PHARMACEUTICAL ENGINEERING®

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# TECHNOLOGY TRENDS

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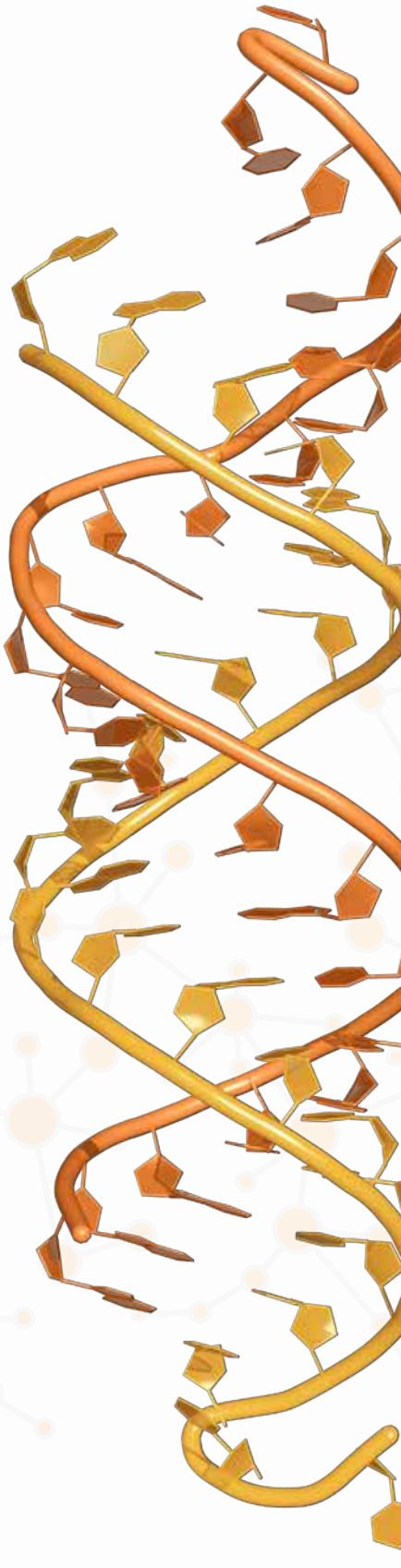

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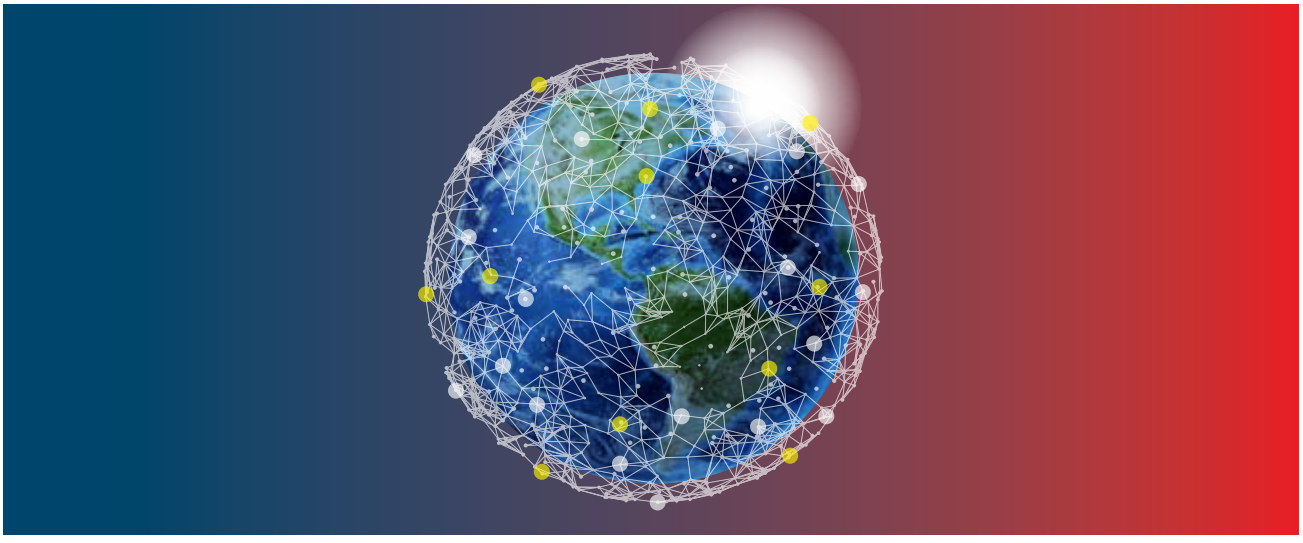



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By Jim Breen

# Technology Innovations and the Pharmaceutical Industry

Jim Breen

Many of us have heard of Moore's Law, named after Gordon Moore, cofounder of Intel [1]. Moore's Law predicted that computing would increase in power and decrease in relative cost at an exponential pace. This allows us to use this power for new technologies such as machine learning and artificial intelligence (AI), which are starting to impact the pharmaceutical industry.

Technology is the theme for this issue of *Pharmaceutical Engineering*. This is an exciting time to be in the pharmaceutical industry as we participate in the rapid waves of technological innovation that allow us to better serve patients.

## TECHNOLOGY BENEFITS

Technological innovation allows us to work across multiple industries, see how technology is being applied in those industries, and learn how we may use it in our industry. It also allows us to work with academia, government, and industry to develop solutions that will truly improve our industry.

In the pharmaceutical industry today, pharmaceutical companies are analyzing how to use blockchain, data analytics, AI, and other technologies to help improve efficiency and effectiveness in bringing products to the patient. These tools are being applied in many areas affecting our daily lives.

Specific technologies impacting the pharmaceutical industry include continuous manufacturing technology and cell and gene therapy.

## HOW ISPE CAN HELP

The pharmaceutical industry continues to evolve to meet accelerated changes from new technology solutions that lead to new business models to meet patient needs.

ISPE offers help with the training and education of our members to understand and implement these new technologies in their careers, including conferences, training courses, and articles in PE highlighting some new technologies and how members can learn about and apply them.

ISPE's new Strategic Plan, which will be unveiled at the 2019 ISPE Annual Meeting & Expo in Las Vegas, Nevada, will outline the areas to focus on as an industry to allow our members to be prepared to help deliver lifesaving medicines to patients. Key to ISPE's strategy is how the pharmaceutical industry will address the speed and pace of change of technology.

I look forward to seeing you in Las Vegas 27–30 October to talk about the new ISPE Strategic Plan. As always, your comments and suggestions are welcome.

### Reference

1. Intel. "Fueling Innovation We Love and Depend On." Accessed 22 May 2019. https://www.intel.com/content/www/us/en/silicon-innovations/moores-law-technology.html

**Jim Breen** is 2019 ISPE International Board of Directors Chair; Vice President, Lead Biologic Expansion, Janssen Pharmaceutical; and Adjunct Professor at Drexel University. He has been an ISPE member since 2000.

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LeAnna Pearson Marcum

# ISPE EUROPE YPS SHOW A PASSION FOR DEVELOPMENT

I've been to numerous ISPE conferences in the United States. This was my first ISPE Europe Annual Conference, held 1–4 April, and it did not disappoint! The Young Professionals (YPs) were an integral part of the conference in Dublin; they led tracks, hosted and participated in the ISPE Europe Annual Conference Young Professionals Hackathon, and made sure that new YPs and students had all the resources they needed.

Following the successful format of the 2018 ISPE Europe Annual Conference, a YP was included as co-chair of the educational track. The YP representative started working months before the conference and became an integral part of the program committee. I was in awe sitting in sessions and seeing YPs introducing speakers, managing Q&A sessions, and encouraging the audience to ask questions and participate.

## MY FIRST HACKATHON

I will be the first to admit that I had no idea what a Hackathon was or what to expect. So when I walked into the conference room and saw the teams of YPs collaborating, I was just blown away! I was honored to be asked to judge the Hackathon on day two and quickly realized during the presentations that this was truly the next generation of the pharmaceutical industry standing before me. The ideas presented were inspiring and thoughtful, with just the right amount of dream and imagination—think Willy Wonka meets Big Pharma. For more about the Hackathon, please turn to page 44 for a report from two participants.

After being part of the event at the Europe conference, I am inspired and excited for the first Hackathon that will be hosted in the US at the 2019 ISPE Annual Meeting & Expo in Las Vegas, Nevada. If you attend the meeting in Las Vegas, 28–31 October, make sure you come out to see the next big thing in the pharmaceutical industry.

## MEET THE INTERNATIONAL YP CO-CHAIR

The Europe Annual Conference also allowed me to meet many YPs I have only spoken to on the phone, including John Clarke, the International YP Committee Co-Chair.


John Clarke

Clarke works as Biopharmaceutical Operations Lead at Pfizer in Dublin, Ireland. He received a bachelor's degree in microbiology from University College Cork in 2008 and went on to hold several quality roles before completing a master's degree in biopharmaceutical engineering at University College Dublin in 2013. Clarke has worked at Pfizer, Dublin, in roles in validation, new product introduction, and operations, and currently leads a manufacturing team through process validation for technology transfer. He is also completing a higher diploma in leadership management at University College Cork. Clarke has played an active role with the ISPE Ireland Affiliate YPs since 2014 and served as Chair from 2016 to 2018. He organized and led the ISPE Europe Annual Conference Young Professionalsl Hackathon that took place in Dublin 30–31 March 2019.

