP has also moved from a primary emphasis on pharmaceutical manufacturing to embrace the whole life cycle for various GxP-regulated areas, including medical devices and blood products.

The integrity and accuracy of records and data are essential throughout the product life cycle, from research and development to preclinical studies, clinical trials, production, and quality control to marketing. This is also reflected in the objectives and activities of GAMP: support for the achievement of data integrity is now a central objective for GAMP, and significant GAMP guidance on the topic has been published.

Publishing reliable and useful guidance on all aspects of GAMP is a major objective for the CoP. By building upon existing industry good practice in an efficient and effective manner, GAMP guidance aims to achieve computerized systems that are fit for intended use and meet current regulatory requirements. GAMP guidance also aims to apply the latest quality risk management approaches to promote innovative and technical advancement, while safeguarding patient safety and product quality. Furthermore, GAMP guidance provides principles and practices to ensure regulated records and data are complete, consistent, and accurate throughout the data life cycle [1].

HISTORY

The organization that we know as GAMP was initiated in 1991 by David Selby (Glaxo), the founding chair; Clive Tayler (Wellcome); Tony Margetts (ICI Pharmaceuticals); and a small team of other experts in the United Kingdom who realized that the pharmaceutical industry needed to consider and meet evolving regulatory

agency expectations for computerized system compliance and validation. This realization was primarily prompted by a number of pivotal US FDA inspections in the late 1980s and early 1990s.

During this period, the FDA and other regulators were taking an increasing interest in the role of computerized systems in regulated processes and had concluded that the reliability and integrity of these systems played an important role in product quality and patient safety. In response to this increased scrutiny, it became clear that an industry reaction was required, including guidance on expectations and good practice.

Tony Trill, Principal Inspector for the Medicines Control Agency (now MHRA) on Computerised Systems, was a strong advocate for GAMP during the 1990s, helping to establish it as a point of reference for suppliers, pharmaceutical companies, and regulators alike. It was Trill who first suggested the GAMP acronym (as shorthand for Good Automated Manufacturing Practice) at the launch event.

The first document, the *GAMP Supplier Guide*, produced by a subteam led by Tony Margetts, was released to the GAMP membership on 1 March 1994 and officially published a year later. As expectations and industry good practices continued to evolve, so did the guide, with the launch of GAMP 2 in Amsterdam in late 1996 and a two-volume GAMP 3 in 1998. By this time, GAMP was a truly international effort with increasing involvement from contributors from around the world.

GAMP became part of ISPE in 2000, supporting the wider global reach that the guidance generated and the opportunities such a collaboration offered.

As GAMP evolved, more and more pharmaceutical companies began to join to share experiences and develop materials that could be shared with other companies and with suppliers. In those early days, suppliers could attend GAMP conferences and comment on GAMP materials but they could not participate in the meetings held for the pharmaceutical companies. This prompted the MHRA to support the creation in 1995 of the "Supplier Forum," where suppliers could discuss emerging expectations for computer validation and coordinate a voice into the work of the GAMP Forum. Under the chairmanship of Guy Wingate (ICI Eutech), the Supplier Forum quickly grew, and in 1998 it merged into the GAMP organization, allowing both pharmaceutical companies and suppliers to work together in a more integrated manner on the development of GAMP guidance. Wingate later joined GlaxoWellcome, served as Chair of the GAMP Industry Board for 10 years, and led the development of *GAMP® 4* and *GAMP® 5*.

The initial GAMP guides were focused primarily on GMP systems. In late 2001, the scope was broadened to all GxP systems with the release of *GAMP® 4*. This version quickly established itself as the definitive source of industry good practice for computerized system compliance and validation. Between 2001 and 2008, a number of ISPE GAMP® Good Practice Guides (GPGs) applied, expanded, and clarified the principles of GAMP good practice to a wide variety of computerized systems and regulatory areas. The topics covered by these GPGs include calibration, process control systems, laboratory systems, infrastructure, global information systems, and manufacturing execution systems (MES).

Two of the most noteworthy GAMP guides are *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* [2] and the ISPE *GAMP® Guide: Records and Data Integrity* [3] (see sidebar). Both of these guides are supported by GPGs exploring selected topics in greater depth.

CURRENT ACTIVITIES

As technology constantly and rapidly changes and advances, GAMP evolves to explore how such new technology and approaches can be used in an effective, efficient, and compliant manner for the benefit of the patient. Some—but certainly not all—of the key areas of GAMP activity are described in the following sections.

Agile Approaches

GAMP supports the use of incremental, iterative, and evolutionary approaches, including Agile, for product development and development of custom applications. Success factors in this area include a robust quality management system within an appropriate organizational culture, well-trained and highly disciplined teams following a well-defined process supported by effective tools and automation, and appropriate customer or product owner involvement.

As part of its efforts in this area, GAMP has advocated for programs such as the FDA Center for Devices and Radiological Health Case for Quality initiative, which supports the adoption of appropriate Agile approaches to encourage innovation, eliminate unnecessary costs, and help focus on real quality and fitness for intended use [4, 5].

The GAMP Agile Special Interest Group (SIG) is working in the following areas:

- Certainty mindset versus a discovery mindset
- User requirements
- Continuous testing instead of testing at the end
- Validation and compliance in an Agile world
- The benefits of tools instead of documents
- Bringing together system development and operations

For further information on the output from the Agile SIG, and other GAMP SIGs, visit ISPE.org/GAMP-resources

Cloud Computing

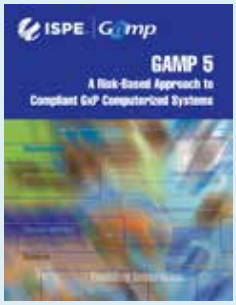
Cloud computing is a significant area with great opportunities for innovation and business benefit. There is a substantial move toward using some elements of cloud computing for some GxP applications, and it seems inevitable that cloud-based applications will increase in importance for the pharma industry. The GAMP Cloud SIG has published valuable guidance [6–8], and is developing more. The life sciences quality assurance and compliance community must define and advocate realistic approaches that encourage innovation as well as safeguard quality and compliance.

Flexible, practical, and pragmatic approaches to assessment and management of technology service providers are further

Spotlight: Two Essential GAMP® Guides

In 30 years, the GAMP® Community of Practice has published many outstanding guides, including *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* and the ISPE *GAMP® Guide: Records and Data Integrity.*

GAMP® 5

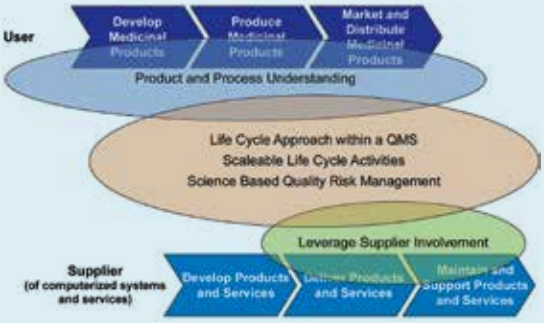


GAMP® 5 is the current iteration of the GAMP guidance and was published in 2008. It was created in response to the changing regulatory and industry environment, which placed greater emphasis on science- and risk-based management approaches, product and process understanding, and the application of quality by design concepts.

GAMP® 5 provides a cost-effective framework of good practice to ensure that GxP-regulated computerized systems are fit for intended use and compliant with applicable regulations. The framework aims to safeguard patient safety, product quality, and data integrity, while also delivering business benefit.

The guide also provides guidance for suppliers to the life sciences industry, including supplier good practice and how to meet the requirements and expectations of regulated customers. Key *GAMP® 5* concepts are illustrated in Figure 1.

Figure 1: ***GAMP® 5*** **key concepts.**



ISPE GAMP® Guide: Records and Data Integrity

Published in 2017, the ISPE *GAMP® Guide: Records and Data Integrity* is a complete and comprehensive reference to records and data integrity (RDI), providing principles and practical guidance on meeting current expectations and requirements for the management of GxP-regulated records and data, ensuring that they are complete, consistent, secure, accurate, and available throughout their life cycle.

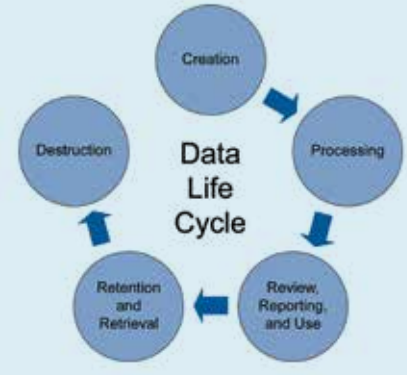
This RDI guide is intended as a stand-alone ISPE GAMP® guide, is aligned with *GAMP® 5,* and has been designed to be used in parallel with *GAMP® 5.* Topics covered in the RDI guide include regulatory focus areas, the data governance framework, the data life cycle (Figure 2), culture and human factors, and the application of quality risk management to data integrity.

The following Good Practice Guides support the *GAMP® Guide: Records and Data Integrity:*

- *GAMP® RDI Good Practice Guide: Data Integrity—Key Concepts* (2018)
- *GAMP® RDI Good Practice Guide: Data Integrity—Manufacturing Records* (2019)
- *GAMP® RDI Good Practice Guide: Data Integrity by Design* (2020)

–Siôn Wyn

Figure 2: Records and data life-cycle model from the ISPE ***GAMP® Guide: Records and Data Integrity.***



discussed in an iSpeak Blog post [9]. The Manufacturing Execution Systems SIG is also working to increase understanding of the implications of implementing systems within the MES domain using applications hosted in the cloud.

Blockchain

Distributed ledger technologies, such as blockchain, are gaining momentum within the life sciences industries, with several use cases being taken into production.

The Blockchain SIG was initiated in 2018 to explore the role of decentralized and distributed networks within pharmaceutical manufacturing, with the primary objectives of learning about the technology by understanding use cases and specific technologies being used and educating stakeholders about these matters.

Periodically, the SIG publishes articles in this magazine. One of these articles, "Blockchain for Pharmaceutical Engineers" (January/February 2019), won an APEX award for technical writing. The article discusses how blockchain technology may disrupt the way data are collected and managed within regulated processes, includes a nontechnical summary of blockchain's features, and discusses blockchain use cases currently being piloted by life sciences companies [10].

The Blockchain SIG is also working in the area of open source software (OSS) in regulated environments. OSS is in mainstream use by life sciences companies and IT service providers because such components can lead to faster systems development, profitable service models, increased use of distributed and decentralized systems (blockchains), and improved social collaboration tools. The work in this area focuses on network protocols and governance models based on user communities.

Software Automation and AI

The pharma industry is increasingly relying on software to automate many functions previously performed by humans. As our computer systems become more integrated and data sets become more robust, computer science is advancing our ability to learn from those data and draw conclusions about what might or should happen next. We are now reaching a point where algorithms are sophisticated enough to begin making decisions for us in the form of artificial intelligence (AI).

The Software Automation and Artificial Intelligence SIG explores the impact of AI on regulated processes, broadly covering the topics of robotic process automation, machine learning, and AI in general. The SIG aims develop a point of view on how to validate and rely upon these technologies in a compliant manner, while managing potential risks to patient safety and product quality. The SIG differentiates between deterministic and nondeterministic systems and focuses on the evolution of self-governing software.

Infrastructure

IT infrastructure management is increasingly achieved using automated deployment, monitoring, and configuration management controls. Traditional approaches to IT infrastructure qualification with manually documented specifications and qualification protocols do not effectively address the need for ongoing operational management of IT infrastructure and continuous verification that controls are operating effectively. The use of traditional documentation-based qualification activities does not ensure the effective operation, security, and performance of IT infrastructure, and does not adequately protect against cybersecurity threats.

CONCLUSION

The GAMP CoP is proud of its many accomplishments over the past three decades and looks forward to contributing to industry growth and innovation for decades to come. For more information, keep checking the ISPE website!

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About the author

Siôn Wyn, Director, Conformity Ltd., is an expert in computer system validation and compliance, data integrity, electronic records and signatures, and international regulations in this field. He assisted the US FDA as a consultant with its reexamination of 21 CFR Part 11 and was a member of the core team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He received the FDA Group Recognition Award for work on Part 11. Siôn is the editor of the *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, co-lead of the *GAMP® Guide: Records and Data Integrity*, and a member of the ISPE GAMP Global Steering Committee, GAMP Editorial Board, and GAMP Europe Steering Committee. An ISPE member since 1995, Siôn received the ISPE Professional Achievement Award, which honors an ISPE member who has made a significant contribution to the pharmaceutical industry, in 2006 and the ISPE UK Fellow Award in 2016.

CLOUD COMPUTING IMPLICATIONS

for Manufacturing Execution Systems

By Paul Irving, Gregory M. Ruklic, and Jonathan Hurle

Cloud computing can be described as networked access and utilization of configurable computing resources such as data and information storage, processing capabilities, applications, and other services on computerized systems provided and/or maintained by a remote organization. As life sciences companies consider the advantages and costs of utilizing cloud services, they first need to invest resources to understand the cloud-based model and implications for applying it in design or migration of the manufacturing execution systems (MES) domain.

The MES domain is defined as all systems with some functionality related to, or otherwise supporting, manufacturing operations [1]. This includes systems such as, but not limited to, enterprise resource planning (ERP), automation, document control (standard operating procedures management), MES software (e.g., recipe and batch management), and laboratory information systems (LIMS).

The impetus for moving to a cloud-based model is to keep various life sciences manufacturing organizations focused on their core businesses while outsourcing computer resources and related activities as necessary to expert providers. For further information on cloud computing standards, refer to the National Institute of Standards Technology's "The NIST Definition of Cloud Computing" [2], and "NIST Cloud Computing Standards Roadmap" [3], which are recommended resources for definitions and other information about cloud computing. For a visual representation of characteristics, service models, and deployment models of cloud computing identified by NIST [2], see Figure 1.

INTRODUCTION TO TECHNOLOGY TYPES

Cloud-based services are typically provided to the end user (your organization) by an external cloud service provider (CSP). Cloud architectures provide a virtualization methodology whereby end users experience computer system–related actions and interfaces running normally in their view regardless of the global CSP location. Dedicated groups within the end user organization may also provide cloud-based services to regional or global facilities without being physically located in those facilities.

This article focuses on three cloud computing service delivery models as defined by NIST [2], each with various advantages and risks for life sciences companies.

- Software as a service (SaaS). The end user accesses applications hosted and managed by the CSP. Data created or utilized by the application reside on the infrastructure belonging to the CSP. Applications are often provided by a CSP; however, applications may be developed by the end user and subsequently hosted and managed by the CSP. The end user does not manage the underlying cloud infrastructure. The end user may define specific configuration parameters of remote applications.
- Platform as a service (PaaS). A CSP hosts a computing platform (hardware, operating system, etc.) accessible to the end user, and the end user installs and manages either their own purchased applications or apps created using tools provided by the CSP. The platform may include network and other connectivity as well as servers and storage devices/systems. The end user does not manage the underlying cloud infrastructure.
- Infrastructure as a service (IaaS). The end user organization typically provides and controls the applications and operating

Figure 1: Visual model of cloud computing.