Clarke and I are collaborating on the US Hackathon and moving forward on the goals set forth for the International YP Committee. With Clarke being based in Dublin and me in the US, we are very collaborative via email. Time management is one of the biggest skills that is required to lead any volunteer committee or organization. With Clarke's dedication and skills, we will make an unstoppable team.

**LeAnna Pearson Marcum** is a QAV Manager with bluebird bio in Durham, North Carolina, and the 2019 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

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# IMPROVING PHARMACEUTICAL CONNECTIONS WITH PATIENTS

By Jen A. Miller

Being on the cutting edge of drug development is the goal of most pharmaceutical companies, but a new drug won't work if the patient doesn't take it. It's a vexing problem that developers of healthcare technologies hope to address.

An overview of such technologies was provided during the "Digital Health: Opportunities and Challenges of Transformed Healthcare Delivery" session at the 2018 ISPE Annual Meeting & Expo. *Pharmaceutical Engineering* followed up with the session presenters to continue the discussion about the technological changes underway to improve patient care.

"There's a growing trend in the pharmaceutical industry to offer other services or value beyond a pill," said Kevin Sooben, Digital Health Program Lead at AstraZeneca. Such services can help deliver results to patients. Digital opportunities include diagnostic, decision support, self-management, optimized treatment, and dynamic dosing tools.

New technologies can make a difference in helping patients. Even where there may be pharmaceutical treatments for disease, improving patient health can still be a challenge, said Sooben. As an example, he cited diabetes mellitus: despite major innovations in treatment, the disease remains a public health crisis, with 1.5 million people in the United States being diagnosed every year [1].

Even where there may be pharmaceutical treatments for disease, improving patient health can still be a challenge.

Added services—and value—are now available in the form of smart technology that is used in tandem with pharmacological products, either to get a better picture of the patient's health status, activities, and lifestyle or to simply remind the patient to take their medicine. Artificial intelligence (AI) is positioned to take these strides to the next level.

## THE PROMISE OF SMART DEVICES

The widespread use of smart devices like phones and watches may revolutionize both personal health management and communica-

tion between patients and providers. Sooben noted that in 2017, IQVIA, a healthcare data science company, reported that about 200 health apps were being released each day to join the more than 300,000 health apps available around the world; at that time, nearly 350 wearable smart devices were on the market [2].

A smartphone or smartwatch "can do a lot with respect to trying to nudge people to manage their medications and provide behavioral change messages and education information," said Sooben. "It's a way for data to flow from the patient to relevant other parties involved in that patient's care and can also send contextual information back to that patient." In his presentation, he noted the intersection of value trends in healthcare delivery that is helping to drive this potential: Patients are increasingly becoming "active and confident participants in their own treatment and more data is being made available to them than ever before." Also, the relationship between patients and healthcare providers is changing, with remote monitoring offering opportunities for improved treatment adherence, health outcomes, and patient identification, and payers are open to exploring more patient-centric delivery models that increase quality of care and reduce care costs.

Smart technology can go a step further if the smart device is linked to a connected item, like a connected pill bottle or device injector. Such technology can be used "all the way through being able to collect medical information that captures medical data that you can use to help patients deliver or decide what to take and when to take therapy," Sooben said.

## REMOTE PATIENT MONITORING

Remote patient monitoring, where patients don't necessarily need to go to a physician's office or hospital, offers exciting opportunities for better care. For example, it could help in treating patients in rural areas, where access to primary care and other services, such as obstetrics, can be especially challenging [3, 4]. (Telemedicine is another area of technological innovation that can expand the reach of patient care [5].)

An example of a remote patient monitoring system that points to the potential of smart devices in pharmaceuticals is Turbu+, a Symbicort inhaler from AstraZeneca. The inhaler is Bluetooth-connected to an app on a smart device, which reminds the patient to use the inhaler, sends motivational messages, tracks adherence, and provides the patient's physician with data about actual medication use that can be used to inform clinical decision-making.

Sooben reported that Turbu+ has 2,900 patients enrolled in eight countries and, so far, AstraZeneca has found significant improvement in both adherence and the participants' control of allergic rhinitis and asthma test (CARAT) scores.

"It's an example of how an existing pharmaceutical delivery device can be combined with an add-on device to provide feedback to the patient and their providers, leading to improvements in the patient's condition," Sooben said.

The second example cited by Sooben is Moovcare, a web-mediated follow-up app for patients with lung cancer developed by Sivan Innovation [6–8]. Moovcare allows patient-reported symptom data to be sent immediately to the oncology care team so physicians can better manage and support patients in a timely manner. "The patient is reporting data back to their providers, and then the providers can intervene and take any necessary actions," he said. In a randomized clinical trial involving participants with advanced-stage lung cancer without evidence of disease progression after or during initial treatment, the median overall survival of those in the Moovcare intervention group was 19 months vs. 12 months in the control group [6]. "If you were developing a drug and you have that increased overall survivorship, you'd be very excited about it, and yet there's no drug involved here at all," Sooben said.

The relationship between patients and healthcare providers is changing, with remote monitoring offering opportunities for improved treatment adherence, health outcomes, and patient identification.

Even so, he points to Moovcare as a technology of interest to the pharmaceutical industry because it exemplifies the potential of remote monitoring "to touch every aspect of drug development." This sort of technology "could change the way you develop drugs from the preclinical stage all the way through clinical stages because digital health can also be used as a data collection tool."

Remote monitoring tools may also allow for the development of drugs that couldn't be developed at all without that kind of constant monitoring and data collection. "There's an opportunity here to understand the potentials for digital therapies and digital health in the pharmaceutical industry," he said.

## ARTIFICIAL INTELLIGENCE AND MORE

The potential of AI to transform healthcare was also addressed during the Digital Health session at the 2018 ISPE Annual Meeting & Expo and in follow-up conversations with a presenter.

"Developing modularized learning systems is a constructive AI path for any regulated use case," said Sundar Selvatharasu, Chief Compliance Officer at Sierra Labs. On the other hand, "trying to

develop an AI platform is a recipe for uncontrolled outcomes if there are no predefined boundaries, even for adaptive AI applications."

AI is science that challenges human cognizance like never before. So far, said Selvatharasu, AI has been through the trajectory of hype that promised it would be a platform that will sense, analyze, and address all interlinked challenges in healthcare. But now, he said, those exaggerated expectations are giving way to reality. AI in action is seen as more adaptable when it is specific and deliberate.

In the biopharmaceutical space, "use cases are showing positive results and wider adoption when an AI algorithm is explainable, instinctive, and replicable," Selvatharasu said. This is occurring "primarily in computer-intensive solutions and in augmenting human decisions. Embedded machine learning can generate algorithms to automate regulatory compliance and shift the regulatory burden to a competitive advantage."

As for cutting through the AI hype, Selvatharasu said "human trust can override rational logic. It is important to ensure that AI-driven decisions are unemotional and purely logical," he said. "The need for good ol' quality and regulatory oversight will still hold, but the approach to oversight needs reinventing. Specifics around data cataloging standards, AI validation models, and quality references can ease the regulatory agency's burden and provide more clarity for the industry," he said.

## REFERENCES


1. American Diabetes Association. "Statistics about Diabetes." Updated 22 March 2018. http://www.diabetes.org/diabetes-basics/statistics
2. IQVIA Institute. "The Growing Value of Digital Health: Evidence and Impact on Human Health and the Healthcare System." Published 7 November 2017. https://www.iqvia.com/institute/reports/the-growing-value-of-digital-health
3. National Rural Health Association. "About Rural Health Care." Accessed 28 May 2019. https://www.ruralhealthweb.org/about-nrha/about-rural-health-care
4. Hung, P., C. E. Henning-Smith, M. M. Casey, and K. B. Kozhimannil. "Access to Obstetric Services in Rural Counties Still Declining, with 9 Percent Losing Services, 2004-14." *Health Affairs* 36 no. 9 (September 2017). doi:10.1093/jnci/djx029
5. Foley & Lardner LLP. "2017 Telemedicine and Digital Health Survey." Accessed 28 May 2019. https://www.foley.com/files/uploads/2017-Telemedicine-Survey-Report-11-8-17.pdf
6. Denis, F., C. Lethrosne, N. Pourel, O. Molinier, Y. Pointreau, J. Domont, H. Bourgeois, et al. "Randomized Trial Comparing a Web-Mediated Follow-up with Routine Surveillance in Lung Cancer Patients." *JNCI: Journal of the National Cancer Institute* 109, no. 9 (September 2017). doi:10.1093/jnci/djx029
7. Sivan Innovation. "Clinical Results: Moovcare, Product." 2017. https://sivan-innovation.com/moovcare2
8. Dangi-Garimella, S. "Study Underscores Value of PROs in Improving Lung Cancer Survival" (report from 2018 American Society of Clinical Oncology Annual Meeting). Published 7 June 2018. https://www.ajmc.com/conferences/asco-2018/study-underscores-value-of-pros-in-improving-lung-cancer-survival


## ABOUT THE AUTHOR

**Jen A. Miller** is an award-winning journalist and author of three books. She has also run 10 marathons and two ultra marathons. She lives in New Jersey.