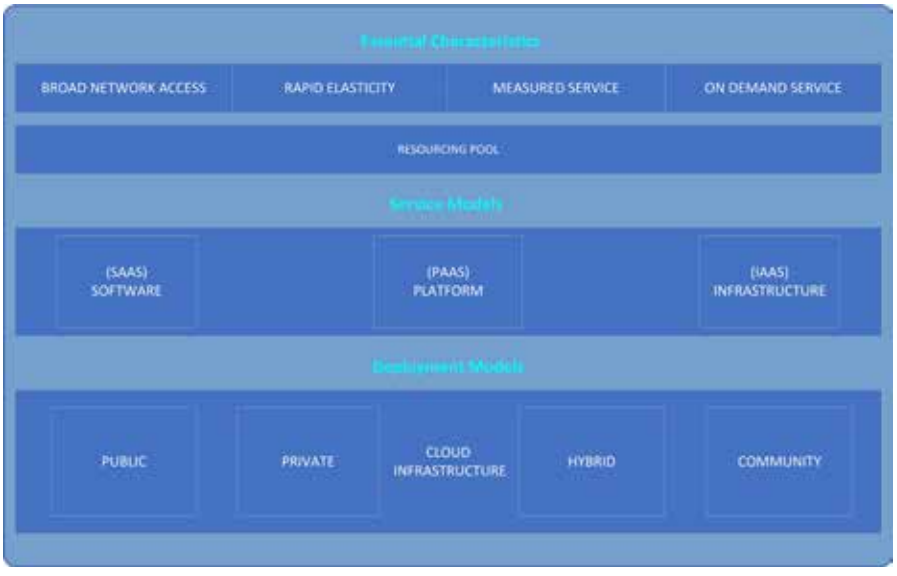
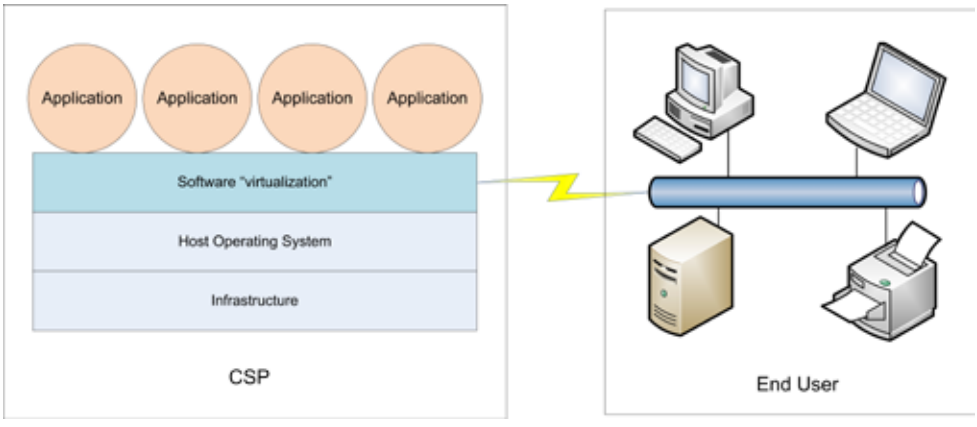


Figure 2: Functional interface overview.



system environments. The CSP is responsible for all underlying computer system architecture, such as networks, servers, processors, and utility or system support software. Depending on company requirements, the end user may control security software such as firewalls, or they may cede control of that software to the CSP.

The three cloud models can be referenced collectively as XaaS. Figure 2 illustrates how XaaS service delivery types can operate in the production environment.

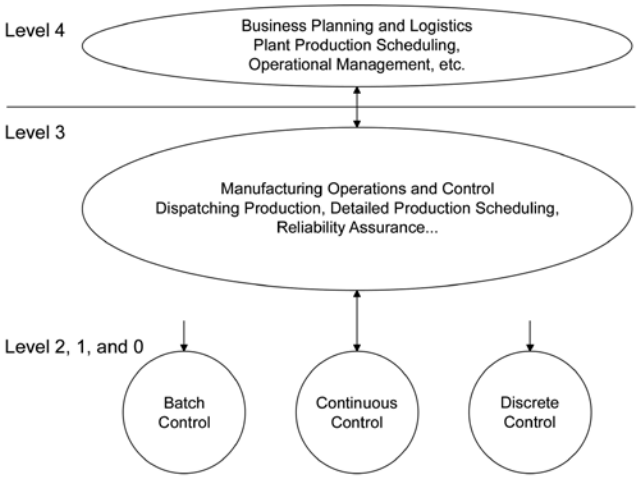
BUSINESS DRIVERS

As part of the ISPE Pharma 4.0™ initiative, companies have opportunities for an increasingly globalized supply chain, improved compatibility of systems and data, and cost optimization. The use of XaaS technologies helps businesses cost effectively and efficiently provide products and services of the highest quality. XaaS can offer the following benefits:

- Reduced internal departmental requirements for designing, installing, and maintaining sophisticated technologies allow internal personnel to be more focused on the actual output of products and services.
- Global deployments can be managed from a single source or a reduced number of sources.
- Instead of managing internal technical environments daily, quality departments can use audits and other periodic oversight to monitor the CSP's quality management system.

To achieve the desired return on investment, companies with diverse suites of products may utilize multiple XaaS delivery

Figure 3: ANSI/ISA-95 functional hierarchy. (Reprinted from *GAMP® Good Practice Guide: Manufacturing Execution Systems* [1].)



models to minimize costs and maximize benefits for each location or process.

The choice of whether to implement IaaS, PaaS, or SaaS should be based on a strategic assessment—a documented examination of the existing company technology processes and performance, as well as the desired future state. This process will be described later in this article.

MES AND THE CLOUD

As noted previously, the overall production environment, or MES domain, is composed of multiple functions provided by various technologies; examples of MES technologies are material management for materials master and inventory data, automation/equipment for processes, recipe management and production records, and quality material testing and status control. From the end user's perspective, a properly vetted single-source XaaS integration of MES functionality may be more cost effective to implement and maintain over time than traditional onsite client-managed systems and infrastructure. The business would typically perform a cost/benefit analysis as part of the strategic assessment to determine the value of using external sources for software and hardware provision or management.

In the design of the MES domain, as noted in *GAMP® Good Practice Guide: Manufacturing Execution Systems* [1], the layers defined by the Purdue Enterprise Reference Architecture incorporated in the ANSI/ISA-95 [4] (IEC 62264 [5]) Enterprise-Control System Integration Standard (see Figure 3) are not tied to any specific hardware or system. Instead, the architecture describes the functionality to be provided by any appropriate computerized system.

In the ISA-95 model, levels 0, 1, and 2 control the execution of defined operations for manufacturing. Level 3 system functions execute the production plan determined at level 4 by the business. The life sciences industry has, for better or worse, assigned whole systems such as ERP or LIMS to only one of the model layers, which has led some professionals within the industry to conclude that the ISA-95 model is not applicable to cloud computing or Pharma 4.0™. However, given the complexity and broad range of functionality in some computerized systems, the ISA-95 model describes an approach whereby functionality residing within any given system is assigned to the appropriate ISA-95 model layer.

For example, some ERP systems contain weigh/dispense functions tied to hardware scales or other automation devices. The business functions of the ERP system reside at the top layer of the ISA model, whereas recipe and dispensing operations are found in lower layers of the model. When considering cloud paradigms, the thought process in modeling and designing the manufacturing environment still basically fits the ISA-95 hierarchical approach.

The life sciences industry is discussing how to apply big data and analytics to level 4 planning systems as well as interactively at level 3, where MES functions such as recipe/batch control, resource management, and production results receive planning information from level 4. These concepts are related to Pharma 4.0™, whereby future big data and analytics will interact with systems at several levels. The details of this industry discussion are beyond the scope of this article; readers are encouraged to use expert resources in planning migrations for MES functionality to the cloud as the evolution of Pharma 4.0™ takes place. One recommended resource with advanced information is "Formalizing ISA-95 Level 3 Control with Smart Manufacturing System Models" published by NIST [6].

In this article, we focus on migrating typical systems functionality and technology in the MES domain to the cloud, although the methods of analysis and planning apply to future paradigms as well. The strategic assessment discussed in this article includes consideration of smart manufacturing, the Internet of Things (IoT), and Pharma 4.0™ to help the end user organization determine the need and methodology to move to those paradigms.

The MES domain of functions can be more complex to analyze for cloud implementations than for business functions alone. GxP production in continuous and live processes often requires data, recipes, quality unit disposition status, and other timely information from electronic production records at any hour from anywhere in global operations. To determine which cloud services models could be best applied to specific facilities and manufacturing processes, the business analyzes production requirements from all manufacturing operations, assessing both current and planned future methodologies. The organization conducts a similar assessment when migrating the existing MES domain to a cloud-based model, with the added constraints that the end user must maintain existing functionality and execute validation activities to demonstrate equivalency of functionality between the existing MES domain and the proposed cloud-based version. A critical decision for the end users is whether to move functionality related to real-time automation and sensor monitoring (including the IoT) to the cloud.

INITIAL STRATEGIC CHALLENGES

Typically, an organization embarking on use of cloud computing methodologies faces the following challenges:

- The organization may lack sufficient cloud experience to develop a cohesive strategy; thus, the goals to be achieved by means of cloud computing are neither clear nor verifiable.
- Critical elements in the introduction process are overlooked due to poor planning or lack of resources. For example, an organization may not fully understand that CSPs themselves often obtain services (e.g., administration or backup of data) from subcontractors; therefore, the organization does not consider how cloud service subcontracting may affect its operations. Subcontractors could increase the risk that personal or proprietary data are leaked in an unauthorized or unintended manner (with possible legal consequences), or a security certificate might be jeopardized because an auditor cannot audit CSP subcontractors. Additionally, business continuity planning and contingencies from the CSP, as well as overall planned integration of cloud services with the client's subcontractors might be inappropriate for the criticality of certain manufacturing operations.

ACCESS CONSIDERATIONS

Systems in the MES domain often require uninterrupted 24/7 operations. Local business operations, especially globally spaced operations, need to access services continuously for time zones different from CSP locations. Access considerations become more complex when CSP applications and local site systems require strict coordination to achieve production with real-time automation systems. Some major considerations are:

- Time stamps for production records, activity logs, and audit trails must be presentable in human-readable format in the context of the local site time of creation/execution for business operations, internal investigations, and regulatory audits.
- Remote data download/upload requirements must be clearly defined and implemented.
- Application interfaces must operate smoothly and efficiently and provide immediate access to production systems, including timely presentation of operator instructions and recording of operator responses.
- Timely coordination of quality unit assessments of activities across systems must be achieved.
- Gating operations must be well defined for activities related to electromechanical systems sequencing and recipe execution, with timely approval steps for production and quality unit personnel.
- Master data for continuous processes must always be available by verified means for reference by real-time downstream systems.
- Updates to master data must be carefully coordinated between end users and CSPs to prevent disruption of operations or unintentional changes to recipes or other processes.
- Inventory usage, creation, and disposition updates across facilities, production lines, and processes must be coordinated.
- Alert/alarm management for production records with timely access to manufacturing and quality unit review/approval must be achievable.
- Timely access must be provided to historical data in formats conforming to regulatory requirements and business analysis.

IT risks related to access of cloud-based systems include:

- Internet/international network disruptions
- Local network disruptions (for the CSP or the end user)
- Inadequate pause and resynchronization methods and algorithms
- Poor data transmission verification
- Data comingling among clients on common servers/systems
- Inadequate disaster recovery elements or lack of coordination between business and provider network facilities and human communications
- Unacceptable provider response times for errors and outages during real-time operations
- Lack of procedures and methods for remote (provider) data correction due to process control upsets coordinated with the business

XAAS MODEL-SPECIFIC CONSIDERATIONS

Each of the XaaS service delivery models may provide a range of risks and benefits for end users [3, 7].

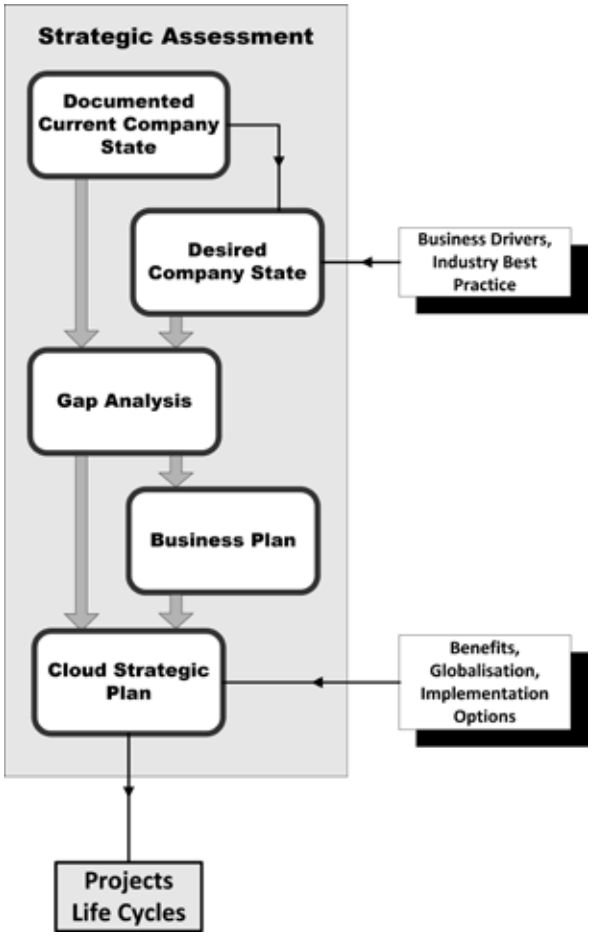
- SaaS. The end user is highly reliant on hosted operational functionality because master, production master, and original data are typically stored in the cloud. SaaS can provide substantial cost savings to end users, but it may require considerable effort to interface with local automation systems.
- PaaS. Standardized applications may not fit end user needs and desires across global sites, languages, and cultures. However, PaaS can reduce verification efforts and software maintenance costs.
- IaaS. Because infrastructure setup/maintenance by end user subcontractor(s) is already a common practice, IaaS is typically the least risky type of XaaS, with relatively modest savings of internal business resources. Thus, it is closer to standard practice and a smaller evolution for many organizations preparing for a cloud model.

CYBERSECURITY AND VULNERABILITIES

Global organizations typically have cybersecurity measures in place, but occasional large data breaches still take place. While moving operations to the cloud has the potential to increase security risks, standard network security systems will mitigate most of them. To provide additional protection either procedurally or technically, consideration should be given to the following:

- Because the IoT seeks to interconnect all digitally connected devices, it improves efficiency but may introduce new security risks.

Figure 4: Strategic assessment for organizations considering CSP services.



- Mobile devices such as smartphones and tablets used on or off site to perform operations must be secured.
- Data encryption is highly effective in preventing data corruption, but it increases network and data demands on systems.
- Employee error or negligence in the end user organization can heighten inherent risks from CSPs and their subcontractors; it is important for organizations to mitigate such risks by vetted hiring, oversight, and training standards and methods.

For further current guidance in this area, the authors recommend guidance from the Cloud Security Alliance, a not-for-profit organization dedicated to defining and raising awareness of best practices to help ensure a secure cloud computing environment [7].

REGULATORY CONSIDERATIONS

The end user is required to validate the MES implementation, including all cloud-based elements (see reference 1 for further information on regulatory requirements). The use of recognized and standardized components as part of the cloud element may reduce the end user's validation burden as the CSP takes on some aspects of validation; however, it does not remove the end user's burden completely, as decided in compliance determination.

The life sciences organization must ensure guidance addressing cloud-based data encryption/decryption, secure data entry and storage, and related issues is appropriate. Data entry will ultimately involve externally supported tools, products, and infrastructure outside of the end user's direct control, and the process must be appropriately recorded, verified, and validated.

It remains the responsibility of the end user organization, based on the target environment, target market, and proposed solution, to identify relevant regulations. Then, the end user must determine how well the proposed XaaS application complies with those regulations, and where deviations exist.

STRATEGIC ASSESSMENT SUMMARY

As mentioned previously, a strategic assessment is essential to efficiently plan and design a cloud-based model implementation or migration. Strategic assessments are defined in detail in the *GAMP® Good Practice Guide: Manufacturing Execution Systems* [1]. Figure 4 outlines the process, and key considerations are outlined in this section.

A project management office with high-level management support is highly recommended to lead the strategic assessment because the MES domain includes cross-departmental functionality. The strategic assessment establishes the current state of the end user organization; target sites and production activities for cloud-based services, with attendant resources, requirements, and constraints; specific goals, benefits, and risks of cloud migration; barriers to implementation; and the basis for a project plan that meets the needs of the company. Such an evaluation should:

- Separate business- and manufacturing-related processes/functions to clearly define requirements.
- Provide information about the overall design. This design should be defined by functions and how they interact, independent of the potential applications; the business should be able to present this type of design to CSPs as high-level requirements.
- Ensure process understanding is accomplished in a documented fashion by the end user for accurate and appropriate systems design and configuration.

The importance of understanding the current and desired states of the end user organization cannot be overstated. There are many CSPs to choose from, and execution of a strategic assessment puts the organization in a position to intelligently evaluate each one and choose the most appropriate vendor. Established CSPs typically are highly skilled at their core services, including global security policies, and they often can provide controls that are more powerful than end user organizations can implement on their own.

A properly vetted cloud service provider provides technical expertise, systems reliability, and business support at high levels on a consistent basis.

The strategic assessment defines the initial and long-term goals by documenting a broad discussion and decisions about the following questions:

- Does the organization need to implement XaaS at one site, regionally, or globally?
- Will implementation be vertical (covering the entire MES domain for the complete site) or partial (addressing certain MES functionalities, processes, or products at one or more sites)?
- What are the organization's timelines and resource constraints?
- How will XaaS impact production schedules?
- What are the costs and benefits of adopting or altering XaaS for MES?
- What are the requirements and scope to implement smart manufacturing (Pharma 4.0™, IoT, etc.)?
- What upgrades or replacements of existing systems would be required if XaaS were adopted?

The strategic assessment answers these questions, and more, to prepare the organization to develop the project plan (or plans) for successful cloud implementations.

Implementation of Pharma 4.0™ models and technologies adds complexity to the strategic assessment. For example, the IoT can involve a vast network of devices feeding information into integrated monitoring and control systems, as well as future decision-making applications based in artificial intelligence. The design of such paradigms and technology must ensure continuing operations and fail-safe conditions because, despite the stellar record of CSPs, no technology can guarantee 100% operational uptime in all circumstances.

Service Provider Selection

A properly vetted CSP provides technical expertise, systems reliability, and business support at high levels on a consistent basis. The following CSP attributes and conditions should be considered and documented in the strategic assessment:

- The vendor's relevant history. CSPs with MES experience or existing clients in the pharma industry are preferable.
- Regulatory expertise. Does the CSP have knowledge and experience in areas relevant to the end user?
- Staffing levels, expertise, and training.
- Evidence of the CSP's financial stability.
- Physical and digital security of the CSP's operations, networks, and data.
- Locations of CSP facilities. Consider factors such as local, national, and regional stability; the locality's network infrastructure; and whether the locality has a qualified workforce.
- Equipment/software to be supplied to the end user.
- Adherence to applicable software and hardware development, implementation, maintenance, and verification best practices, such as those found in *GAMP® 5* guidance,, ASTM International standards, the Information Technology Infrastructure Library, and ISA standards.
- Proof that the CSP's internal auditing capabilities are established and verified.

End User Responsibilities and Capabilities

During the strategic assessment and CSP selection process, it is important to understand that the end user remains ultimately responsible for the following:

- Service level agreements, support models, quality agreements, and escrow concerns
- Performing software and hardware development and verification audits
- Performing regular infrastructure and audit reviews
- Determining the extent and rigor of customer versus service provider maintenance (requirements will vary depending on service type)
- Clear policies and procedures for requirements gathering and communication
- Testing to ensure rigorous data integrity controls

Though the use of CSPs may lessen the end user's risks for IT implementations and maintenance, there are many CSP- and XaaS-related risks to be evaluated. For example, the end user needs to assess the likelihood of widespread area or regional internet/network disruptions beyond its control, and evaluate contingency plans for scenarios such as denial of service attacks with the potential to take a global system offline.

During the strategic assessment, the end user should review and document:

- Pause and resynchronization algorithms for with real-time control systems that must be coordinated between the CSP vendor and the end user organization, and possibly across time zones
- Policies and procedures for external data updates and transmission verification, both from the end user organization to the CSP and from the CSP to the organization
- Typical disaster recovery elements to be applied to the loop between the end user organization's networks and the CSP's networks, and to human communications

- The CSP's response times for errors and outages during real-time operations
- Policies and procedures for remote (CSP) data correction due to process control upsets, including how data correction will be coordinated between the CSP and the end user organization

The end user organization must put in place procedural and, whenever possible, electronic controls to ensure that its cloud-based systems are reliable, with minimal risk for the MES. To maintain the validated state of its MES, the end user's transfer and updates of information to XaaS must be accurate and thoroughly documented. Validation concerns include, but are not limited to the following types of data:

- Critical quality attributes
- Critical process parameters
- Critical aspect information
- Work instructions/recipes
- Metadata
- Audit trails

A CSP is not responsible for misconfigured systems caused by inadequate controls at the end user organization. End user and CSP personnel must be clearly identified and dedicated to the validation process, which must be coordinated within the end user's oversight structure.

CONCLUSION

This introductory article introduces the concepts and considerations of applying cloud-based models to the strategic and implementation phases of an MES for a life sciences organization. The authors encourage readers to learn more by exploring the publications cited in the references.

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A BEGINNER'S GUIDE to IT System Inspection Readiness

By Anders Vidstrup

This article provides a beginner's overview of how organizations can achieve a state of preparedness (readiness) for inspections, with a specific focus on IT systems.

Computerized systems are increasingly integrated into the pharmaceutical business, including within regulated Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Pharmacovigilance Practice (GPvP), and Good Manufacturing Practice (GMP) domains and supporting activities. In turn, regulatory authorities conduct inspections to ensure that life sciences companies, clinical research teams, and other related organizations understand and comply with the regulations established to protect patient safety, product quality, and data integrity. As a result, computerized systems are a key focus area during audits and inspections.

"Computerized systems" is a broad term. In this article, it will be a synonym for process control systems, laboratory equipment with embedded computerized systems, and applications used for GxP purposes in general that are made up of infrastructure, software, supported processes, and "people aspects" such as training and qualification. This definition can relate to solutions from cloud-based services such as infrastructure, platform, and software as a service (IaaS, PaaS, and SaaS) or on-premises solutions.

RESOURCES

Simple questions often have extremely complex answers. It may take time to find the right individuals to provide the appropriate information.

Information on general approaches to inspections of computerized systems and the documentation to support such inspections can be found in:

- ISPE *GAMP® 5 Guide: Compliant GxP Computerized Systems* [1]
- Appendix M6: Inspection Readiness in ISPE *GAMP® Guide: Records and Data Integrity* [2]
- US FDA's "Inspections of Computerized Systems in Drug Processing" [3]
- Section 24 (checklists and memory aids) in the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme's "PIC/S Good Practices for Computerised Systems in Regulated 'GxP' Environments" [4]

General requirements to support inspections of computerized systems can be found in:

- Chapter 7: Outsourced Activities in "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use" [5]
- Annex 11: Computerised Systems in "EudraLex, Volume 4" [6]
- US FDA Compliance Policy Guide, Section 425.200, Computerized Drug Processing; Vendor Responsibility (CPG 7132a.12) [7]
- EMA's "Q&A: Good Clinical Practice (GCP)"[8]

PREPARING FOR INSPECTION

Regulators usually announce inspections ahead of time. Depending on the type of inspection, they may commonly provide between two and six weeks' notice.

Once notice is given, the initial activities are to identify and confirm the scope of the inspection, its location, and the type of inspection (e.g., new drug application [NDA], routine, or a combination thereof). This information will help to identify which IT systems will potentially be covered within the scope and remit of the inspection.

An organization should plan to be inspection-ready at all times, and to support this, it is necessary to have a governance structure led by an inspection steering committee that can coordinate several key activities, including the following:

- Providing an overview of IT systems in scope and the related business processes
- Managing communication setup, planning, and availability of persons to be involved (e.g., system owners, system managers, specialists, and suppliers)
- Handling any necessary gap analysis activities, including corrective actions (refer to the checklist mentioned later in this article)
- Preparing technical setup for inspections (e.g., demonstration of the IT system, tours of facilities including data centers)

Figure 1: Example of a spreadsheet to handle all documentation requests during an inspection.

Inspection/audit:			XXXX		Unit:	XXXX				Date:	XXXX
Track	Priori-tization	Status	Provided date	ID nr.	Requested documentation	Responsible [Init]	QA [Init]	Provided in inspection room (time)	Provided (shown) documentation	Supporting documentation	Copied documentation for the auditor

- Ensuring it will be possible to respond to technical questions and provide evidence at short notice (e.g., test evidence related to backup and restore processes)
- Planning mock inspections if the organization is not accustomed to receiving regulatory inspections
- Planning the process for provision of electronic records in a secure format to the regulator if required during, or after, the inspection

It is the steering committee's responsibility to ensure the organization is well prepared for upcoming inspections. A good way to substantiate this preparedness is to hold mock inspections so that everyone involved becomes familiar with inspection procedures and expectations of the process.

ORGANIZING DURING INSPECTION

During the conduct of the inspection, several activities will require attention. They can be briefly summarized as:

- Collecting, interpreting, distributing, and controlling questions raised by the inspector
- Locating the appropriate documentation and delivering this to the inspector upon request in a timely manner
- Coordinating answers and documentation to the inspector
- Communicating daily with relevant parties to share information on questions raised, answers, and the plan for the next day of the inspection

Inspection and Preparation Rooms

For practical purposes, it is valuable to have at least two dedicated meeting rooms established for the inspection process: one room designated the "inspection room," where the inspector conducts requests plus a room (or two) where the organization's employees may prepare.

The inspection room is where the inspection is hosted and the dialogue between the inspector and relevant employees is conducted. It is recommended to assign an employee to the role of secretary to record requests. For the secretary, the use of an online/real-time tool is useful so individuals supporting the inspection within or outside the inspection room can see the requests. It is vital that those in the preparation room(s) have the ability to follow the progress of the inspection in the inspection room without interrupting the inspector.

During the inspection, one or more support staff members should be assigned to serve as runners. Their responsibilities are to move between the inspection and preparation rooms, coordinating the requests and provision of responses, while also escorting additional people, as required, into the inspection room to respond.

All coordination for the inspection takes place in the preparation room(s). In this space, employees manage all requests for materials and plan and prepare those materials for presentation to the inspector. Runners communicate timelines and status from the preparation room(s) to the host (typically an accountable person from the business and quality management team) in the inspection room. Figure 1 demonstrates how documentation requested for the inspection can be tracked.

Members from the steering committee or management team related to IT systems are represented in the preparation room(s), where they continuously follow the trend of questions and identify potential IT areas/systems within the inspection scope. Based on this surveillance, the prioritization of activities at the system owner/manager level can be determined and communicated. Particular lines of questioning associated with an IT system (for example, access control, backup testing, or data integrity) can also be communicated to those responsible for other in-scope systems during the inspection to allow them to prepare for similar questions and provide responses in a timely manner.

The use of preparation rooms also allows coordination of the flow of people into the inspection room to present materials and respond to questions. Depending on the size of the team and the office setup, a separate room could be used for this purpose. The goal is to limit the number of people within the inspection room at any one time, and to ensure that the movement of people in and out of the room does not disturb the flow of questioning/topics from the inspector's perspective.

It is important that a person experienced with inspections oversees the person answering the inspector's questions and providing supporting documentation. To further support the inspection in the best way, the person answering the inspector's questions is typically expected to:

- Provide a brief description of the working procedures and documents
- Answer questions from the inspector
- Seek clarification for any questions that are not clearly defined or understood

During preparation, it is recommended that attention is focused on the following areas to prevent misunderstandings or errors:

- Ensuring that the documentation presented answers the questions asked
- Ensuring that the result/conclusion is clear from the documentation presented
- Reviewing the documentation to make sure that it can be used: for example, no notes pinpointing faults are attached, all applicable signatures are applied, and the correct document version is presented
- Applying tags (#1, #2, etc.) to longer documents, as appropriate, so the relevant information can be easily located
- Presenting only the information necessary to support the answers to questions raised, while excluding too much or irrelevant documentation
- Ensuring that all documentation is copied, registered, and stamped in line with the organization's documentation policies

When these tasks are satisfactorily completed, the person is "released" as ready to enter the inspection room. Staff in the preparation room(s) will manage this entrance; it is recommended that the person attends the session before their allocated time slot to help them become comfortable with the style of the inspection and the atmosphere in the room.

Case Example

The following is an example of IT systems–related questions provided by an EMA inspector on a GxP application about the organization's handling adverse events, and the related preparation activities.

The inspector's questions are:

1. How do you manage backup?
2. Is the backup qualified?
3. I would like to see the disaster and recovery plans.

Preparation Room Discussion

To address question 1 (How do you manage backup?), staff in the preparation room cover the following issues:

- Are procedures in place internally and at the service provider as well?
- Are all servers included in the backup according to the configuration item list for the application?
- If the backup has failed, do we follow the procedure? How is information provided between the service provider and us?
- What backup method is used?
- What is stated in the agreements (service level agreement/statement of work) between our company and the service provider handling backups?

For the inspector's second question (Is the backup qualified?), key areas for preparation are:

- What version of <product name on backup system> is used?
- Are all the required documents in place (qualification)?
- What has been included in the challenge test supported by the conducted risk assessment?
- What is the split of responsibilities between the backup service provider and the system/application owner?
- Are there any issues with the backup system which we need to be aware of?

For the inspector's third request, about the disaster and recovery plans, the staff in the preparation room review:

- Are procedures in place specifically for the applications?
- What is the split between our procedures and service provider procedures?
- When was disaster and recovery planning last tested?
- What is the process for data recovery?

Inspection Room Strategies

The employees meeting with the inspector provide a high-level explanation that <Name of Service Provider> hosts the backup on servers related to the specific application. Their strategies include:

- Having documentation about daily backup operation procedures ready to show to the inspector
- Providing the name of the backup system
- Explaining that the servers are backed up daily following the standard operating procedure (SOP), which also describes the retention period, and being prepared to present the SOP documents
- Confirming that the backup system is qualified according to the quality management system (QMS) process, and having any relevant reports available to present
- Confirming that backup and restore functionality is a part of qualification

Regarding the inspector's request to see the organization's disaster and recovery plans, the employees explain that the overall disaster and recovery plans for the service provider and central backup system are confidential and may not be disclosed to third parties (a reference to the specific company policy is provided). The employees further explain that the overall plan is implemented by an instruction in both the service provider's QMS and the company's own QMS, and they have the instruction available to show to the inspector.

Finally, to demonstrate that the organization properly conducts backups, the employees are prepared to provide evidence for the previous week's completed backup.

THE CHECKLIST

Based on this author's experience, the regulated company should always be able to answer five basic questions about computerized systems:

Figure 2: Example of a spreadsheet to handle the inventory of computerized systems.

Unique ID	System/Tool/Name	Standard software/Tool name	Department	Division	Local System ID	Version	Vendor/Supplier name	System Owner Dep. No.	System Owner Initials	Administrator Initials	System used by Dep. No(s).	Type: GxP, SOX, Critical, Other	Validated [Yes/No]

1. What does the system do?
2. What are the potential product quality, patient safety, and data integrity aspects of the system?
3. Who has access to the system?
4. What does the system consist of?
5. How do you know the system works as it should/is it fit for intended use?

The checklist in the Appendix (available at ISPE.org/it-systems-checklist) can be used to prepare to answer these questions. It is built upon good practice gained from knowledge of auditing, previous inspections, and guidelines from the authorities. It does not cover all situations. However, if the company can respond "yes" to all questions and individuals are able to practice answers and responses, significant problems are unlikely to occur during the inspection. The checklist is generic and therefore does not take into consideration any local requirements.

SPECIFIC SCENARIOS

The following sections review some scenarios that can be especially challenging during inspection of computerized systems.

Providing an Up-to-Date Inventory

Larger companies should have a dependable enterprise architecture in place to provide an up-to-date inventory of computerized systems when inspected. Some companies have a holistic IT solution that covers all information; other companies have a local inventory list in each department and then consolidate those lists as a part of the inspection-readiness process. Figure 2 illustrates a spreadsheet tool for inventorying computerized systems.

The following data could be stored in a central repository, or system inventory, to support inspections:

- Software/service name and possible vendor(s)
- Software category
- Current version
- Original go-live year
- Criticality
- Life-cycle status
- Level of user access
- Security measures
- Link to user guides
- Agreements/operational level agreements
- System access
- Dependencies' business processes
- Responsibilities
- Interfaces

The process of maintaining the system inventory should be described in an SOP. If those data are not held in a central repository such as a system inventory, a job aid specifying the location and points of contact could be useful.

Inspector Access to Computerized Systems

In the past, it would have been very unusual for an inspector to request direct access to systems. When such requests are made, the host will usually have an experienced system user log on to the system and then the inspector indicates which transactions or data they wish to see. Demonstration of systems should be planned in advance to make sure relevant functionality and related data are shown appropriately.

A significant barrier to inspector access is the need to create an approved user ID and provide the appropriate system training to the inspector. Typically, inspectors should only be granted access to a guest network for administrative purposes. During an inspection, segregation between the internal network and guest network must be possible.

Requests for Electronic Computer Records

During inspections, it is not unusual for an inspector to request an electronic copy of records from the computerized system. Inspectors may also request access to audit trail data, which they then analyze using tools that search for unusual patterns in the audit trail that could hint toward data integrity issues.