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# APPLICATION OF THE SOC 2+ PROCESS

## to Assessment of GxP Suppliers of IT Services

By Arthur D. Perez, PhD, James Canterbury, Emily Hansen, Judith S. Samardelis, MS, Heather Longden, and Rick Rambo, MBA

To facilitate the assessment and mitigation of compliance risks associated with a third-party service organization, its services, and the systems used to provide the services, this article proposes adopting an approach from the financial sector that, with a little modification, could be used to assess suppliers of GxP-regulated IT services.

One of the presiding tenets of GxP (good manufacturing, laboratory, or clinical practices) compliance is supplier management. Regulators recognize that many life sciences companies outsource activities that they either do not wish to or cannot effectively execute themselves, but regulatory agencies nonetheless expect the companies to manage the quality of such activities. In the past, the largest concern involved managing organizations like contract manufacturers and clinical research organizations. Concerns regarding information technology (IT) groups were generally limited to verifying that software applications had been developed and were supported in a controlled manner.

However, a recent trend in IT is the broadscale outsourcing of services, including a wide variety of cloud-based services. Some companies have effectively reduced their internal IT capability to little more than project management, while outsourcing virtually all traditional IT support activities for infrastructure and applications.

This state of affairs means that the need for IT supplier management is much greater, but the existing approaches are hardly more sophisticated than they were two decades ago. For lower-risk suppliers, simple research may be sufficient, or GAMP® 5 suggests the possibility of remote audit via questionnaire [1]. The primary tool for higher-risk suppliers is often a direct audit by the life sciences company's quality assurance (QA) organization, perhaps augmented by some metrics. An added complication in higher-risk scenarios is that many of the cloud-service providers that are ideal partners from a financial standpoint have little or no experience in the GxP realm. Furthermore, some of the larger providers are likely to decline to be audited by their customers.

Fortunately, within the financial sector, there is a process many businesses use to facilitate the assessment and mitigation of compliance risks associated with a third-party service organization (i.e., supplier), its services, and the systems used to provide the services: the Statement on Standards for Attestation Engagements (SSAE 18) Service Organization Controls (SOC 2) reporting process, as defined by the American Institute of Certified Public Accountants (AICPA) [2]. With a little modification, this approach could be used to assess suppliers of GxP-regulated IT services.

Under this process, an IT service provider engages an independent third-party audit firm to perform a detailed examination, supported by documented testing. This audit provides evidence about the design, operation, and effectiveness of controls within the supplier's systems and their key compliance processes. The SOC 2 examination report includes a detailed description of the supplier's system as designed and implemented, and whether

the controls stated in the description were suitably designed and operated effectively to provide reasonable assurance that the service organization's service commitments and system requirements were achieved based on criteria relevant to the security, availability, processing integrity, and confidentiality or privacy of its system. The SOC 2 report is intended for users seeking information assurance regarding information handling and can be distributed to customers or users having sufficient knowledge of the service organization's system and services. This process is heavily leveraged by companies' vendor management programs to support vendor compliance and monitoring; it is also used in support of regulatory oversight or risk-management processes (e.g., compliance with the Sarbanes–Oxley Act, which regulates corporate financial disclosures).

Key tools in the SOC 2 process are the Trust Services Principles and Criteria, which provide a framework to address IT-associated risks and opportunities. The Trust Services Principles and Criteria were jointly developed by AICPA and the Canadian Institute of Chartered Accountants (CICA) and are used for SOC 2 and SOC 3 reports [3]. Trust services are defined as a set of professional assurance services based on a common framework, which comprises a core set of principles and criteria. The framework has been designed to address the risk and opportunities associated with IT. The existing SOC 2 process and trust service criteria already overlap significantly with the needs of GxP organizations: they address issues such as change control, incident management, security management, access control, and so on. In fact, for a large percentage of cloud-service suppliers, the existing SOC 2 process and the associated trust services criteria probably provide sufficient evaluation of supplier processes without any additional criteria. Infrastructure as a service (IaaS) and platform as a service (PaaS) suppliers will generally fall into this category.

However, for software as a service (SaaS) suppliers, the question of validation arises. There is no question that the life sciences company is accountable for the validation state of a SaaS application and that the company owns and is accountable for the data. However, many of the processes involved in validation (e.g., specification, verification, operational management) are the responsibility of the supplier. Evaluating these activities is not within the scope of current trust services criteria.

Under recent changes to the standard, a service organization may request that the service auditor's report address either criteria in addition to the applicable trust services criteria or additional subject matter related to the service organization's services, using additional suitable criteria related to that subject matter, or both. The result is an SOC 2+ report, which is intended to create flexibility for industries and service providers to define controls that were not historically covered.

## THE CASE FOR A GXP SOC 2+ PROCESS

The responsibility for the quality of IT software and services will always reside with the life sciences company that uses them. Having a vendor or even an independent third party produce an independent attestation regarding the control environment's effectiveness does not affect that obligation. However, with the expanding use of such services, the need to maximize the efficiency of quality assessments has become a more significant challenge. In addition, suppliers are starting to offer services with significant GxP risk, such as laboratory information management systems (LIMS) as an SaaS application. The use of such high-risk services is a driver for a structured and controlled approach to supplier assessment.

Key tools in the SOC 2 process are the Trust Services Principles and Criteria, which provide a framework to address IT-associated risks and opportunities.

An adaptation of the SOC 2+ process geared toward assessing supplier suitability to support a GxP process would be of great utility. The potential benefits of this are threefold:

1. A life sciences company could examine an existing report when evaluating whether to engage a supplier. Based on risk, the company could elect to accept the report as adequate evidence of quality processes, or it could opt to conduct its own additional audit, which could require fewer resources and less effort because the SOC 2+ report allows auditors to focus on perceived weaknesses. In addition, reviewing the annual report would provide a degree of assurance that the supplier is maintaining an acceptable level of control over the client's processes.
2. Service suppliers with a substantial GxP customer base currently devote considerable resources to audit support. Adopting this process would allow them to reduce the footprint needed to support customer audits, because one comprehensive audit would provide much of the evidence that is currently presented repeatedly during customer audits. The production of an SOC 2+ report could also be used as a differentiator for the supplier when attracting new customers.
3. Regulators would be assured of a consistent process for supplier evaluation carried out by an independent third party. The documented testing generated during the audit would

provide stronger and more comprehensive evidence that appropriate controls are effectively executed. In addition, with an approach modeled after the SOC 2+ process, audits would be carried out annually and provided to customers routinely, which would provide more frequent evaluations than most companies' direct audit policy.

This article proposes an SOC 2+–type tool usable by life sciences companies in support of supplier management and adapted to leverage the SOC 2+ process with modification to address the gaps between the SOC 2+ process and GxP expectations. Although this type of tool does not negate the need for a quality agreement between the customer and supplier, it can be a significant aid to transparency and thus strengthen the confidence of all parties involved that controls are appropriate, comprehensive, and being followed.

If the SOC 2+ report is not enough to satisfy the life sciences company of the supplier's ability to meet expectations, additional evaluation may be necessary.

## PROPOSED PROCESS

### Initiation

The SOC 2 report is clearly essential from a customer perspective because it provides evidence that processes are not only implemented but also followed. However, the decision to initiate an SOC 2+ audit lies with the supplier. This decision may be driven by a request from a life sciences customer, but, generally, the supplier will engage the audit firm and fund the process. The third-party audit firm should not have any conflict of interest with the supplier that would inhibit a willingness to honestly appraise an unsatisfactory audit.

Before a service auditor can accept a new SOC 2+ examination, certain preconditions must be met. This is a requirement for financial evaluations as defined by AICPA and an expectation for application of the process in the GxP world. These preconditions include service auditor requirements and engagement set forth by professional standards. An understanding of management's and the service auditor's responsibilities in the SOC 2+ examination must be established.

Service organization management is responsible for making decisions that define the scope of the examination, which include, but are not limited to:

- Identifying the services and system to be the subject matter for the examination
- Specifying the type of SOC report to be performed and the period of coverage (i.e., Type 1 [point in time] or Type 2 [period of time])
- Identifying risks that could prevent the achievement of the service organization's service commitments and system requirements
- Selecting the trust services categories to be included in the scope (e.g., security, availability, processing integrity, confidentiality, and privacy) as well as any supplemental subject matter
- Identifying relevant subservice organizations and determining the method of presentation (e.g., an inclusive approach, in which the auditor directly evaluates and reports on the effectiveness of the control activity carried out by a subsupplier, or a carve-out method, in which the subsupplier's control activity is indirectly evaluated, such as through a separate SOC report from the subsupplier)
- Designing, implementing, operating, monitoring, and documenting controls that are suitably designed and, in a Type 2 examination, operating effectively to provide reasonable assurance that the service organization's service commitments and system requirements were achieved based on the applicable trust services criteria
- Specifying complementary user-entity controls

Service organization management may require additional clarification from the service auditor to address these responsibilities. Whereas a service auditor can provide assistance to management to help clarify questions about scope and timing, the service auditor is required to maintain independence from management and cannot make decisions on management's behalf. Once the service auditor's and service organization management's responsibilities have been established, they are acknowledged in an engagement letter or other suitable form of written communication.