When considering such requests, the company should clearly understand what data are requested, in which format records should be provided, and on what media. When providing an electronic copy of a record, it is preferable to use a validated export function in the computerized system. If data are to be extracted from a database or similar system, it might be necessary to make a script to transfer the data. This script must be specified, reviewed,

and tested to make sure it works properly. In all cases, the method for copying electronic data should be documented.

To verify what data are delivered to the inspector, a digital fingerprint on the files should be made. This could be done via an MD5 (message digest algorithm 5) hash code. This is documented together with an electronic copy of the record. In addition, company security protocols (e.g., regarding the use of removable media, virus checking, and data encryption) must also be followed.

Global Multisite System Inspection

Some systems (e.g., enterprise resource planning) might be maintained at the corporate level. If the inspection is at a site level, it is important that the system owner can provide the necessary support to the local site. In general, validation of generic features is done centrally, and specific flows and functions are validated locally. This split should be clearly identified in the validation documentation and associated SOPs. As a part of the planning for inspection, planning participants should determine who will provide what kind of evidence to inspectors. Special attention should be given to SOPs covering how change control for the IT system, risk management, and incidents are managed between the corporate level and site level.

Supplier Involvement

In today's world of cloud-based systems (IaaS, PaaS, and SaaS), much of the essential documentation discussed in this article may only be available from the cloud computing service provider (supplier).

The QMS at the regulated company should include the management of outsourced activities because the regulated company retains ultimate responsibility for the system validation and therefore must ensure processes are in place to ensure the control and review of outsourced activities. The regulated company is responsible for the suitability of computer systems (hardware and software) used in the manufacture, processing, or holding of a drug product.

Basic Recommendations

As a minimum, it is recommended that organizations ensure the following:

- Quality system and audit information relating to suppliers or developers of software and implemented systems/services is made available to inspectors on request.
- The organization has formal quality agreements with all suppliers, and these agreements include clear statements to:
  - Define the system owner's and suppliers' roles in making and maintaining original documents or true copies in accordance with cGMP or other GxP regulations
  - Explain how those records will be made readily available for inspection
  - Indicate that electronic records will be stored in accordance with cGMP or other GxP regulations and will be immediately retrievable during the required record-keeping time frames established in applicable regulations
  - Indicate how suppliers will support inspections both through specialists and documentation
- The organization documents its monitoring and review of the supplier's performance, including the identification and implementation of any required corrective and preventive actions or improvement(s).

Requirements for Clinical Trial Sponsors

Regarding the level of qualification/validation required of a clinical trial sponsor when using an electronic system previously qualified by a supplier, the EMA Q&A for GCP states [8]:

> *The system in question may be a system validated by the supplier, but installed at the sponsor, or a system provided as software-as-a-service (SaaS or cloud solution)....*
>
> *According to ICH E6(R2), sections 5.2.1 and 5.5.3.a, respectively, "the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor" and "the sponsor should ensure and document that the electronic data processing system(s) conforms to the sponsors established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)."*
>
> *According to ICH E6(R2), section 1.65., validation of computerized systems is "a process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system."*

The sponsor may rely on qualification documentation provided by the supplier if the qualification activities performed by the supplier have been assessed as adequate. However, the sponsor may also have to perform additional qualification/validation activities based on a documented risk assessment.

The conditions for a sponsor to use the supplier's qualification documentation include, but are not limited to, the following [8]:

- The sponsor has thorough knowledge of the vendor's quality system and qualification activities, which will usually be obtained through an in-depth assessment/audit.
- An assessment/audit has been performed by qualified staff, with sufficient time spent on the activities and with cooperation from the vendor.
- An assessment/audit has gone sufficiently deep into the activities, and a suitable number of examples for relevant activities has been reviewed (and documented).
- The assessment/audit report determined that the vendor's qualification documentation is satisfactory, or that

shortcomings can be mitigated by the sponsor (e.g., the sponsor is performing part of the qualification).
- When required during a GCP inspection, the qualification documentation is made available to the inspectors in a timely manner, irrespective of whether it is provided by the sponsor, the contract research organization, or the vendor.
- Both the sponsor and the vendor establish full configuration management for qualification and production environments, and establish that the sponsor can fully account for any differences between the vendor's validation environment and the sponsor's production environment; subsequently, the sponsor should justify any differences that are considered insignificant. If this is not done, the qualification effort potentially does not justify the use of the system.
- The sponsor performed an installation qualification/performance qualification if the system depends on trained users.

The EMA Q&A for GCP notes the following about potential pitfalls in contractual relationships with electronic systems vendors in relation to clinical trials [8]:

> *Special consideration should be given on relevant training and quality systems. Experience suggests that vendors accepting tasks regarding electronic systems are frequently knowledgeable about IT systems and sometimes data protection legislation, but not necessarily on ICH E6(R2) requirements, quality systems, etc.*

Vendors must be able to document knowledge on, for example, GCP and compliance. Agreements should state that the clinical trial sponsor can access conduct audits at the vendor site, and that the vendor site agrees to allow inspections by national and international authorities. In addition, agreements need to specify that vendors shall provide the necessary documentation (e.g., qualification documentation prepared by the vendor concerning the system) when requested during a GCP audit/inspection process.

Vendors should have appropriate documentation in place. Any qualification documentation prepared by the vendor concerning the system should be available for inspection.

Furthermore, agreements should stipulate that the vendor will escalate any potential serious breaches to the sponsor in a timely manner. Serious breaches should be defined to include security breaches which the supplier becomes aware of (e.g., by notification from other sponsors using the same system), if the breaches could have any impact on the data integrity, reliability, and robustness, or the safety and rights of the trial subjects.

DATA INTEGRITY

Data integrity is a topic that spans processes and products in the regulated company. Some of the recommendations already mentioned in this article refer to data integrity. In addition, special attention should be given to the following areas.

General Procedures

General procedures focused on data integrity must be in place. Regulated companies should:
- Consider record and data integrity within the context of broader inspection-readiness programs
- Establish and maintain policies and procedures that ensure a constant state of inspection readiness
- Have robust established procedures for all aspects of the system life cycle
- Be prepared for regulatory inspections:
  - Focusing on the management of record and data integrity to verify the adequacy of controls
  - Using a forensic approach that challenges the data integrity of specific records

Accountability

The process owner and system owner are normally accountable for responding to system-specific questions during regulatory inspections. Process owners and system owners should be:
- Knowledgeable about the documentation supporting the implementation, control, maintenance, use, and history of the system
- Able to discuss any technical and procedural controls implemented to support the integrity of the creation, processing, and reporting of records and data
- Able to share information about the requirements and testing of the data integrity relating to technical and procedural controls
- Able to discuss the key computer system documents including requirements for data integrity controls and system security controls

Procedure Monitoring

From an operational point of view, there should be robust monitoring of the system, business, and IT support procedures to ensure that the processes are adequate and are being followed. Areas that should be routinely reviewed as part of monitoring to ensure inspection-readiness include:
- Access control:
  - Access SOPs are in place and being followed.
  - Available user roles are documented and managed by change control.
  - Documentation shows that only authorized and trained people have system access.
  - Evidence shows that access is periodically reviewed (by automated checks where available).
  - Segregation of duties is enforced.
  - Generic accounts are not used for data modification.
  - Backdoor changes requiring IT tools and skills are authorized, verified, and documented.
  - Historic access records are properly retained.
- Backup and disaster recovery:
  - Procedures for backup, restoration, disaster recovery, and record retention are documented and verified.

- Documented evidence shows that records and data are periodically backed up.
- Records retention policies are clearly defined and followed.
- Records and data can only be accessed by authorized users (network and system).
- Archived records are secure and accessible for the retention period.
- Record and data maintenance is done correctly.

Audit trail:

- Use SOP governs the timely recording of data.
- Records are approved/signed only by authorized users.
- Approvals are enforced at specific points in the business process.
- Audit trail review (in accordance with risk) is integrated into the business process.

CONCLUSION

The purpose of inspections is to demonstrate to regulators that the regulated company complies with requirements and implements controls in their QMS with the goals of patient safety, product quality, and data integrity. Inspections are more likely to have a successful outcome when organizations follow recommendations for validating and maintaining computerized systems. Further recommendations and guidance to support planning and preparing for inspections are available from ISPE [1, 2].

Above all, remember the 5Ps: Proper planning prevents poor performance.

ONLINE APPENDIX

To access the inspection checklist mentioned in this article, visit ISPE.org/it-systems-checklist

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DATA SCIENCE FOR PHARMA 4.0™, Drug Development, and Production—Part 2

By Stefan R. Kappeler, Frank Nygaard, Michelangelo Canzoneri, Stacy L. Springs, Jacqueline M. Wolfrum, Richard D. Braatz, Valentin Steinwandter, and Christoph Herwig

This second of a two-part series explores digital transformation and digitalization in the biopharmaceutical industry with information about how data science enables digitalization along the product life cycle. (Part 1 was published in the March-April 2021 issue of *Pharmaceutical Engineering* [1].)

In the biopharmaceutical industry, the entire product life cycle—from the fundamentals of medicine and biological science to research and development, to manufacturing science and bioprocessing validation—is being transformed and even disrupted through the capabilities of data science, digitalization, and the industrial internet of things (IIoT), all of which fall under the umbrella of Industry 4.0. Data-driven innovations can improve the flexibility of production by enabling rapid adjustments of scale and output to reflect sales forecasts, and they allow quick adaptations of product ranges to new market demands based on a profound knowledge of the manufacturing platform.

However, Industry 4.0 features can only succeed in the biopharmaceutical industry if they build upon and improve established concepts. For example, Industry 4.0 should advance defined procedures (such as batch reviews) and corrective and preventive actions (CAPA) management following ICH Q10 principles [2], and it should support the introduction of novel life-cycle management concepts, such as those exemplified in ICH Q12 [3].

In this article, we analyze how data science enables digitalization along the product life cycle. We start with technology transfer, as Part 1 of this series already addressed the general tools relevant to the process development stage. We discuss data science tools relevant to manufacturing and its augmented periphery, such as logistics and the supply chain, as well as new modalities such as advanced therapy medicinal products (ATMPs). Finally, we discuss what is needed to ensure the industry is ready to use these tools effectively, provided they are available.

Figure 1 illustrates how Industry 4.0 enablers, including digitalization, affect the product life cycle, starting with the establishment of a quality target product profile (QTPP) in drug discovery and development. Figure 2 highlights the uses of data science tools throughout the life cycle.

TECHNOLOGY TRANSFER AND PROCESS VALIDATION

A shift of emphasis from flexibility to increased control is inevitable as the development of biopharmaceutical products matures via technology transfer from process development to process validation. Statistical software for design of experiments and multivariate analysis is widely used in the transitions from process development through process characterization to process validation. However, software use is hindered by format incompatibility issues, the complexity of the data sets, responsibility questions, organizational boundaries, and other challenges. Consequently, early research and development data and technology transfer data may not be captured, processed, and stored in a structured manner that would allow them to be used to their full potential.

ICH Q12 outlines how product quality assurance is achieved through established conditions (ECs) for manufacturing and control, which are legally binding information in regulatory applications [3]. Companies should provide supportive information for

Figure 1: Effect of Industry 4.0 enablers on the product life cycle. Upper arrow: Conventional approach. Lower arrow: Extended product life cycle using IIoT enablers. The red elements operate as a feedback loop, with platform knowledge and sales data informing subsequent market analysis and QTPP definition.

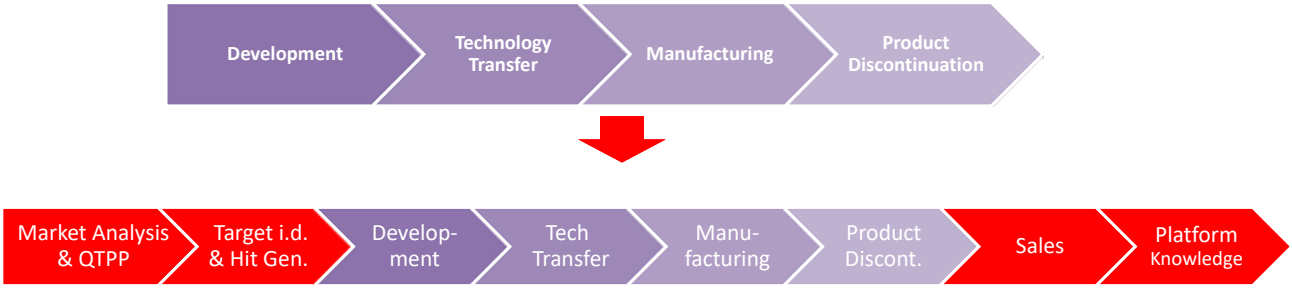
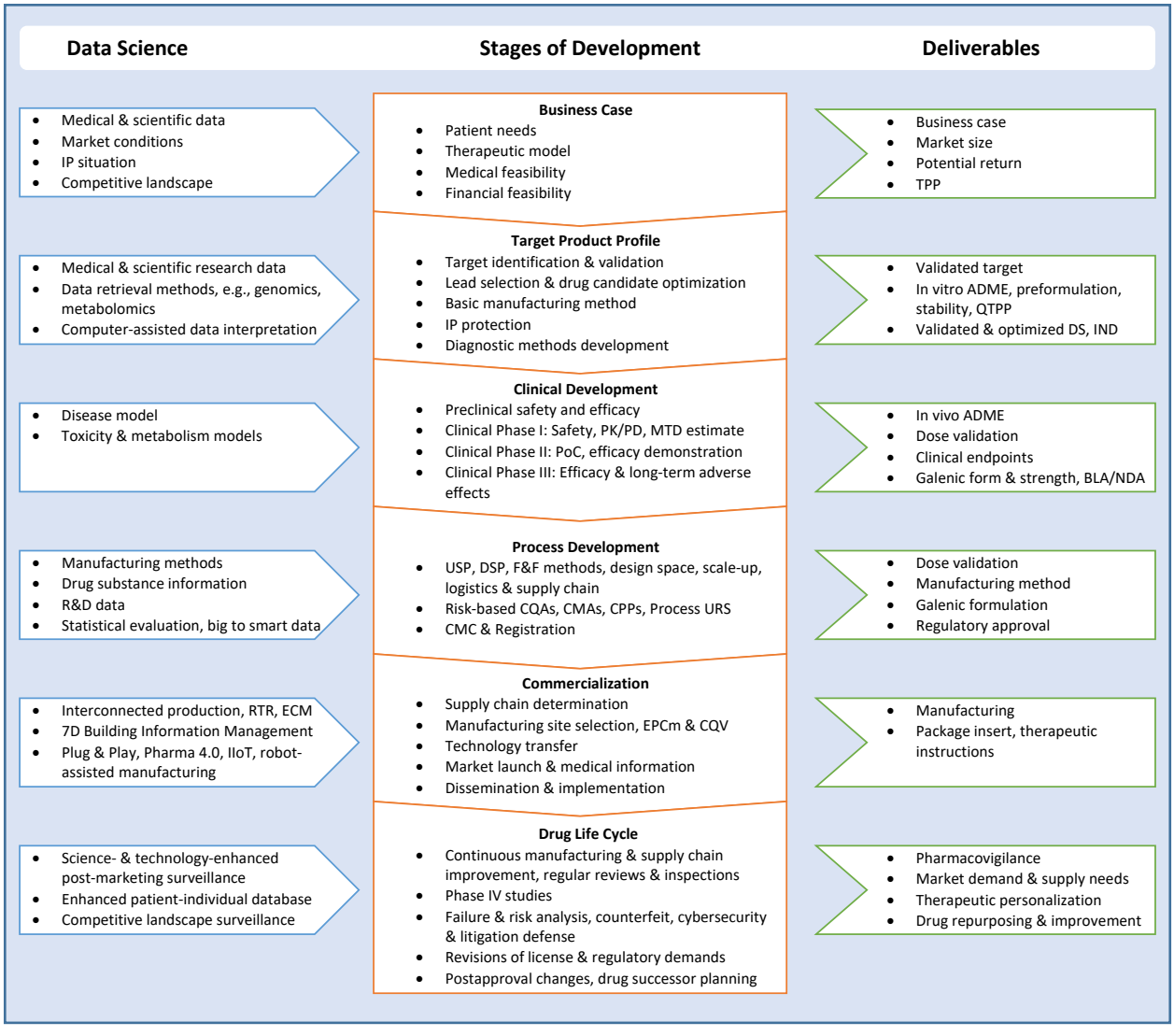


Figure 2: Linkage of data science with activities and outputs of the product life cycle.



ECs in regulatory documentation to justify their selection. In our experience, the biopharmaceutical industry lacks the establishment of an initial design space in practice and its maintenance throughout the life cycle as part of continuous improvement. Provided data integrity is in place, data science can create a holistic production control strategy [2–7] for technology transfer and process validation, and this strategy could be a key enabler for generating information to support selected ECs in regulatory submissions.

In the bioprocessing industry, the appropriate data science methods to generate supportive information for ECs are highly dependent on the product type. Although the bioprocessing industry is generally considered a novel segment of the pharmaceutical industry, there is considerable diversity in the degrees of maturity and complexity among different bioprocesses. This diversity strongly affects how one should implement data science.

Monoclonal antibody (mAb) manufacturing represents, by far, the main bioprocessing class, and it is characterized by a sequence of very similar and relatively well-known process steps. These processes are usually placed into a platform process, which is applicable for different mAb products. This enables manufacturers of mAb products to apply the same knowledge to different products, thus shortening development timelines by, for example:

- Prealigning the sending and receiving units for smooth technology transfers
- Using established equipment scalability
- Establishing platform knowledge to support the control strategy
- Ensuring consistency in the starting materials used throughout the product life cycle

A data science implementation strategy to support these relatively standardized bioprocesses may be empowered using generic tools as the starting points. Those tools include:

- Automated data import via real-time interfaces, API configurations, and file crawlers, as well as linking data lakes with laboratory information management systems (LIMSs), historians, and electronic laboratory notebooks (ELNs)
- Data contextualization between the various data sources and data types, such as aligning time-value pairs with discrete product quality measurement and with features extracted from morphological images

Using these types of data science tools for mAbs allows an immediate return on investment (ROI) in technology transfer and process qualification tasks by supporting risk assessments and mitigations. Also, in the long term, such tools support biological license application (BLA) submissions and continued process verification (CPV) in commercial production. Note that any generic tool will need some level of customization because process and analytical data are currently automatically captured in a variety of formats and often need to be cleaned from noise.

ATMPs represent another class of products within the bioprocessing industry. Recently, an increasing number of ATMPs have received market approval; however, some have subsequently been taken off the market [4]. Unlike mAbs, ATMPs are manufactured by "nonstandard" processes with a high degree of complexity characterized by the following:

- Varying equipment and procedures, even for the same product category
- Limited prior knowledge to ensure smooth technology transfer
- Unavailability of some raw materials and reagents in large-scale amounts or at GMP grade

Data science implementation for ATMPs probably cannot leverage prior knowledge to the extent achieved with mAbs. Customized tools may therefore be required from the start. The short-term ROI from data science implementation in ATMP development may be more limited than in the more standardized mAb manufacturing process. However, the mid- to long-term ROI of data science for ATMPs may be considerable. By capturing all available process and analytical data for ATMPs, data science tools may help investigators detect critical correlations that would not become apparent from conventional data analysis. Thus, data science is likely an enabler for ATMP manufacturing, not despite the complexity of these products, but because of it.

Technology transfers often involve multiple organizations or companies (e.g., contract manufacturing organizations), a range of operational procedures, and even multiple languages. Data science integration may therefore be complex even for well-known, almost commodity, bioprocessing products, such as mAbs. This complexity may be one of the main obstacles in the implementation of a comprehensive data science strategy. Another implementation challenge may be the lack of a dedicated data science representative on the technology transfer team.

A quality agreement between the sending and receiving units defining the responsibilities and operational modes of data sharing is an important priority. Many important relationships between process inputs and outputs have already been established for mAbs. Therefore, data science innovations may be less urgently needed for successful technology transfer and process validation in mAb manufacturing than in the ATMP sector.

LIFE-CYCLE CONSIDERATIONS

Following process validation, manufacturing operations must demonstrate process compliance within established proven acceptable ranges, following isolated process parameter control strategies as well as holistic production control strategies [5]. Demonstrating compliance requires that the ECs be clearly identified as per ICH Q12. Companies therefore need to:

- Demonstrate that the product is continuously within its specifications through CPV;
- Predict that the product will meet specifications through real-time release testing;
- Perform trend analysis and identify batch-to-batch variability, which may occur due to variations in raw material, human

interactions, or equipment aging, and set appropriate actions for preventive maintenance and CAPA (data science is an acknowledged tool for root-cause analysis);
- Manage postcommercialization data regarding sales, regulatory changes, published data, change management; and
- Provide the assembled process knowledge and wisdom obtained for the product in a comprehensible format to the company's product pipeline.

Production Control Strategies

Biopharmaceutical manufacturers need the data gained during process development to be reduced and integrated into a manufacturing environment at production scale. Because this transformation process is highly demanding for biopharmaceutical drugs due to the complexity of process parameters and product characteristics, it should be anticipated from early development. The data science concepts and tools described in Part 1 of this series and the previous sections of this article not only help stakeholders characterize the manufacturing process, specify the relevant critical quality attributes and critical process parameters, and prepare an application dossier and a master batch record, but also are required to design a verifiable, robust, reproducible, and highly intensified manufacturing strategy that will pay off quickly. The current data reduction processes can miss some key information in the technology transfer to commercial production. A more holistic approach to production control based on process and data maps from development to production should help improve the reliability and robustness of the production process greatly. The necessary tools are available and need a regulatory framework for implementation [5].

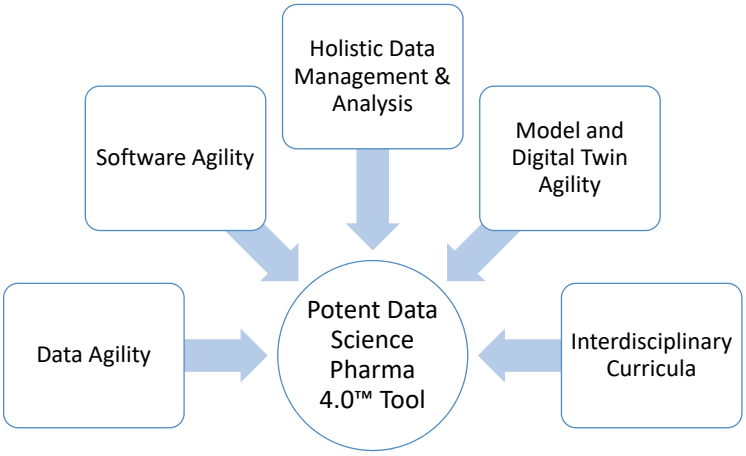
Facility Design

When it comes to designing a production plant, the quality of process simulation for concept validation requires special attention. Results strongly depend on the quality of the underlying data and the simulation model setup; experienced specialists are needed for this work. Data quality must address errors, outlier detection, and, above all, data integrity.

Currently available models depend on extensive data reduction and cannot completely mitigate scale-up risks. A recent and increasingly popular alternative is the scale-out approach, which avoids the scale-up and thereby provides data from late development directly to the market production scale, and vice versa. Starting from a concise process description, a suitable manufacturing environment needs to be designed, accessory processes and systems identified, and the scope and interfaces defined. Plant engineering, construction, and life-cycle management become increasingly reinforced by integrative data platforms with the ability to take in all necessary information from various sources and provide a real-time overview of any aspect of the plant at the push of a button. Highly desirable for engineering and life-cycle plant management are standardized and interchangeable formats being fostered in the Data Exchange in the Process Industry (DEXPI) project. Currently, DEXPI mainly focuses on a common format for the exchange of piping and instrumentation diagrams, and, as mentioned in Part 1 of this series, it is of increasing interest to stakeholders in the process engineering industry.

A good facility design provides for optimal manufacturing conditions based on the information gained in process development. GxP compliance further needs to be ensured throughout the main supply, support, manufacturing, release, and distribution chain. The amount of data generated to guarantee reliability and compliance in manufacturing is huge, and the data require continuous reduction, evaluation, and correlation to maintain safe production and support continuous improvement. Data from several systems are considered to be highly critical [6], and in the United States they require initial validation and compliance with Title 21 CFR Part 11. Automation concepts currently rely on manual configuration of data transfer protocols and are static by design. Therefore, they cannot meet the current needs for flexibility in process flow and scale, support a unified data storage and exchange method, or help with a swift integration of improved processing methods into the manufacturing environment. Here, plug-and-produce concepts are beneficial alternatives: They offer standardized formats for data exchange between the lower and higher functional levels, and they promise both the seamless integration of equipment and systems and the integrity of data by design.

Figure 3: Success factors for the introduction of data science in the biopharmaceutical industry.



However, some systems in the automation landscape (namely, building management, enterprise resource planning, and document management systems) are designed for general purposes, and will continually need manual adaptation for use in a pharmaceutical production environment.

ATMP Manufacturing and Logistics

When a chimeric antigen receptor T cell (CAR-T) therapy needs patient cells as a starting point for drug manufacturing, the process of blood sampling and cell preparation at the hospital has to be documented in a GxP-compliant manner, the integrity of both the transport conditions and the patient's information needs to be ensured, and all those data finally have to be included in the product's batch record. This is a real paradigm shift: ATMP manufacturing must not only attend to product safety and quality aspects, but also protect the integrity and confidentiality of patient information. The procedures established for organ transplants across extended distances and relying on a central database and assisted transport may illustrate the complexity of such concepts, but those procedures are far too expensive for application in ATMP therapies. Given the pressures, ATMP production calls for holistic data acquisition along the therapeutic and manufacturing chain; this approach is already partially applied to the compounding of cytostatic drugs.

Some gene therapeutic concepts have even deeper connections to data science. The possibility of producing an RNA vaccine based on the gene expression profile of a patient's tumor directly links patient information to drug manufacturing. In the manufacture and distribution of this type of product, the patient's identity and clinical data that may be of interest to third parties must be protected. An integrated data safety model consisting of different layers of protection for data safety and integrity for all aspects should be implemented. Starting with a system that is validated according to *GAMP® 5* [7] for all critical parts of the diagnostic and manufacturing chain, data integrity must be ensured by the system operations that control the validated state. A third layer of data integrity should be set up for the complete IT management system involved, including, for example, hosted services. Finally, a concept should be in place to ensure cybersecurity throughout the data chain. For these reasons, digitalization and data integrity shall be seen as requirements for data science.

Another consideration is that the drug manufacturer could possibly use a scientific data model to intervene directly in the therapeutic strategy chosen for a patient. Data science may thus not only enable progress in drug manufacturing, but also enhance therapeutic success. Detailed therapeutic data may further return from the patient's hospital to the drug license owner and improve the data model, with implications for both the therapeutic strategy and the manufacturing process.

HOLISTIC DATA SCIENCE CONCEPT

Industry 4.0 involves the integration of many individual tools. Some data science tools already exist and are in use. However, the individual data science tools have no Pharma 4.0™ relevance unless they are integrated into a holistic data science concept.

Several levels of integration are needed to turn individual data science tools into a powerful Pharma 4.0™ environment (Figure 3). Integration of such tools needs to be flexible by design because the outcome should be a flexible manufacturing platform for multiple products and include a product life-cycle approach. The following are key priorities:

- Software agility: We propose DevOps techniques and a DevOps mindset, as an agile approach, without gigantic deployment, test, or validation overheads. Although DevOps

applications are currently successful, especially for software-as-a-service (SaaS) deployment, DevOps is not yet fully established for IT/operational technology (OT) environments in pharmaceutical companies (see Part 1 of this series).

- Data agility: SaaS cloud solutions will be the future basis for data and knowledge exchange, although cybersecurity concerns must first be solved technically and at the political level. Moreover, we are convinced that SaaS tools will provide the agility required for exchanging data as well as model and digital twin life-cycle management.
- Holistic data management and data analysis: Plug-and-produce solutions, as exemplified in the Pharma 4.0™ Special Interest Group (SIG) initiatives, include standardized data interfaces and consistent data models. Data availability, however, is not sufficient. We also need the ability to holistically analyze different data sources and integrate time-value data sets, spectra, images, ELNs, LIMSs, and manufacturing execution system data—these are being targeted in the Pharma 4.0™ SIG Process (Data) Maps, Critical Thinking work group.
- Model and digital twin agility: To ensure that data models and digital twins can be adapted along the life cycle and continuously deployed in a GxP environment, the industry needs a flexible, but still validatable, environment for capturing and deploying knowledge. This environment may include artificial intelligence and machine learning, as well as hybrid solutions developed for all kinds of scenarios. Therefore, we need validated workflows for automated model development and digital twin deployment, including integrated model maintenance, model management, and fault detection algorithms [8, 9]. This should be an extension of the *GAMP® 5* guidance [7].
- Interdisciplinary teams: Numerous data scientists will be required to run the facilities of the future. Standardization of workforce development should help ensure that expectations for training and proficiency are uniform across the industry. Agreement on standard curricula and assessment measures would facilitate this. Initiatives should be launched at universities and governmental organizations but should also involve industry training centers.

CONCLUSION

Digitalization in the bioprocessing industry is advanced by focusing on knowledge and integrating the complete spectrum of data science applications into the product life cycle. The industry needs life-cycle solutions, such as feedback loops in CPV, for knowledge management. The data science framework for these solutions is already set, but we need to set up business process workflows according to ICH Q10 guidance, automate PCS workflows, and agree on core plots for trending of regular manufacturing and CPV solutions. We have to "live" ICH Q12, facilitated by data science tools.

The main obstacle to achieving this goal is convincing all industry stakeholders—individuals, teams, groups, departments, business units, management, leadership, and C-level executives—of the benefits of making value out of data. Google and Facebook may serve here as well-known examples of companies that have translated data into value.

The industry urgently needs to invest in interdisciplinary curricula as a midterm strategy. And those of us who are data science–trained engineers are obligated to show the benefits of integrated tools and workflows and explain what the industry essentially needs throughout the product life cycle.

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Valentin Steinwandter currently leads the inCyght software group at Werum (previously named Exputec). The software allows use of high amounts of biotechnological process data from development and manufacturing by combining data engineering, data science, and process knowledge into an integrated software framework. After he finished his MSc in biotechnology (2015), he earned his PhD for the development of data science workflows for biopharma, focusing on data integrity, data accessibility, and data complexity (2019).

Christoph Herwig, Bioprocess Engineer from RWTH Aachen, worked in industry in the design and commissioning of large chemical facilities prior to entering interdisciplinary PhD studies at EPFL, Switzerland, in bioprocess identification. Subsequently, he positioned himself at the interface between bioprocess development and facility design in the biopharmaceutical industry. Since 2008, he has been a Professor of Biochemical Engineering at the Vienna University of Technology. His research focuses on the development of data science methods for integrated and efficient bioprocess development along PAT and QbD principles for biopharmaceuticals. In 2013, he founded the company Exputec addressing data science solutions for the biopharma life cycle. Christoph has been an ISPE member since 2002.

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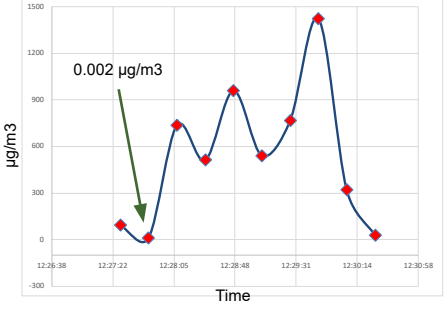

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An Inside Look at ISPE's First Virtual International Hackathon

By John Clarke

ISPE Emerging Leaders (ELs) held the first fully virtual International Hackathon in February. Fifty-one participants from over 22 countries encountered real-life challenges with working remotely and across time zones. Innovation was key to generating solutions to the problem statement provided by Bayer. This article shares insights from some of the "hackers" who participated in the event about what it was like to be part of the virtual Hackathon experience.

Input from four participants during the time they were at work on the Hackathon is included.

Prudence Edwards is an engineering student at the University of Queensland, Australia, majoring in chemical and biological engineering. She is completing a dual degree program in Marseille, France, at Ecole Centrale de Marseille and will graduate in 2022.

Noella Masengesho is in her senior year at Iowa State University. She is studying chemical sciences and intends to work in the pharmaceutical industry.