When assessing IT service suppliers for GxP purposes, some additions or modifications to the approach used for financial clients are appropriate. The online version of this article (https://ispe.org/pharmaceutical-engineering) includes an appendix that presents a trust services table that augments the commonly evaluated trust services criteria with additional criteria geared toward specific GxP aspects. It should be noted that the table is not a boilerplate suitable for all scenarios. In all cases, the final assessment of the audit content and the approach to evaluating the testing of the controls must account for the specific nature of systems or services being provided. This process is intended to be an industry standard and should suffice for most user companies; however, if the life sciences company

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Whereas a service auditor can provide assistance to management to help clarify questions about scope and timing, the service auditor is required to maintain independence from management and cannot make decisions on management's behalf.

is doing something unique that is not covered by the standard criteria, additional evaluation might be warranted.

### Audit Execution

Upon acceptance of an SOC 2+ engagement, the service organization's management is responsible for preparing a complete and accurate description of its system and for providing a written assertion that will accompany the system description, both of which will be provided to report users.

The service auditor is responsible for obtaining an understanding of the service organization's system and developing the test plan to evaluate whether the controls specified by management were designed, implemented, and operated effectively to provide reasonable assurance that the service organization's service commitments and system requirements were achieved based on the applicable trust services criteria. During the examination, management must provide unrestricted access to records, personnel, and other resources requested by the service auditor. Management must also disclose any known instances of noncompliance with laws or regulators, fraud, deficiencies in control design or operating effectiveness, or other significant incidents that resulted in the impairment of the system or service. The service auditor is required to consider the materiality of any identified risks during the course of executing its examination procedures.

### Generating the Audit Report

The service auditor is responsible for issuing a report that expresses their opinion about whether the system description was presented fairly, the controls were suitably designed, and, in the case of a Type 2 report, whether controls operated effectively during the specified period to achieve the service organization's service commitments and system requirements based on the applicable trust services criteria. The service auditor includes descriptions of the tests of controls performed and the test results in the final report. If uncorrected misstatements or control deficiencies are identified, the service auditor may design and perform additional procedures to obtain sufficient appropriate evidence needed to form a conclusion. However, if sufficient appropriate evidence cannot be obtained, the service auditor is required to modify its opinion.

At the conclusion of the examination and prior to report issuance, service organization management will modify their assertion (if required) to align with the service auditor's opinion and will provide the service auditor with written representations. The service organization management is responsible for controlling distribution of the final report once it is issued.

### Supplier Response

When control testing deviations are identified, supplier management can choose to disclose root cause, mitigating factors or compensating controls, and/or remediation activities performed to respond to the deviation within the examination report. This information may help users of the report to evaluate and understand the impact of the identified deviations, as well as reduce the need for users to request this information from the service organization. Management can describe this information in the description of its system, in which case it is considered within the scope of the examination and requires the service auditor to perform audit procedures to validate the information described by management. Alternatively, management can include this information within an "Other Information" section, which is not covered by the auditor's report and is considered an "unaudited" section.

### Sustaining the Audit

The general expectation in the financial sector is that SOC audits are repeated annually. Many life sciences firms do not conduct their own onsite audits that frequently. However, review of an annual SOC audit is appealing because this process will often be the sole source assessment for those suppliers that would not normally permit a QA audit (e.g., large cloud-service companies). Furthermore, the supplier will want to present reasonably fresh results to potential new customers. Ergo, suppliers should plan on an annual cycle for SOC 2+ audits.

### Leveraging the Audit at the Life Sciences Company

It is imperative for the customer who plans to reference an SOC 2+ report to understand that this is simply one tool for supplier evaluation, albeit a very important one (and, sometimes, the only one). Nonetheless, the life sciences company is still ultimately responsible for ensuring that any supplier-managed applications are appropriately validated and that the data managed by the supplier have integrity.

The life sciences company will obtain the most recent audit report from the supplier. Ideally, it should be a Type 2 report, which examines the controls over a defined period, rather than a Type 1 report that only considers a point in time.

Before evaluating the SOC 2+ report, the life sciences company will need to document its own user requirements and assess them for risk. If this step is not taken, the company will find it very difficult to recognize critical deficiencies and drive appropriate corrective actions (either internal or at the supplier), if any are uncovered.

### Acting on the SOC Report

There are two potential reasons why the SOC 2+ report might not satisfy the life sciences company.

1. The report may reveal deficiencies that the company deems unacceptable. It is important to realize that this conclusion is based on customer risk and may be reached even if the auditing firm finds that the supplier is adequately controlled.
2. Even if the auditing firm has concluded that all controls are in place and operating effectively, the life sciences company may still conclude that the SOC 2+ report alone is not evidence of control, either because of the report's level of detail or because some service aspects are insufficiently covered.

If the SOC 2+ report is not enough to satisfy the life sciences company of the supplier's ability to meet expectations, additional evaluation may be necessary, most commonly via an onsite audit that focuses on controls deemed inadequate or missing. If the concerns are minor, they might be addressable via remote evaluation of additional evidence.

In some cases, a supplier (e.g., a large cloud-service supplier or a software developer whose main customer base is in not the life sciences industry) may be reluctant to support a customer audit, especially in view of the fact that the supplier has spent a considerable sum for the SOC audit. In such cases, the life sciences company may need to make a somewhat uncomfortable judgment as to how much evaluation is really enough. Some companies may conclude that they cannot use a supplier with an unsatisfactory or incomplete SOC 2+ report if that supplier refuses to support an audit.

## CONCLUSION

In the constant effort to both control costs and ensure maximum performance and flexibility, life sciences companies will likely need to leverage services from suppliers whose primary customer base is not the life sciences industry. Several factors make the SOC 2+ process a potentially valuable tool in the QA arsenal.

## Appendix: Example of a Trust Services Table

The appendix to this article is available on the *Pharmaceutical Engineering* website at **www.ispe.org/soc-2+**

- The SOC 2+ methodology has been proven effective for years in the financial sector, where data integrity concerns are every bit as serious in the healthcare sector.
- The SOC 2+ audit provides stronger evidence of compliance for the controls being evaluated because the conclusions are supported by testing.
- The cost of supplier evaluation processes should decrease for both the life sciences company, which is receiving the audit report for no cost, and the supplier, which must support one expensive audit but is relieved of the repetitive process of supporting multiple single-client audits. If further evaluation is deemed necessary by the life sciences customer, it will be briefer and much more focused, even if it involves an audit.
- Audit results should be more consistent because they are generated by experienced auditors from an independent third party who test evidence in support of conclusions.
- The ability to do an annual review of a refreshed SOC 2+ report provides assurance that supplier processes remain in a state of control. This is a substantially more frequent period of assessment than most companies can currently achieve.

Given these factors, it would be highly advisable for the life sciences industry to take advantage of this process, and for regulators to recognize its value as a tool for ensuring data integrity.

### References


1. Bredesen, A., S. Brooks, J. Buffi, W. Cappucci, M. Cherry, C. Clark, G. Evans, H. Hambloch, C. Jones, P. Kane, T. Margetts, A. Perez, P. Robertson, K. Samways, D. Selby, G. Wingate, and S. Wyn. "M2 Supplier Assessment." In *GAMP 5 Guide: Compliant GxP Computerized Systems*. Tampa, FL: ISPE, 2008.
2. American Institute of Certified Public Accountants. "Clarified Statements on Standards for Attestation Engagements." Accessed 21 May 2019. https://www.aicpa.org/research/standards/auditattest/ssae.html
3. SSAE16. "Trust Services." Accessed 30 May 2019. http://www.ssae16.com/SSAE16_trustservices.html


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# THE DIGITAL TWIN:
## Creating Efficiencies in a Virtual World

By Andrew Whytock

The Pharma 4.0 Special Interest Group is focusing on key technologies that will modernize pharmaceutical manufacturing and facilitate digital transformation. These technologies include digital twins, augmented reality, artificial intelligence, big data and analytics, mobiles, cloud, advanced robotics, and three-dimensional (3D) printing. This first article of a series about these enabling technologies discusses the digital twin.

German manufacturer Bausch + Ströbel plans to make engineering at least 30% more efficient by 2020 (source: Siemens).

How are pharmaceutical companies getting value from their data, both in production and development? What technology is needed to build a 3D model of a plant or equipment so that a process can be pretested or programmed? How do we simulate a complex production line or process so that we can build it quickly and efficiently? The answers to these questions lie in the creation of a virtual world, and, more specifically, the creation of a digital twin (a virtual replica of a physical entity).

Digital twins are widely used in the pharmaceutical world, from the creation and modeling of manufacturing processes to enabling the analysis of how a medicine will work inside the human body. The common factor in these various applications is using software to create a virtual replica and then performing simulations on that model.

In drug development, companies create digital twins to create models and then analyze and predict how a process or material will behave. For example, how will materials react together in a machine or how will a device, such as an inhaler, distribute a drug substance?