Andrew Svetozarov is a student at the Peoples' Friendship University of Russia, studying pharmacy and pharmaceutical technology.

Moneem Ahmed is in his last year of undergraduate studies in chemical engineering at the National University of Singapore. Moneem was the team leader for the 2020 ISPE Hackathon winning team representing the ISPE Singapore Affiliate, tackling a data acquisition and data integrity problem case.

How are you involved with ISPE?

Prudence: I have been a student member since 2018 and have been increasingly involved with the organization since relocating to Europe. I have particularly enjoyed taking advantage of the networking opportunities within the ISPE community, getting to

know people in diverse roles from a variety of backgrounds across the world.

Noella: I am currently a member of ISPE and Women In Pharma® (WIP). I joined during the summer of 2020. I do volunteer work with the WIP forum.

Andrew: I recently became an ISPE member to sign up for the Hackathon. I'm already looking forward to other great events and seminars.

Moneem: I joined last year as a student member of the Singapore Affiliate. Initially, I was attending ISPE events such as Technical Tuesdays, where industry professionals discuss pharma-related topics. I hope to be more involved with activities in ISPE in the future and am looking to being part of the task team for the next ISPE Singapore Hackathon in 2021.

Why did you sign up for the Hackathon?

Prudence: I thought it would be an excellent opportunity to familiarize myself with current issues and working practices in the pharmaceutical industry. It was certainly daunting knowing that I would be working with considerably more experienced professionals, but I was keen to challenge myself to contribute to the team as much as possible.

Noella: I got interested because I knew that it would be a great opportunity for me to educate myself by working on this project I had not worked on before. I love meeting new people, so I knew that by participating in the Hackathon, I would meet other ELs from all over the world to learn new skills from collaborating with them and making new friends.

Andrew: I was introduced to the event by the director of my university laboratory, who is involved with ISPE. He highly recommended that I take part in the Hackathon and I'm very grateful to him for this advice.

Moneem: I have participated in hackathons before, and with each one, I learn something new. I love working with people to come up with new ideas and trying to solve problems. It's really fascinating to see the creativity and ingenuity of others. Being able to harness these to come up with an innovative solution is a process I find incredibly fulfilling.

What are you enjoying most about the Hackathon?

Prudence: Being the team leader has been an incredibly rewarding opportunity. It has been a test of my leadership skills: working collaboratively with industry professionals throughout Europe, overcoming language barriers, and juggling the Hackathon with day-to-day commitments. Our team and coaches have been very supportive, which has made the whole experience really enjoyable. I have most appreciated everyone's willingness to share their own experiences, working together to refine our solution for the best result possible.

Noella: The thing I enjoy most is the Friday social. I get to see other ELs, our coaches, and mentors in a relaxed, casual setting with our preferred drink, depending on our time zone. I am always looking forward to Friday socials.

Andrew: People, of course. It is a great pleasure to meet so many skilled and vigorous people from different countries.

Moneem: My favorite part of this Hackathon is its international nature. I really like that it provides a platform for us to work with and learn from peers and professionals all around the world. Hearing and seeing the different perspectives from each member's and coach's unique background was particularly interesting for me! I was able to learn how to think differently in order to tackle a challenge from multiple angles.

How does the topic relate to your coursework/job?

Prudence: It has been a long-term goal of mine to work in the pharmaceutical industry. I chose the dual major in chemical and biological engineering because the idea of working at the intersection of healthcare and engineering has always really appealed to me. Since then, through opportunities both in Australia and in France, I've discovered the field of biopharmaceutical production, which is where I plan to work after graduation. I hope to undertake a six-month internship in the industry later this year to gain further experience as well.

Noella: When I saw the problem statement that we must solve in this Hackathon, I got a little excited because it is similar to a xo-op/internship I did with the Renewable Energy Group (REG) in Ames, Iowa. As a student preparing myself to work in pharmaceutical engineering, I believe that working on this project will give me an idea of what to expect once I start working in the industry.

Andrew: I'm going to work in pharmaceutical manufacturing, so it is an excellent occasion to enlarge my knowledge in this field.

Moneem: In my major, I have taken classes in pharmaceutical manufacturing. In addition, I am also taking a management of technology minor. This topic is essentially an intersection of both since we look into technology innovations and disruptions in the pharmaceutical industry and how companies can adapt to the digital revolution we are seeing.

What are the challenges and benefits of participating in the event virtually?

Prudence: After the experience of the last 12 months, we were certainly well prepared for a virtual competition! In my opinion, the benefits of the virtual format have significantly outweighed the challenges. Slack was a highly effective tool for coordination,

and it was very straightforward to hold team meetings over Zoom. The three-week timeline did present its challenges in keeping everyone motivated and involved throughout, but with the complex problem statement, there was plenty of work to be done! Most important, the key benefit of a virtual competition was making this event accessible for participants all over the world, particularly those who would not otherwise have had the chance to be involved.

Noella: Working from home is challenging. Sometimes the motivation is completely lacking, but keeping in mind that the end goal will be rewarding helps me stay focused. Virtual meetings with people from different corners of the world can also be challenging because we have different time zones and it is hard to have everyone meet at once. But virtual events have made networking very easy.

Andrew: Virtual events offer an opportunity to involve a larger number of people. It is a huge benefit also to work from home. But it's difficult sometimes to deal with time zones. This "time shift" can be a cause of misunderstanding in a team.

Moneem: The benefits of having this event virtually is that we can fit working on the problem into our schedules much more easily and it allows people who otherwise would not have time to physically travel to the host city to participate. On the other hand, I do miss the face-to-face interaction, which I feel makes discussion and ideation easier, and it's nice to have that human connection, as opposed to seeing a face on a screen.

John Clarke is a Process Lead with Pfizer in Dublin, Ireland, and the 2020–2021 ISPE International Emerging Leaders Chair. He has been an ISPE member since 2014.

All team videos and judging for the 2021 ISPE International Hackathon are available on the ISPE website:

ISPE.org/membership/emerging-leader

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New Edition of Good Practice Guide on Maintenance Is Available

Maintenance can impact both the quality of products and the compliance of pharmaceutical processes, and maintenance programs have long been recognized as critical to the success of the operations they support.

The *ISPE Good Practice Guide: Maintenance*, Second Edition, can be used as a tool for the development, implementation, and execution of maintenance programs. It focuses on achieving cost-effective compliance while describing current established practices. This edition reflects alignment with the ICH Q9 risk-based approach with respect to maintenance and the industry as a whole.

"Since the first edition of the Guide was published, new and more efficient maintenance practices, trends, and technologies have been developed, while at the same time, the ICH Q9 risk-based approach has been adopted worldwide," said Guide Co-lead Constantino Rodriguez, Director of Engineering, Catalent Cell & Gene Therapy.

Guide Co-lead Peniel Ortega, Managing Director, Pharm Allies, added, "In the second edition, we seek to provide guidance on the latest trends in maintenance programs, recommend flexible standard practices that can be applied globally, and offer suggestions to control the escalation of non-value-generating requirements and costs."

The Guide is focused on maintenance in GMP areas and provides a practical and consistent interpretation of the necessary elements of a pharmaceutical maintenance program. Other updates to this edition include consolidating basic and good practice categories, adding clarification on terminology for users, and updating examples.

To order your copy of the *ISPE Good Practice Guide: Maintenance*, Second Edition, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Editorial Assistant

MEET THE ISPE STAFF

KIRSTEN MILLER

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Kirsten Miller, Continuing Education Program Manager, Program Development, in the Continuing Education department.

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

My primary responsibility is managing program design, development, and delivery within an established business plan and timelines. It is crucial to engage, collaborate, and cooperate with industry professionals, regulators, colleagues, vendors, and other partners daily to successfully execute these programs each year.

Communication is key—hundreds of emails, conference calls, calendar appointments, and task reminders to planning committee members, speakers, and session leaders, all of whom have volunteered their time and expertise to ISPE.

What do you love about your job?

My colleagues and I have such great respect for each other, and the volunteers are wonderful, smart, interesting people. I am passionate about professional education and lifelong learning, and it is very satisfying to provide educational opportunities to the industry with valuable, relevant material, developed by extraordinary professionals.

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

I like spending time with family. I have two teenage sons and a 1-year-old golden retriever, Hemingway. I enjoy paddleboarding with my son, "taste-testing" some local brews, attending a concert-in-the-park event, or practicing yoga. I have family in Sarasota, and we visit as much as possible.

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ANALYZING SYSTEM PERFORMANCE

Through Process Instrumentation Data

By Albert Dyrness, PE, Andrew Lamore, and Ravi Shankar

What if the reliability of a system could be improved by accessing the standard data provided with modern process instrumentation? These data, accessed from existing instrumentation, can be used to analyze the fitness of processes, equipment, and instruments; better understand processes; support discrepancy investigations; and provide a data-driven basis for the timing of maintenance and calibration. Most instruments in a modern biopharmaceutical manufacturing facility can provide this type of information; this article covers a few particularly illustrative examples in detail.

Biopharmaceutical manufacturers rely on process instrumentation to measure and record key and critical process parameters, which are often the basis for regulatory licensure. Risk control strategies include the use and interpretation of these instrumentation data to ensure compliance. For GMP systems, any data management and usage must comply with *GAMP® 5* guidelines [1], ensuring data reliability and integrity.

Process failure detection in system design is critical to reducing the overall risk to the patient and to improve process reliability. The design of process failure detection can be fortified through redundancy, which is typically accomplished through the addition of redundant instrumentation [2]. However, it is also possible to create redundancy by correlating existing data from process instruments that are already part of a unit operation.

Most unit operations include multiple instruments to monitor and control critical process parameters. Many individual measurements within a unit operation can be correlated to provide redundancy without additional instrumentation. The rapid development of instrumentation in recent years has resulted in standard instrumentation that has the inherent capability to not only measure the primary process parameter but also produce additional process parameters and other valuable information available to the user.

CORRELATING PROCESS VARIABLES IN UNIT OPERATIONS

The idea of correlating two or more independent process variables to establish the process conditions is not new. Dalton's law states that the sum of the partial pressures is equal to the total pressure. In other words, when noncondensable gases are present in saturated steam, the total pressure indicated will be higher than the corresponding saturated steam pressure.

This is the basis for a typical "air-in-chamber" alarm on standard automated steam sterilizers; the alarm signals when a pressure measurement does not equal the saturated steam pressure at the corresponding temperature. This alarm is critical in a sterilization unit operation, as the presence of noncondensable gases can significantly reduce the efficacy of moist heat sterilization. The following are examples of unit operations used in bioprocessing where correlations among independent process parameters can be used to better understand the state of the process.

CLEAN-IN-PLACE UNIT OPERATION

One critical parameter during a clean-in-place (CIP) process is flow rate. In addition to a flow meter, most CIP systems include a pump discharge pressure transmitter, as shown in Figure 1.

For a centrifugal pump with a known pump speed, the pump curve and affinity laws can be used to draw a direct correlation among flow rate, pressure, and pump speed (the latter is often inferred from the output of a frequency-controlled variable speed drive). Trending and interpreting all three parameters can provide valuable information regarding any changes to the system due to wear, damage, or instrument degradation.

Another critical parameter for a CIP unit operation is chemical concentration. The concentration of common cleaning chemicals, such as sodium hydroxide and phosphoric acid, can be determined by their conductivity at a given temperature, which is often inferred via a reading from a temperature-compensated conductivity instrument. A modern conductivity sensor can accurately measure both the chemical wash and water for injection (WFI) rinse process steps—even though they are orders of magnitude apart—by using a single probe 4-pole conductivity sensor.

The actual chemical concentration is determined by the combination of circuit volume, CIP tank level, and actual volume of chemical quantity dosed. Chemical dosing control systems independently deliver a specific quantity of concentrated cleaning chemicals to the CIP system in one of two ways: by calculating the "pump-on" time or by calculating the number of pulses given to the pump.

Both the steady-state conductivity and the dosing quantity can be correlated. The variance between these established correlations is an indication of a change to the system performance, or a change in the repeatability or accuracy of the associated instrumentation.

CHROMATOGRAPHIC UNIT OPERATION

Creating redundancy by developing correlations between independent parameters is also applicable to chromatographic unit operations. Precolumn conductivity is used in chromatography to monitor chemical concentration during inline dilution. An inline flow cell assembly that integrates pH, conductivity, and ultraviolet measurements with a single transmitter can be used to reduce holdup volume. In addition to the conductivity meter, chromatography systems are generally equipped with flow meters (one for WFI and one for the concentrated buffer), as shown in Figure 2.

Even though the pump speed ratio may be controlled by the resulting conductivity measurement, a change in the ratio from the established value will indicate whether the supplied buffer concentration has changed or whether the instrumentation or pump performance is starting to degrade.

Sometimes redundancy exists, but only for specific points in a unit operation. During a typical chromatographic process, there will be points where the conductivity of the supplied buffer does not change as it flows through the column. These points present an ideal opportunity to record and compare the pre- and postcolumn conductivity as a health check on the conductivity probes.

Sometimes the data exist but a calculation is required to evaluate the effectiveness of a unit operation. It is standard practice to perform an asymmetry test to assess the column integrity after packing and prior to use. Introducing a narrow pulse of a known solution into a column (see Figure 3a) will result in an uneven spread due to axial dispersion as the solution exits the column.

Figure 1: Simplified CIP skid system.

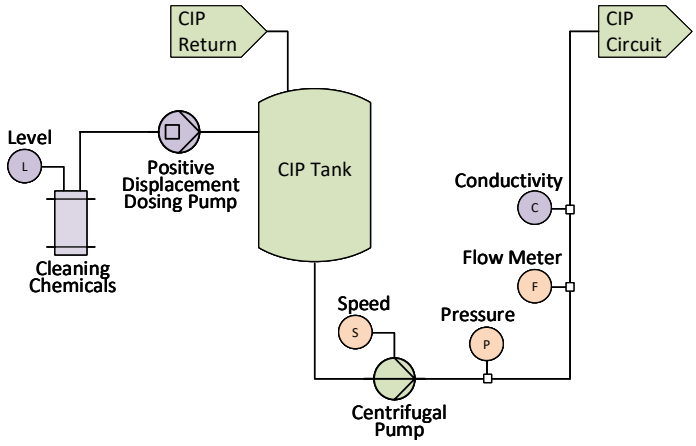


Figure 2: Simplified chromatography skid system.

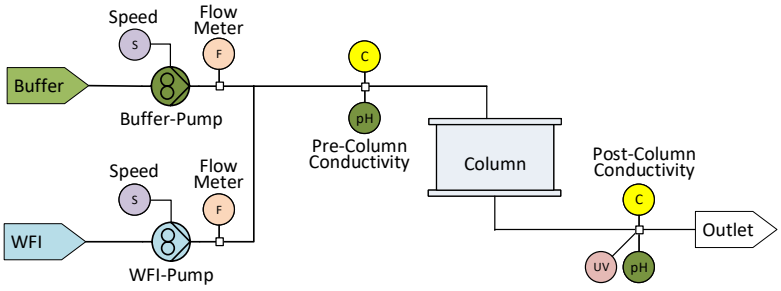


Figure 3: Impulse trace versus step change trace in evaluating asymmetry.

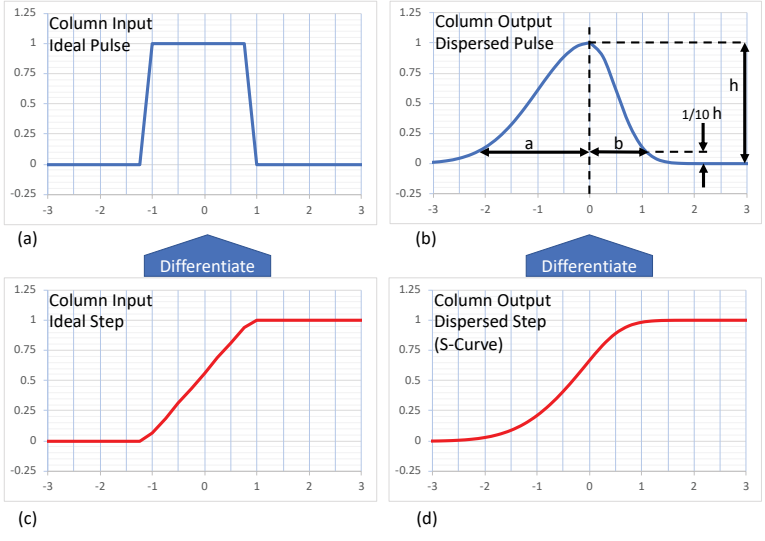
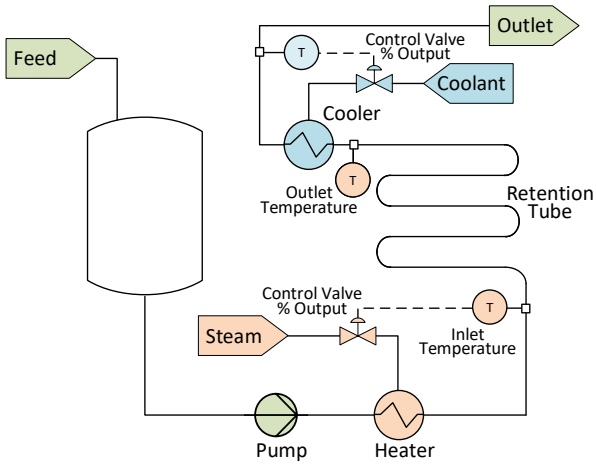


Figure 4: Simplified HTST skid system.