In production, a digital twin can be useful for entities ranging from individual machines to entire production lines. Complex production routes can be calculated, tested, and programmed with minimal cost and effort in a very short time. Simulation and testing of a production environment can optimize the design of operations or identify and prevent potential failures. Capital investment can start later in relation to the clinical trial process and closer to actual commercialization, obviating the need to invest significantly before market authorization. The digital twin can also permit virtual commissioning, revealing potential defects and enhancing engineering efficiency by 30%.

Digital representation of a chemical API process (source: Siemens).

The objective of the digital twin is to constantly gather operational data from products or production. Information such as the status of a piece of equipment or energy data can be continuously monitored, making it easier to perform predictive maintenance, prevent downtime, or optimize energy consumption.

The digital twin can also permit virtual commissioning, revealing potential defects and enhancing engineering efficiency by 30%.

Pharmaceutical companies are increasingly employing digital twins to develop solutions for the digital design of products, the digital engineering of plants, and the use of digital tools to simulate and monitor performance. There is enormous potential for the pharmaceutical industry to maximize benefits from the numerous use cases that the digital twin can offer, and it is reassuring to see that many companies are already investing in the different tools and skill sets that are needed.

**About the author**

**Andrew Whytock** works in a global pharmaceutical expert center for Siemens in Karlsruhe, Germany. He has global responsibility for the Siemens digitalization and innovation initiatives in the pharmaceutical industry. His principal focus is to work with different organizations to provide insight on Industry 4.0, Pharma 4.0, and digitalization, facilitating the transition toward the digital pharma enterprise. Andrew is an active member in both the ISPE 4.0 Special Interest Group and the BioPhorum Technology Roadmap Steering Committee. He has been an ISPE member since 2017.

# 2019 ISPE ASEPTIC CONFERENCE:

## Interactive Regulatory Panel Addresses Multiple Aseptic Issues

By Jörg Zimmermann and Susan Sandler

The Interactive Regulatory Panel session at the end of the 2019 ISPE Aseptic Conference is one of the most popular conference sessions each year, and the 19 March session at this year's conference was no exception.

Regulators from the US Food and Drug Administration (FDA) addressed a broad range of questions from attendees on topics from restricted access barrier systems (RABS) to smoke studies and artificial intelligence in the aseptic arena.

### PANEL MEMBERS

This year's panel roster:

- Christian Lynch, Consumer Safety Officer, Office of Compliance and Biologics Quality, FDA/CBER
- Lynne Ensor, PhD, Deputy Director (Acting), Office of Process and Facilities, FDA/CDER
- Rebecca Dombrowski, Facility Reviewer, Division of Inspectional Assessment, FDA/CDER
- Richard (Rick) Friedman, Deputy Director, Science and Regulatory Policy, Office of Manufacturing Quality, FDA/CDER
- Robert Sausville, Director, Division Case Management, FDA/CBER

Sausville acted as moderator for the session and participated in the discussion. He noted that the FDA has been coming to the ISPE Aseptic Conference for 25 years and observed the emphasis on cell culture at this year's conference.

The regulatory panel

### Q AND A

The following are selected questions posed (in bold) and the panel's responses.

**We have a conventional filling line in operation and we are considering upgrading to a RABS. However, we are afraid that we make our current line look bad when we submit. How can we overcome this?**

If the questioner is adding a new line in addition to a legacy line, then a RABS or isolator is definitely recommended, Friedman said. He noted that adding a RABS around an existing line will not necessarily make it safer and, in fact, could have unintended consequences or risks. The aseptic processing line should be replaced or thoroughly redesigned.

"We do want to note that we encourage and hope that any new line would be a RABS or an isolator," Friedman added.

### How do "live" viable monitoring systems (fluorescence and light scattering) fit in with traditional EM [environmental monitoring] setups? Can settle plates be removed if utilized?

Because vendor products may vary, Friedman said the panel would not "make large, broad pronouncements." If the product under consideration is good, and the user has qualified it, the product could be a good addition to the aseptic processing line. He noted that some methods allowing microbial capture and identification should still be in place and active air monitors are recommended. "The origins of microbial contamination can be understood, but you must know the hazards to address them and the route of contamination. Microbe identification is a key part of any investigation."

Ensor said that emerging technologies may be used: "Qualify them to meet testing needs and have backups" to be able to identify organisms.

### What are the expectations for automated glove testing for nonisolator applications, given that existing technology cannot detect holes smaller than 100 micron?

Dombrowski noted that by asking this question, the questioner showed that they understood the limits of testing systems and current capabilities of visual eye and existing systems. She noted the potential to investigate whether a higher rate of failure is attributed to docking or a system malfunction. "Expect that you are looking for leaks in those systems," she suggested. "Focus on some limits and capabilities of the systems and considerations for alternates."

### Our firm is moving toward single-use bulk bags. Is a postuse integrity test of the bag necessary?

Lynch responded that there are two categories, depending on what is being stored. Either sterile bulk or bioburden controlled bulk. For sterile bulk CCIT [container closure integrity control] qualification or stability testing is expected to show whether the bag maintains sterility. Lynch's division focuses on integrity and sterility; this scenario may warrant contacting a product office expert. "If you have a bioburden control bulk in the bags, we are not recommending that pre- or post-integrity inspecting be required at this time."

Dombrowski commented on incoming controls for single-use technologies for bagging materials, noting that it is necessary to identify the vital components upon receipt of that system. "What is important in the single-use technology? All the different ports and connections as part of incoming component controls?"

### What are the expectations for glove testing for an open RABS or a barrier with glove ports that is not quite a RABS? Most regulations are for isolators.

Sausville noted that there are no US regulations for isolators, only guidance. Dombrowski said this relates to the previous discussion about glove testing. "The onus is on the operations/facility to understand the risks of the system you are using to detect leaks in the system," she said. While the previous response addressed leak detection, other considerations include the ergonomics of glove locations. "Are there risks in those glove ports that could be addressed through simple changes in design?" Dombrowski asked.

### Do all interventions need to have a separate smoke study? Or can setup-type interventions be utilized to justify?

Friedman explained that smoke studies are a little different from media fill; you can still perform interventions in a program in a representative way, depending on the severity of the intervention. "Smoke studies may be able to do more grouping of types of interventions that occur," he said. However, he noted that smoke studies are subject to inspection and should include rationales and representative interventions.

### Does the FDA allow the use of AI [artificial intelligence] in the product manufacturing process? Or is there some limitation to introduce AI to process?

Dombrowski said there is no prohibition on AI use in manufacturing processes and noted some ways it is used in training simulations for operators. "There are limitations and you should understand what they are to your process. What is the risk of introducing the new technology? It is the same questioning as with any new technology. We don't have a prohibition, but we need to understand what the system is being designed for." She noted that the question was broad; therefore, her response was broad.

"Humans are still responsible for monitoring and supervising operations," Friedman added. "Humans write software." Sometimes, we have to do work-arounds for unexpected scenarios encountered in software, or the right type of actions were not prescribed by the software to address those risks. Therefore, "software has limitations and you should not expect it to be a panacea." Complexity and complex processes warrant consideration. "Don't be afraid, but don't be overconfident that AI will solve everything. Risks from new technology will be different, but there will still be risks."

### What is the expectation for qualification of aseptic operators? Can we create a separate media fill/process simulation solely for the qualification of operators?

"It's a media fill, not a practice run—it counts," Friedman said. He also noted that the FDA has seen an incremental introduction of operators into line interactions. "There's that kind of apprenticeship that generally takes place. A lot of companies do broth testing and have them do some work in a hood with broth exposed to see if there is good aseptic technique." The FDA sends its own staff to hands-on aseptic processing courses, and Friedman noted that there are various options for the training, including in-house opportunities at some companies, offerings at local universities,

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and training via partnerships between industry and universities.

Ensor asked, "Why do you need to qualify operators outside of the media fill process? Is there a shortage? If [a manufacturer is] carving out the qualification just for operators and not having media fill, what does that do for any product made on that line? It has to be a media fill and it will count, and you are accountable if things fail. Build skills and talents of aseptic processors so when there is a media fill opportunity they will be successful."

### With the movement toward closed system, what is the expectation of sterile filtration in relation to the filling equipment? Is it better to have preuse, poststerilization integrity testing?

Regarding sterile filtration prior to filling, Lynch said, "We can't cover every scenario. There are three general ways: SIP [sterilize in place], do connection in grade A, or use a sterile connect system. The latter is what many have chosen; as long as you are following established procedures and GMP, these have been acceptable for years in CBER from the biological side. So you could use it on grade C."

Ensor added, "In CDER we have seen them in biologics or biosimilars in large molecules. Typically, this is done in the grade B area."

Friedman said, "A true, fully exposed aseptic connection would be grade A. We have seen leaks at times and other deviations that would have to be investigated. There are different vendors for closed systems. Whether truly closed or not is a question. You have to address it, just like disposable bags: make sure the incoming closed system is really reliable."

Addressing integrity testing of sterile filters, Sausville asked, "Should you do a preuse, poststerilization integrity test? We expect a postuse integrity test, but not sure if you need to do a preuse test."

### Can you tell us how a modern, highly automated BFS [blow/fill/seal] system compares to isolators and cRABS [closed RABS] fill/finish systems? (Related to work from Ljungvist, Reinmuller, Sinclair, and Tallentire.) [Addressed to Friedman]

Friedman said that BFS technology is better than cRABS because BFS does not require stopping to resterilize. "cRABSs are often manually disinfected but some are autodecontaminated and just as good as BFS."

### In response to a sterility failure event, what is the expectation for recovery and investigation prior to resuming commercial production?

Dombrowski said it could range from days to weeks. "Understand the scope of the impact of the failure of sterility. Get a very thorough understanding of the potential root cause" of the infection. "Different root cause analyses can be gone through to understand how the event occurred. Understand corrective actions to address the root cause and preventive actions moving forward in addition to the scope and impact of other products," said Dombrowski.

Friedman added, "That's a good answer. Look at existing guidance! Baseline for sterility failure event, look at aseptic guidance. Understand routes of contamination that can exist." He urged the attendees to look at all possibilities, including those related to original design, because the source of contamination could be further away than you might think.

### What is the FDA position on quantity filled during routine media fills?

Ensor said to look at the FDA's 2004 aseptic manufacturing guidance. The general rule is 5,000 to 10,000 units for larger batch sizes, but media fill expectations for a smaller batch should be largest batch size. Regarding exposure time, Ensor said to expose components used in the manufacturing process to worst-case environmental contamination scenarios. This should be done for the same situation for the longest filling time; piggyback after production and media fill after; or start/stop. Production parameters should be assessed to see how to capture all worst-case scenarios. Regarding frequency expectations for a routine lyophilization process, the best recommendation is to matrix those to different sizes that need to be lyophilized. If there are different lyophilizers, the same or similar lyophilizers should be checked and the differences noted for the agency. Finally, for frequency of interventions, Ensor said to, perform worst-case checks through media fills.

### Lyo [lyophilized] vial transport to loading through full HEPA coverage workspace using closed carts: Should carts also have HEPA coverage or is ceiling HEPA sufficient?

Lynch said, "We don't recommend just ceiling HEPA as sufficient coverage, given stoppers are only partially seated at this point. We prefer an automated transfer system if possible with grade A coverage over that. From the biologics side, a lot of firms are going to transfer trolleys with full HEPA availability within the transfer trolley."

Friedman added, "Closed carts without HEPA filters—we have seen media fill failures with lyo transfer. Transfer really is a critical control point. A cart without a HEPA filter is a dead space. When taking exposed units out, there is a real chance to contaminate. Carts with HEPAs have their own deals. Integrated, automated transfer from filling machine to the lyophilizer is where you should be," and that will be economical for most lines. Admittedly, this might not be the case for very small batch sizes.

### Is it reasonable to risk-justify using two-way traffic flow and combined PALS/MALS [personal airlock system/material airlock system] airlocks when transitioning into the grade C background surrounding an isolator?

Dombrowski said it can be reasonable to risk-justify that. The size of operations may be a valid reason for facility design, although she noted that it is not ideal. Separating those processes would be more appropriate; however, "there is no hard-and-fast yea or nay."

Friedman noted there are myriad facilities, and all are different. "In a conventional facility, it is frowned on, less important in isolator technology. There are reasons for unidirectional material and personnel flow even in an isolator paradigm," he said, which prevented him from being able to answer the question.

### Can open RABS be surrounded by grade C environment? Modifications: (1) alarmed airflow sensors at critical room/RABS interfaces; (2) frequent VHP [vaporized hydrogen peroxide sterilization] of RABS and room; (3) strict closed-door SOP (like isolator)?

Lynch said it would typically be a grade B environment, depending on how closed around the unit is, but this is dependent on many specifics. In a grade C environment, Friedman can only imagine having a highly automated isolator unit.

### What is the driver around sampling the external surrounding environment (grade A/B) of aseptic production when there is an ample amount of sampling in the critical processing area as well as barriers?

Dombrowski said, "Broadly, a continual state of understanding of your operations is the driver. Inputs: personnel, materials, daily facility and equipment functioning, equipment moving into spaces—there is a lot of activity in these spaces that would lend to driving force for understanding what is happening in that environment in that dynamic state. Each under its own separate controls is one separate aspect."

Friedman agreed that there is a need to understand the factors raised by Dombrowski. He said, "There's nothing like aseptic processing to make everyone humble! Problems may come up 10 years into an operation, and it could take a year to resolve." Dombrowski concurred, saying, "There are so many sources of variability."

### What is the agency's stance on rejects during the filling process vs. inspection process where only critical rejects are allowed to be removed? Specifically for partially stoppered lyophilized products.

Sausville asked, "Simulation in aseptic process? It depends. Some will need to be incubated."

Ensor asked, "What denotes a critical reject? Learn about process or state of control; anything that could be incubated, you could learn information about your system. Identification for rejects should be very similar to process simulation and production. If there are any critical rejects, it is important to investigate the root cause. If intact, where is the organism coming from?"

### What is the opinion and recommendation for using a facility for both GMP and non-GMP activities?

Sausville said it depends on the size of the facility—some do both.

Dombrowski had no blanket opinion. She asked about controls and differentiating requirements, as well as differences in requirements, for pharmaceutical products. She does not see this occurring on the same lines in research but some of the same requirements apply.

Sausville added that cleaning and changeover would be important in this scenario.

Friedman suggested following the World Health Organization's guidelines, stating that nonpharmaceutical and pharmaceutical products should not be made in the same facility. On using GMP and non-GMP standards, he asked, "Isn't it hard enough to get people to follow one standard?"

### When validating a lyo process at a CMO, three lyo units are considered identical but their qualifications are 14+ years old. What type of validation is required? (One run in each? How much mapping?)

Ensor noted, "When things are considered identical, what does that mean exactly? We need to know. Have the old lyophilizers been requalified? Use them once annually on a media fill. If older equipment is not qualified, you would do initial qualification, and have a defined protocol for qualification and requalification."

Lynch agreed, suggesting that manufacturers "have a validation master plan with appropriate requalify parameters and timelines." Dombrowski asked, "Older equipment, changes—how can you consider them identical with life-cycle changes?"

**Disclaimer:** This is an abridged, unofficial summary of FDA regulators' responses to attendee questions and related discussion during a panel dialogue at a conference. It has not been vetted by the agency. The responses are an informal and brief synopsis of the panel's views and do not represent official guidance or policy of the FDA.


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# ACCELERATED PHARMACEUTICAL

## Product Development, Registration, Commercialization, and Life Cycle

### CMC LESSONS, PART 1

By Christopher J. Potter, PhD, Huimin Yuan, Nina S. Cauchon, PhD, RAC, Liuquan Lucy Chang, Derek Blaettler, Daniel W. Kim, PharmD, Peter G. Millili, PhD, Gregory Mazzola, Terrance Ocheltree, PhD, RPh, Stephen M. Tyler, Geraldine Taber, PhD, and Timothy J. Watson

This article is Part 1 of a two-part series exploring what we can learn from examples of pharmaceutical products being approved using accelerated programs. The series focuses on challenges that chemistry, manufacturing, and control (CMC) development teams may encounter when a project is given accelerated development status. Part 1 introduces key considerations and themes in general terms and highlights future opportunities in accelerated pharmaceutical product development. In Part 2, which will be published in the next issue of *Pharmaceutical Engineering*, we will provide more detailed discussion of the considerations and themes and present several case studies.

The series concentrates on lessons from small chemical molecule (synthetic chemical) and biotechnological and biological molecule projects. However, many of the key considerations and themes will be applicable to those involved in development of newer, more advanced therapies. (Note: This article uses the terms "small molecule" and "large molecule" as shorthand for small chemical molecule [synthetic chemical], and biotechnological and biological molecule, respectively.)

During the past decade, there have been significant scientific and clinical advances resulting in more drugs being developed to treat patients' unmet medical needs. These advances have led to patient expectations that these new drugs will be quickly made widely available. In response, regulators globally have developed improved regulatory pathways and issued guidances. However, as demonstrated in case studies, companies face significant challenges when managing postapproval changes globally. Such challenges can have a substantial impact on the supply chain and on a company's pharmaceutical quality system (PQS).

## REGULATORY TRENDS AND DEVELOPMENT IMPLICATIONS

New regulatory guidelines intended to expedite the treatment of unmet medical needs through small molecule and large molecule products tend to fit broadly into two categories:

- Improvements to regulatory pathways
- Technical guidelines for newer types of advanced therapy (e.g., gene therapy)

Significant changes in regulatory pathways began in 2012, when the Breakthrough Therapy designation was included in the US Food and Drug Administration (FDA) Safety and Innovation Act [1]. This

development was followed by associated FDA guidance in 2014 [2], and the PRIME scheme [3], which launched in the European Union (EU) in 2016. These pathways and guidelines can streamline regulatory processes; however, there is potential for differences in interpretation of clinical entry requirements for the pathways, which could lead to inconsistencies in criteria for acceptance, and timing of acceptance, into the appropriate regulatory program.