The uneven spread is characterized by the asymmetry, As = a/b, as shown Figure 3c.

Although the typical chromatographic recipe does not include pulses, it does include step changes in buffers that run through the column, and these buffers often have different conductivities. The sharp step, as seen by the change in buffer conductivity (Figure 3b), will leave the column in an S-shaped curve—sometimes referred to as a frontal curve [3]—due to the same axial dispersion observed in the asymmetry test shown in Figure 3d. The area under the curve of the dispersed pulse also results in the S-curve [3]. So, by differentiating the S-curve (Figure 3c), a dispersed pulse can be calculated, from which the asymmetry can be estimated, as shown in Figure 3b. This calculation allows the column integrity to be confirmed during and between batches, providing a real-time assessment of the column integrity. The data are readily available from those already typically used in a standard low-pressure liquid-chromatographic unit operation.

HIGH-TEMPERATURE-SHORT-TIME UNIT OPERATION

A critical parameter during a high-temperature-short-time (HTST), or pasteurization, unit operation is the temperature in the retention tube. Most HTST systems monitor both inlet temperature and outlet temperature of the retention tube (see Figure 4). Except for external heat loss, these two temperatures should be identical, as retention tubes are insulated sufficiently to maintain a nearly constant temperature. During steady-state operation, the difference between the inlet and outlet temperature, if any, should be the same over time, and any change to this difference could be an indication of instrument degradation. In these situations, if one instrument is found to be outside the established calibration tolerance, the second instrument is then relied upon to access any resulting discrepancies. Through continuous monitoring and comparison, predictions can be made about the timing of the next calibration of the temperature instrument(s). This approach puts the calibration program on a data-driven schedule instead of requiring a rigid, fixed schedule, which could lead to premature or wholly unnecessary calibration.

Another good example for the HTST unit operation is an open-loop control strategy versus a closed-loop one. Typically, the heating and cooling of an HTST system are controlled by modulating temperature control valves. During steady-state operation (constant flow conditions), the temperature control valve stem position should remain within a narrow range, unless the feed product temperature varies significantly. Even so, the energy required to raise or lower product temperature is directly related to the position of the temperature control valve. Monitoring the temperature control valve position as a closed-loop control circuit can provide an early indication of changes to the heat exchanger performance or potential fouling. Over time, if the control valve positions are then historicized, these data can provide an indication of the system performance—even when all the critical process parameters are being met.

SMART INSTRUMENTS

In this article, the term "smart instruments" does not refer to the internet of things. Rather, it is used to describe instruments that have a level of sophistication that allows for detecting process conditions well beyond the process parameter of interest. One of the simplest types of instrument in the smart instrument class is a conductivity meter with integrated direct temperature compensation, as referenced in the previous CIP unit operation example. This instrument measures an additional process parameter (temperature) as well as the parameter of interest (conductivity). Although operators do not typically rely upon the conductivity instrument as a replacement for a resistive temperature device (RTD), the temperature measured by the conductivity instrument can provide a redundant measurement of process fluid temperature for a specific unit operation.

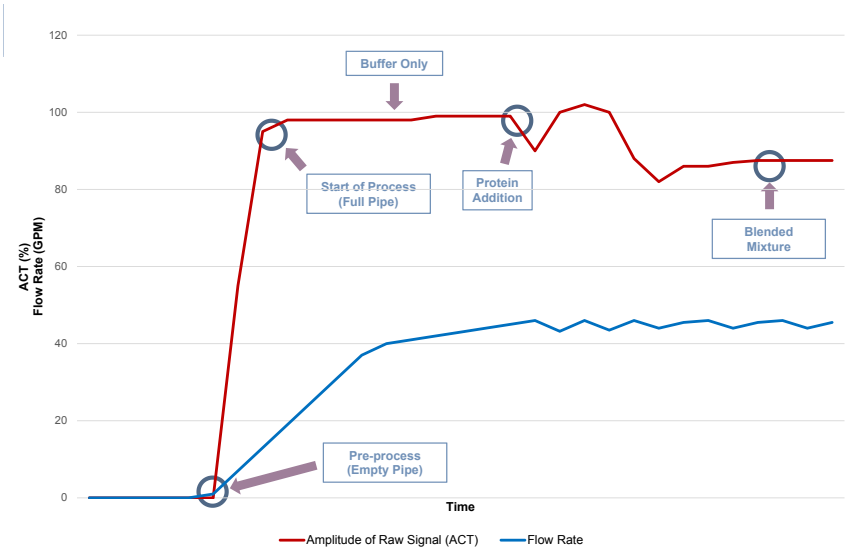
The following are other examples of modern process instrumentation that have a similar level of sophistication and can provide additional data in a similar way.

Smart Liquid Flow Meter

Today's modern smart liquid flow meters provide much more than the process parameter of interest (flow rate), including instantaneous mass and volumetric flow rates, totalized mass flow, density (specific gravity), viscosity, turbidity, flow turbulence, temperature, amplitude and speed of raw signal, percentage of gas entrainment, gas bubble size, concentration of a known liquid, deviation from original calibration, and out-of-specification flags. Accessing these additional parameters only requires establishing the input/output (I/O) communication from the instrument and the control system and then determining whether it is repeating (cyclic) or on-demand/on-event (acyclic).

One example of a smart liquid flow meter application concerns the timing between bowl discharge operations of a disk stack centrifuge, which depends on the time it takes to load the bowl. A strong indication of bowl loading is supernatant turbidity. Using a

Figure 5: Contextual data for an ultrafiltration process.



smart liquid flow meter, the turbidity can be monitored and used to establish the timing of bowl discharges.

The smart liquid flow meter can also be used to instantaneously differentiate between two fluids when monitoring the retentate—or permeate—of an ultrafiltration process, as illustrated in Figure 5. Deviations in the flow instrument's raw signal amplitude and speed, in addition to the expected volumetric flow rate, can help determine whether the process fluid contains protein in suspension or only buffer. These data can then be interpreted to identify the condition as abnormal (e.g., a filter membrane failure when there is protein present in the permeate outlet) or normal.

Sensor Health

Many of today's smart instruments have the ability to self-diagnose and perform instrument self-checks. For example, pressure transmitters can self-diagnose electrical loop integrity and process connection integrity [4]. Smart instruments also often include internal diagnostics. The process instrument parameter verification is a method of "confirming" that a predetermined condition is fulfilled and the instrument meets the intended output based on the manufacturer's specifications. This differs from a standard calibration check in which the instrument output is verified against a reference standard.

Smart liquid flow instruments also provide other diagnostic information as standard: the tag/P&ID number; hours of operation; manufacturing date and firmware version; internal diagnostics; buildup on, coating of, or corrosion of tubes; maintenance due date; calibration state; name of person who performed the last calibration; date of last calibration; all device I/O registers at that time (a snapshot in time); sensor integrity; and regulatory reports.

For a smart liquid flow meter, onboard verification can provide reliable data to prove it is operating according to its specifications. When a device is equipped with built-in algorithms, all test sections (sensor, front end, reference, and I/O loop) are monitored continuously and are part of the standard device diagnostics. If a verification is initiated, the current status of all diagnostics parameters can be read and stored for periodic review.

In the case of a Coriolis mass flow meter, the mechanical stiffness—or rigidity—of Coriolis flow tubes is directly related to the meter's flow calibration factor. The verification can identify changes, damage, or degradation in the measurement performance of the instrument. This could be especially important in verifying the flow meter's integrity after process disturbances or upset conditions.

Smart Proximity Sensors

Proximity sensors, or limit switches, have historically been characterized as the antithesis of a "smart" instrument. Proximity sensors are ubiquitous in systems that require valve position feedback, and, historically, they have been simple mechanical devices that rely on an extension of the valve stem to close a contact. However, in recent years, these devices have undergone revolutionary technological developments that have broadly expanded their capabilities while maintaining simplicity in all other aspects.

Control valve stem travel can be characterized as a function of actuator pressure [5], and the sensing of the valve stem movement is no longer limited to typical noncontact proximity sensor technologies such as those using inductive, capacitive, photoelectric, or ultrasonic principles. With the inclusion of Hall effect and variable differential transformer technology applied to both linear and rotary modes of operation—commonly known as linear variable differential transformers and rotary variable differential transformers, respectively—these once-simple devices are now

capable of providing over 30 different parameters, which range from an autoconfiguration of the limit switch tolerances to measuring the current actual valve stem position to a fraction of a millimeter of measurement resolution. Evaluation of these data by a supervisory control and data acquisition or distributed control system—either cyclically or acyclically—can be extremely useful to the system user in determining preventive maintenance requirements and process changes.

Self-Diagnosing and Intelligent RTDs

The most common temperature sensor used in bioprocess applications is the three-wire, platinum-100-ohm RTD instrument, which can also have an integral digital or analog transmitter. These sensors are regularly calibrated to maintain measurement accuracy and process reliability for any unit operation.

Temperature redundancy is sometimes achieved through the use of dual thin-film element RTD instruments. For standard temperature instruments with transmitters, the instrument itself can detect failures and changes from the initial calibrations. This is typically achieved by comparing signals from the two elements, and should the first element fall out of tolerance, the onboard diagnostics are programmed to switch over to the second RTD element as the primary process variable.

In addition, some modern RTD instruments with integral transmitters can perform a live "self-calibration" check. This is accomplished using a physical fixed point known as the Curie point, or Curie temperature, which is the temperature at which the ferromagnetic properties of a material change abruptly. This change in properties can be detected electronically. The sensor uses this value as the reference against which the RTD instrument measurement is compared.

Given that temperature is one of the top three process control parameters used worldwide (along with flow and pressure), it is certainly one parameter that could benefit from the use of these advanced diagnostics provided by "smart instruments." Examples of ideal applications of smart RTDs with self-calibration check capabilities include steam sterilization of equipment or autoclaves, HTST operations (viral inactivation or pasteurization), lyophilization operations where shelf temperature is a critical parameter, depyrogenation/dry heat ovens, cleaning operations, and steam-in-place operations.

CONCLUSION

A vast amount of data is available through correlating existing instruments [2] or by accessing the internal data of modern smart instruments, and these data can be used to improve process knowledge, support discrepancy investigations, increase production, minimize risk in critical processes, schedule maintenance cycles, and assess the entire system or simply process instrumentation performance over time.

The practice of using the information available from an instrument for purposes other than its primary parameter of interest has been suggested by others and is not unique to biopharmaceutical manufacturing, as evidenced by the cited references. The data can be accessed by existing control systems and analyzed via asset management systems or processed via data historians and other similar data acquisition tools. Although it takes a deliberate effort to profile these processes, historicize data, and perform comparative calculations, there are clear value propositions to any biopharmaceutical manufacturer, such as real-time sensor health checks and process performance measurement, batch release through discrepancy resolution, predicting equipment or instrument degradation, data-driven maintenance and scheduled downtime, and processes running at maximum availability and stability.

Accessing "hidden" data inherently available in modern process instrumentation helps a facility not only achieve these goals but also improve both overall process knowledge and understanding of unit operations.

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MASTER SOIL SELECTION

for Cleaning Validation of Parts Washers

By Paul Lopolito, Olivier Van Houtte, Dijana Hadziselimovic, and Si Myra Tyson

One of the goals of the cleaning validation design phase is to define critical process parameters (inputs) and acceptance criteria (outputs) of the cleaning process. This article explores the selection of a master soil as part of the cleaning validation design phase for automated parts washers. The selection and qualification of a master soil through laboratory testing and during factory acceptance testing (FAT) can be leveraged during onsite qualification to reduce the time and cost of cleaning validation processes.

It is standard practice in the industry for cleaning validation and equipment validation to embrace the process life-cycle three-stage model (design, qualify, and monitor) [1, 2]. The integration of cleaning process design testing with FAT execution and cleaning validation of automated parts washers has been well documented [3–5]. Standard performance tests that can be performed during FAT include coverage and cleaning tests, which can be leveraged during commissioning and validation of the automated parts washer [5].

A coverage test uses riboflavin (at approximately 0.2 g/L in water) as the test residue due to its ultraviolet (UV) fluorescence at 385–395 nm and high solubility in water, and UV light as an inspection method. The clean parts are then inspected by various methods, such as conductivity, UV spectroscopy, or total organic carbon (TOC). The main advantage of performing these tests during FAT is that the automated parts washer or accessories can be modified at the factory, as opposed to the final location.

Working with or sending process residues to the equipment manufacturer is not always possible or practical. Challenges may include:

- Unavailability of process residue
- Testing restrictions from the manufacturer
- Cost of process residue
- Environmental restrictions
- Health and safety concerns for the operators
- Shipping regulations
- Confidentiality risks

To reduce the time and cost of multiple cleaning validations, a grouping or bracketing exercise can be performed to select the worst-case product, active ingredient, or process residue. Grouping products, such as drugs, and selecting a worst-case product, which is manufactured on the same equipment and cleaned by the same method, is well accepted by US FDA, Health Canada, Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), ICH, WHO, and other regulatory agencies [6–11].

MASTER SOIL SELECTION

A master soil is a surrogate residue and can be considered to be either a representative process residue or worst-case process residue, depending on the selection criteria. The worst-case soil can vary based on the equipment train or cleaning method used. A worst-case residue is generally selected based on a risk-based approach. Common factors considered include cleanability, solubility, toxicity, and availability. If the worst-case residue is sent to the equipment manufacturer, environmental hazards, operator health and safety, and shipping concerns also need to be considered.

Other factors to consider in master soil selection include the analytical method support, absence of animal-derived material, understanding of the rinse profile, defined soil characteristics, availability, cost, and a visible residue limit (VRL). For example, bovine serum can be easy to attain, low cost, and difficult to clean; however, it is an animal-derived material, is complex, and has an undefined residue. Mineral oil can be difficult to clean, is free of animal-derived material, is simple, and has a defined residue; however, discharging it into a municipal drain may not be acceptable. Refer to Table 1 for a list of possible master soils and factors to consider during master soil selection. The list of proposed master soils is based on literature related to pharmaceutical, biopharmaceutical, and medical device master soil selection and cleaning applications [12–16], as well as the authors' industry experience. The selection of a master soil within a manufacturing facility may be a long process, but the efforts may be worthwhile due to the resource and cost savings achieved during qualification and validation.

LABORATORY EVALUATION

Figure 1 shows the application of a master soil to laboratory glassware. Laboratory testing has been effective at defining critical cleaning parameters for removing process residues [17, 18], and it is the best way to develop successful standard operating procedures (SOPs). The

Table 1: Master soil selection and factors to consider during selection. For each factor, the master soils are ranked as low risk (1), medium risk (2), or high risk (3).