Other countries and regions have also introduced expedited registration pathways [4]. Examples of countries with accelerated pathways are:

- Japan [5]
- Australia [6, 7]
- Canada [8]
- China [9]

The World Health Organization (WHO) has issued a collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities [10]. Publications from other regulatory authorities (Brazil and Saudi Arabia) are listed in the references [11, 12]. In addition to these options for accelerating registration of medicinal products, the FDA issued a final guidance in 2018 on its Breakthrough Devices Program [13]. This final guidance outlines program policies and features and describes the process for manufacturers pursuing the Breakthrough designation.

Regulators have been challenged to keep pace with the tremendous advances in medicine in the last two decades, which have resulted in ongoing development of novel modalities as clinical therapeutics. Cell therapies include both autologous and allogeneic approaches based on T cells, lymphocytes, antigen-presenting cells, and dendritic cells. The diverse array of other modalities includes oncolytic viruses, novel engineered antibodies, antibody-drug conjugates, protein machinery for gene editing, neoantigens, highly modified peptides, and nucleotide-based therapies (including mRNAs, small interfering RNAs [siRNAs], antisense oligonucleotides, and aptamers).

In 2017, the FDA introduced an additional expedited regulatory pathway applicable to advanced therapies, the Regenerative Medicine Advanced Therapy (RMAT) designation [14]. For sponsors of a qualified regenerative medicinal product (i.e., cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products) intended to treat serious or life-threatening conditions, RMAT can provide advantages similar to those of the Breakthrough Therapy designation, such as priority review and access to early and frequent interactions with the FDA.

To provide more technical guidance, in 2018 the European Medicines Agency (EMA) issued a revision of the Guideline on the Quality, Preclinical, and Clinical Aspects of Gene Therapy Medicinal Products [15]. The quality section addresses mainly the specific requirements for the development and manufacture of a gene therapy medicinal product (GTMP). In this revision, the guideline has been completely reworked to give guidance on design, manufacture, characterization, and testing of a wider spectrum of delivery vectors (novel viral vectors, as well as nonviral and bacterial vectors).

Cross-regulatory authority interaction is occurring. For example, in November 2018, FDA representatives participated in a one-day workshop hosted by EMA, at which industry experts presented case studies of CMC challenges and approaches to accelerated development. A report of this workshop is anticipated later in 2019; slide presentations are currently available [16].

Recent efforts to streamline regulatory processes benefit sponsoring organizations and patients by expediting the approval of medically needed treatments (advancements). Case studies show that, because of the fluidity and evolving nature of the regulations, sponsors must negotiate with each regulatory authority separately on a case-by-case basis. This has to be done quickly so that output from the negotiations can be used as feedback to shape the evolving CMC project development plan. Practitioners tend to determine the latest requirements by directly contacting regulatory authorities. The websites of ICH and/or a regulatory authority may be helpful resources; however, these sites may not contain the latest information relevant to a sponsor's project.

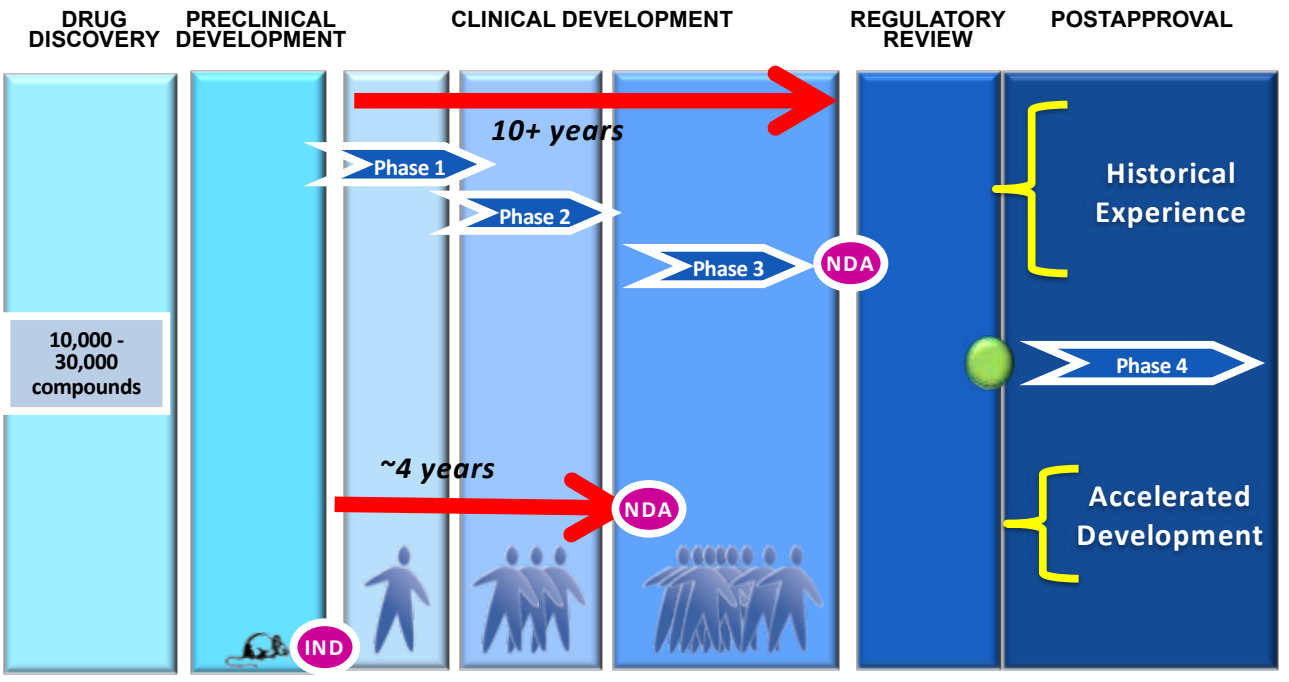
Case studies demonstrate that CMC/quality-related issues are rate limiting for all modalities, and especially so for cell and gene therapies. Aside from safety-related issues that occur in the clinic, the greatest hurdle to approval for cell-based therapies is often not clinical efficacy, but CMC and manufacturing due to the nature of many of these therapies, their inherent high biological variability, and the speed of the development program. It seems that risk-based solutions for CMC issues for all modalities such as identity, potency, specification testing, stability, and comparability are being worked out one case at a time.

However, the regulatory expectations and regulations associated with the CMC portion of a submission for small chemical molecules and biotechnological and biological molecules as defined by the scope of ICH guidelines Q6A and Q6B [17, 18] have not changed.

A 2015 article by Dye and colleagues [19] suggested that a regulatory filing for a drug in an expedited (accelerated) development program could be 18 to 24 months shorter than a conventional program, which would pose significant challenges for those parties responsible for delivering the normally expected CMC information. At that time, there were few examples of regulatory agencies having approved Breakthrough Therapy development programs at an early stage in development (i.e., after receipt of preclinical or early clinical positive information). Therefore, the paper by Dye and coauthors was based on examples—some real, some projected—of accelerated development of both small and large molecules. In the intervening period, companies and regulators have gained experience from actual cases of making exciting new medicines available to patients from accelerated development programs.

Regulators are taking a positive approach and supporting accelerated development regulatory pathways. For example, the FDA's Center for Drug Evaluation and Research (CDER) approved

Figure 1: An example of comparative drug development timelines: Historical experience vs. accelerated development.




71 Breakthrough Therapy designations as of 31 December 2018 for original new drug applications (NDAs) and biologics license applications (BLAs) and the FDA's Center for Biologics Evaluation and Research (CBER) approved 6 BLA Breakthrough Therapy designations through 30 September 2018 [20, 21]. EMA accepted 48 medicines into the PRIME scheme as of 19 December 2018 [22].

Part 2 of this series will present an actual small molecule case study that illustrates how an accelerated pharmaceutical (clinical) program impacts the CMC program and its associated studies. In this case, the time from first dose in humans to NDA submission was about 4 years, whereas historical experience indicates that "typical" development timelines can take up to 10 years (see Figure 1).

## CMC CHALLENGES, KEY CONSIDERATIONS, AND THEMES

Like other stakeholders in the pharmaceuticals industry, ISPE recognizes the importance of accelerated development to patients, regulators, and manufacturers. Notably, the success of accelerated development programs has resulted in more instances where the CMC program is on the critical path to approval and supply to patients. Therefore, an ISPE team has been working for over a year on collating and sharing experiences among companies relating to the actual challenges faced by CMC development teams that are working to obtain initial approval while, at the same time, supplying products for ongoing and new clinical studies, and, most importantly, supplying products to patients globally.