Master Soil	Availability	Ease of Cleaning	Solubility in Water (at 25°C)	Toxicity (Oral LD_{50} Rats)	Complexity (Defined–Undefined)	Environmental Risks	Operator Safety Risks	VRL
Albumin, bovine	1	3	1	1	3	1	1	1
Aluminum phosphate	1	1	2	1	1	2	1	2
Browne residue	2	3	1	1	3	1	1	2
Egg, chicken	2	3	2	1	3	1	1	1
Hemoglobin	2	3	1	1	2	1	1	1
Ibuprofen	2	1	2	1	1	1	1	2
Lactose	1	2	1	1	2	1	1	1
Magnesium stearate	1	2	3	1	1	1	1	2
Mineral oil (petroleum)	1	2	3	2	1	2	1	1
Phosphate-buffered saline (PBS)	1	1	1	1	2	1	1	3
Sucrose	1	2	1	1	1	1	1	1
Sodium bicarbonate	1	1	1	1	1	1	1	1
Cornstarch	1	2	2	1	2	1	1	2
Tryptic soy broth (TSB)	1	2	1	1	3	1	1	2

following is an example of steps in a laboratory test procedure:

1. Weigh dry, clean 304 stainless steel coupons (7.5 × 15 cm) on an analytical balance (±0.1 mg) to obtain the precoating weight.
2. Coat coupons coated with 3–5 mL of the sample. The amount of residue per surface area is controlled and recorded; it varies by the application form (dry powder, compressed powder, or slurry).
3. Air-dry the samples at ambient temperature.
4. Weigh the conditioned coupons on an analytical balance to determine precleaning weight.
5. Clean each coupon by agitated immersion, spray wash, or cascading flow.
6. Remove each coupon and visually observe it for cleanliness.
7. Rinse each side of the coupon with tap water for 10 seconds at a flow rate of 2 L/min.
8. Rinse each side of the coupons with deionized water and examine for a water break–free surface.
9. Dry coupons and then weigh them on an analytical balance to determine the postcleaning weight.

Cleaning parameters for evaluation include the selection of the cleaning agent, time, temperature, and cleaning agent concentration. These specified cleaning parameters are confirmed with scale-up or field evaluations.

Figure 1: Master soil (Browne soil) applied to laboratory glassware. Browne residue is similar to the Edinburgh soil used to simulate the residue observed naturally during hospital surgical procedures.

To evaluate different factors, such as safety, environmental impact, ease of cleaning, and the cost of raw materials, we elected to investigate the following soils for consideration as a master soil: bovine albumin, aluminum phosphate, Browne residue, egg (chicken), hemoglobin, ibuprofen lactose, magnesium stearate,

Table 2: Summary of master soil cleaning results and visual residue limits.*

	Type of Cleaning Agent				
Master Soil	Water Only	Acid Detergent	Neutral Detergent	Alkaline Detergent	VRL, µg/cm²
Albumin, bovine	–	–	–	Yes	2
Aluminum phosphate	–	Yes	–	–	10
Browne residue	–	–	–	Yes	10
Egg, chicken	–	–	–	Yes	2
Hemoglobin	–	–	–	Yes	2
Ibuprofen	–	–	Yes	Yes	10
Lactose	–	–	Yes	Yes	2
Magnesium stearate	–	–	Yes	Yes	10
Mineral (petroleum) oil	–	–	Yes	Yes	1
PBS	Yes	Yes	Yes	Yes	100
Sucrose	Yes	Yes	Yes	Yes	1
Sodium bicarbonate	–	Yes	–	Yes	1
Starch, maize	–	–	Yes	Yes	10
TSB	–	–	–	Yes	10

*The yellow areas represent a high-temperature cleaning condition. "Yes" indicates that the residue was successfully cleaned with the cleaning agent. A dash represents a cleaning failure. VRL is the quantity of residue on stainless steel that can be seen by the inspector; it is determined through visual inspection and control of critical parameters.

mineral oil, phosphate-buffered saline (PBS), sucrose, sodium bicarbonate, starch, and tryptic soy broth (TSB). These residues represent different industry segments, such as pharmaceutical (oral solid dose and parenteral), biopharmaceutical, and medical device. These industry segments or others may be subdivided into smaller groups for master soil selection and qualification.

Table 2 summarizes our laboratory findings. A coupon was considered clean if it was visually clean and water break–free, and if its precoating weight and postcleaning weight were equal (<0.1 mg residue per 7.5 × 15–cm coupon). It is important that the master soil and process soils can be cleaned to predetermined acceptance criteria, and the decision is not based on a percentage of residue removed.

As a part of the cleaning evaluation, we also explored VRLs for the proposed master soils. Visual inspection is usually the first step in determining whether the equipment is clean before scheduling analytical testing. In 1993, Fourman and Mullen specified a visual limit for small molecule active ingredients of 1–4 µg/cm² [19], and this article is referenced in the US FDA "Guide to Inspections Validation of Cleaning Processes" [11] as well as Parenteral Drug Association Technical Report 29 [20]. Forsyth and colleagues published at least one article that includes testing and definitions of critical variables and presents case studies [21]. The case studies include spiking a 1 cm² surface with residue at various concentrations and on different substrates. Once the residue is dried, it can then be inspected visually at different distances, angles, and light intensities, with the use of mirrors and by different analysts [21–23]. By defining the operators' qualifications, visual inspection tools and conditions, procedures, training, and retraining activities, a company can quantify and validate the visual inspection procedure [23].

The VRL study procedure was employed as follows:

1. Coupons made of 304 stainless steel with 2 B finish were precleaned.
2. Test master soil samples were serially diluted at 1 µL and 20 µL of low-TOC water and applied over a 1 cm² area of each coupon.
3. Samples were air-dried for 16 hours.
4. Coupons were inspected in duplicate (by two analysts) at one of the following distances (0.45 meter, 1.0 meter, or 1.5 meter), lighting conditions (250 lux, 500 lux, or 1,000 lux), viewing angle (30°, 45°, or 90°), and with and without a viewing mirror. A Cooke Corporation Cal-Light 400-lux meter, digital protractor, and Hamilton 10-µL syringes were used in the study.
5. The VRL results were reported (Table 2).

EQUIPMENT EVALUATION

The first step in an optimal rack design evaluation is to collect information on the parts that need to be cleaned, such as materials of construction, dimensions and shapes, type of process soil, and condition of the soil on the surface [4]. This information is critical in developing a grouping strategy, designing the cleaning cycle, and defining the loading configuration of the parts. Once this

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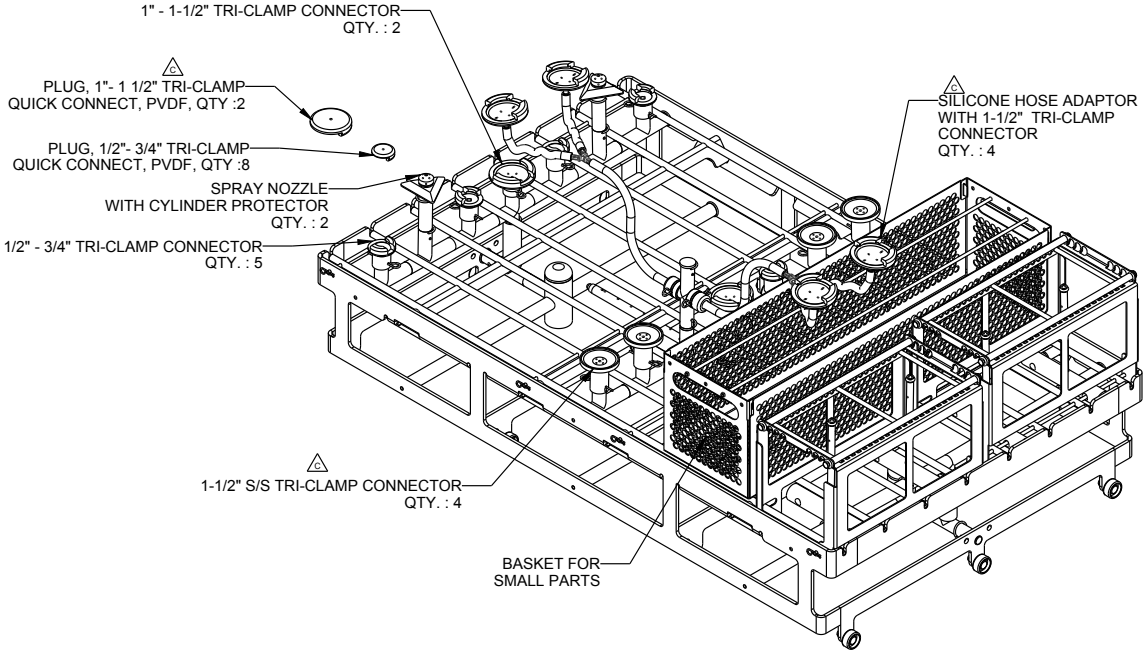
information is gathered, the loading configuration can be established, and laboratory cleaning evaluations can be performed to support cycle development. Figures 2 and 3 show how parts may be loaded in a washer rack.

Grouping or bracketing of items is important in testing worst-case load configurations during this design stage. A single process soil can be cleaned (as would be the case with filling equipment), or several soils can be washed in a single cycle. The cleaning cycle needs to be effective at removing residues. To demonstrate cleanliness, the residue is evaluated when selecting the analytical method and setting acceptance criteria. Once the loading configuration is defined, loading rack options should be investigated to determine what could be suitable based on the parts list and grouping strategy.

After loading patterns are identified and racks are designed and assembled, it is important to verify that the rack design allows proper coverage on process parts. To do so, equipment manufacturers can conduct coverage tests using riboflavin diluted at

Figure 2: Production parts loaded in a pharmaceutical-grade washer.

Figure 3: As-built drawing of the loading rack from Figure 2.



0.2 g/L, or another solution. Components are soiled by spraying or gently misting the solution onto the interior and exterior surfaces [24]. (See Figure 4 for an example of the soiling process.) The main objective of coverage testing is to assess coverage efficacy of standard or customized racks and associated process parts. This field trial ensures that water reaches all surfaces, items remain secure in the rack, and any soluble cleaning agent used can be successfully rinsed. This performance test is normally done as part of FAT and should ideally be conducted with the parts that are used onsite, or representative parts.

In washing applications, coverage is the most important critical cleaning parameter because incomplete coverage means that the cleaning solution does not reach internal and external surfaces of the components to be cleaned. Some parts, like tubing or hoses, are typically harder to clean because of their surface geometry and higher flow velocity requirements. Coverage efficacy is

Figure 4: Filter housing being soiled with riboflavin.

Figure 5: Inspection of filter housing under UV light for traces of riboflavin.

determined by visual evaluation of remaining soil on glassware and parts. No detergent is added to the cycle, and only water is used. Dry time can vary between seconds and hours, depending on preference. It is important to mention that coverage testing is not a cleaning challenge; therefore, the solution should be water soluble and easily removable from the surface.

Before spraying the actual parts with riboflavin or other soiling solution, apply a small quantity on a stainless steel surface and use a UV light to verify that the solution fluoresces. After verification, spray the parts and rack and load them into the washer for a short rinse phase. Parts can then be unloaded from the washer chamber and immediately inspected with a UV light for traces of riboflavin (Figure 5). It is important to inspect areas that are harder to reach. Modifications may be made to the rack following a coverage test to improve parts orientation and, therefore, coverage.

APPLICATION OF MASTER SOIL

The master soil can be applied to perform a cleaning test using a similar technique as the riboflavin test described previously. The master soil could also be used in combination with the riboflavin; however, omitting the initial coverage test using riboflavin only is not recommended. As noted earlier, the coverage test is important to confirm that all areas are wetted during the rinse step. This test helps identify potential areas to sample as well as significant engineering concerns.

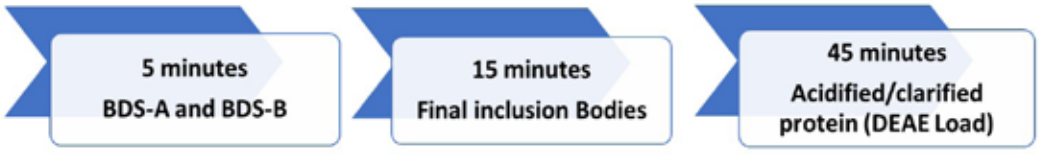
The cleaning test is performed using a standard or normal parts washer cycle. This cycle may include a prerinse, a series of wash steps, post-wash-step rinses, a final rinse, and a heated drying step. During the cleaning test, the washer cycle should run uninterrupted and without alarms. Based on the authors' experience, adding riboflavin to the proposed master soil does not adversely affect the cleaning parameters of these residues. Adjusting the master soil concentration or conditioning process can significantly change the cleaning parameters required to remove the residue.

Upon completion of the parts washer cycle, the cleaned parts can be visually inspected to confirm the removal of the master soil to acceptable levels (refer to the earlier discussion on VRLs). Additional swabbing of the parts or rinse-water testing may be warranted based on the sensitivities of the residue and detection method. The analytical testing methods available to equipment testing facilities during FAT may be limited; therefore, it is important to have confidence in the quality of visual inspection or rinse-water analysis.

CASE STUDY

A process development and cGMP manufacturing facility of recombinant proteins for a large multinational company was interested in identifying a master soil that would be more difficult to clean than their worst-case process residue and could be used for cleaning cycle development and validation. The process soils included final inclusion bodies, acidified/clarified protein (diethylaminoethyl [DEAE] load), bulk drug substance A (BDS-A), and

Figure 6: Cleaning time of process soils with 2% v/v alkaline detergent at 80°C.



bulk drug substance B (BDS-B). The master soils for screening included xanthan gum, starch, TSB, and soy protein isolate. The selection of the master soils for screening included the following criteria: availability, solubility in water, low toxicity, low complexity, no animal-derived material, no dyes, no perfumes, low operator safety, ease of detection, ease of soil conditioning, and a worst-case cleaning procedure compared to the process soils.

The cleaning of the process soils and master soils at various percent weight-per-volume (% w/v) concentrations were performed following the procedure described previously. The dirty hold time for the process and master soils was more than 16 hours at ambient temperature. The process soils were cleaned within 45 minutes using a 2% volume/volume (v/v) dilution of an alkaline detergent at 80°C, as detailed in Figure 6. The starch, TSB, and soy protein isolate at 3% and 6% w/v were cleaned within 5 minutes. At 1% w/v, xanthan gum was cleaned within 15 minutes, and at 3% w/v, it was cleaned within 45–60 minutes. Xanthan gum at 3% w/v was selected as the master soil.

CONCLUSION

Regulatory guidance documents and published industry best practices agree that grouping or bracketing of residues and the use of placebo or master soils are acceptable with justification. In the review of FATs conducted over the past few years, the authors found that almost all end users would elect to include a coverage test during an automated parts washer FAT, but almost no FATs included a cleaning challenge. The work performed during the FAT is generally repeated during the site acceptance testing and then again during the installation qualification and operational qualification of the washer. This practice leads to delay and risk when advancing to the performance qualification and cleaning validation of the automated parts washer.

The risk can be reduced by performing laboratory studies. For example, coupon studies (as described earlier) can help define critical cleaning parameters (inputs) and acceptance criteria (outputs) before testing with the washer is performed. This is a sound scientific approach, which would be improved if a placebo or master soil were included as part of the laboratory study and as part of FAT of the automated parts washer. This approach also supports the inclusion of analytical process tools, such as inline conductivity and TOC testing of rinse water [25, 26].

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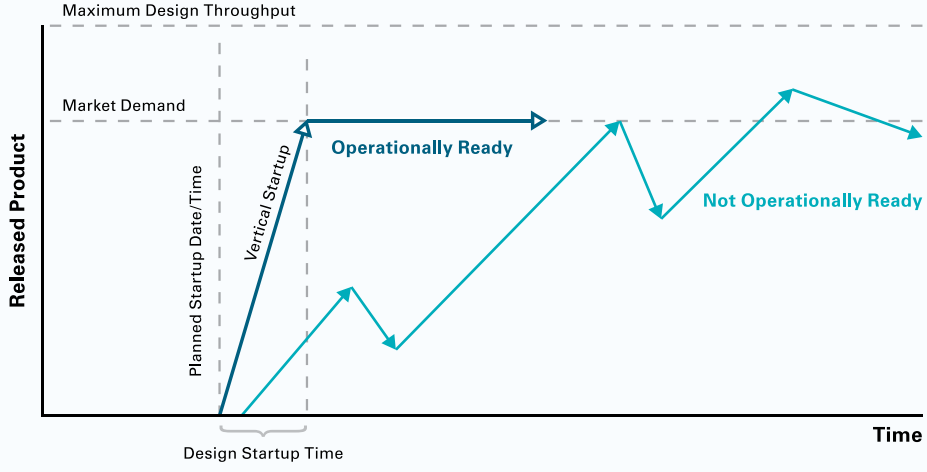

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