Although each accelerated development program is unique and faces its own distinctive challenges, some CMC issues may be common to most or all programs. Review of the case studies on which this series of articles is based indicates typical CMC stress points are:

- The potential for suboptimal drug substance route/process and drug product formulation.
- Site readiness for commercial supply for a suboptimal process—for example, use of a clinical process and site to support initial submission, approval, and launch, followed by postapproval changes using an improved process, which is potentially developed in parallel with initial submission.
- The amount of stability data to support a practical shelf life at the time of approval.
- The process validation strategy, particularly for large molecules, where there may not be time to complete at least three batches manufactured at commercial scale with data submitted in the BLA application.
- Setting specification acceptance criteria, particularly for a large molecule, where there may have been relatively few batches of product administered to patients.
- Studies and/or planned changes proposed to be conducted and submitted postapproval. This approach leads to great supply chain and regulatory complexity. For example, companies may need to use the clinical process to produce supplies for clinical studies, and potentially for the product launch, while simultaneously introducing a more efficient manufacturing process to supply patients more reliably. Supply chain issues, regulatory submissions, and, most importantly, approvals

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all must be juggled, which creates a significant resource and logistics burden, especially because the timing of approvals varies by region or country.
- The availability of resources, in terms of both quantities and levels of expertise. Depending on the company situation, resource issues may be partially mitigated by, for example, moving people from lower-priority projects (for a large company) or outsourcing. However, given the specific nature of the technology, it is highly unlikely that resources to support all desired studies can be accessed in the desired time frame.

Although there is no "one-size-fits-all" approach to accelerated development programs, some key considerations and themes can be highlighted from the case studies that inform this series of articles. Table 1 summarizes considerations of accelerated development programs, which include not only the expectations of regulatory authorities, but also the needs of the patient and company.

Underpinning many of these key considerations and themes is use of prior knowledge (for example, from platform processes or technology). There is also a need to accelerate the development of new knowledge to support justifications in discussions with regulatory authorities, regulatory applications, risk-management processes, and project planning. The case studies in Part 2 of this series will highlight where prior knowledge has been used, and one case study will show how computational modeling, simulation, and predictions can assist with decision-making and risk mitigation.

## FUTURE OPPORTUNITIES

Case studies point to many opportunities for both companies and regulators to consider. ICH has started addressing some of these, as evidenced by the technical and regulatory considerations for the pharmaceutical product life cycle in ICH Q12 [23]. However, the scope of this ICH topic does not address the major challenges associated with postapproval changes, such as differences in the regulations themselves, differences in content requirements, and, most importantly, differences in time frames for approval to support certainty of making such changes.

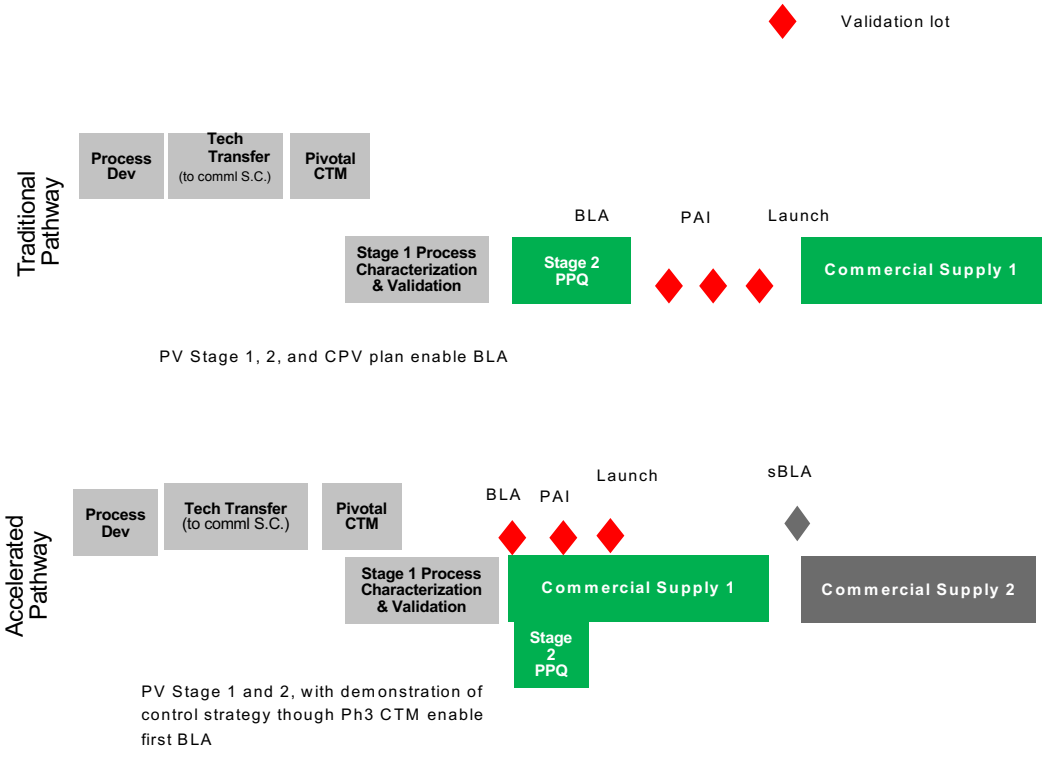
Nonetheless, some flexibilities and lessons are emerging from accelerated product programs and approvals—which could be considered for wider adoption. Future opportunities include:
- More cooperative engagement between a sponsor of an accelerated development CMC program and regulators globally to agree on a harmonized CMC strategy.
- Use of a life-cycle approach to process and analytical validation for both small and large molecule programs.
- A global review of approvals granted via accelerated pathways, with the aim of expanding risk-based assessment and

**Table 1:** Key considerations and themes in accelerated development programs.*

| Key Consideration | Themes |
|---|---|
| Teamwork and project planning | Ensure support by all internal stakeholders.<br>Engage in continual and extensive scenario planning and close monitoring of clinical data expectations.<br>Plan for varying timelines in different countries.<br>Evaluate risks and benefits.<br>Consider a life-cycle approach.<br>Evaluate supply chain options and manufacturing site selection and scale-up options. |
| Control strategy | Estimate and agree with authorities about the level of process and product understanding possible within the timeline.<br>Leverage prior knowledge and platform technologies.<br>Consider analytical readiness.<br>Consider purity and continuity of supply of reference materials.<br>Project how specifications will be justified, especially with low amounts of batch data.<br>Estimate amounts of stability data that could be available at submission and during review.<br>Consider starting material options for small molecule drug synthesis. |
| Process validation | Consider a life-cycle approach.<br>Use a science- and risk-based approach to justify strategy. |
| Pharmaceutical quality system readiness | Consider PQS readiness in line with site-selection strategy.<br>Consider how PQS can adapt to planned and unplanned postapproval changes. |
| Regulatory | Communicate with regulatory authorities as much as program requires and is possible.<br>Use as many postapproval regulatory processes as possible and desirable to support a life-cycle strategy.<br>Produce an easy-to-review dossier that contains scientific justifications and references and is in line with regulatory agreements.<br>Consider the global filing strategy as part of the project plan. |

*In each category, many themes are common to large and small molecules; however, some are specific to a type of molecule. More detailed discussion and considerations for CMC development teams will be given in Part 2 of this series.

Figure 2: Breakthrough Therapy designation based on Phase 1 data.




flexibility into all pharmaceutical development submission and approval processes. Risk-based regulatory decisions (reviews and inspections) were proposed in ICH topics Q8, Pharmaceutical Development and Q11, Development and Manufacture of Drug Substances.

- Harmonized guidelines for some aspects of novel modalities and advanced therapies.

## Improving Cooperative Engagement Between Sponsors and Regulators Globally

Currently, sponsors of products have multiple pathways for communication with the FDA; however, similar levels of interaction with EMA regulators are not always easily achievable. Additionally, sponsors lack assurance that different regulators share the same expectations and requirements for a proposed CMC program.

For sponsors of accelerated development programs, establishing a global CMC program is a key future step.

## Process Validation

Regulatory authorities have sometimes granted, on a case-by-case basis, flexibility in the timing of process validation studies for some large molecule approvals from accelerated programs. Consideration should be given to using risk-based criteria to extend flexibility in the timing of process validation studies to all molecules.

Currently, in the United States and EU, an absolute requirement at the time of file for a biological/biotechnology molecule is that process performance qualification (PPQ) (stage 2) must be included in the submission. An open question is whether some flexibility could be employed.

For example, if pivotal supplies of drug substance and drug product have been manufactured in the commercial supply chain and the subsequent process characterization does not lead to significant alterations of the process, the pivotal batches could perhaps be considered adequate, repeated demonstration that the process control strategy will reliably deliver a drug substance and product that meet the predetermined acceptance criteria. Resulting satisfactory stability data supportive of the commercial shelf life might provide further evidence to support the process control strategy. PPQ data could then be provided during the review cycle (as is common for new chemical entities) or within a BLA supplement or marketing authorization application (MAA) variation.

Figure 2 highlights examples of potential CMC challenges by comparing traditional and accelerated pathways for large molecule process development and validation. A traditional large molecule development approach to process development and validation is given in the top line of Figure 2. The bottom line shows a generalized CMC program for an accelerated pathway, such as one arising after Breakthrough designation is granted for

a large molecule after promising phase 1 clinical data demonstrating efficacy. In the accelerated case, stage 2, PPQ, is proposed in parallel with BLA review and preapproval inspection (PAI).

While the specifics of process validation are critical to agreements reached between sponsor and regulatory authority, a generalized model can be used for illustrative purposes. Nomenclature is based on US Process Validation Guidance [24].

Important to the strategy is the degree of control strategy understanding that accumulates during process development and that can be demonstrated adequately during pivotal manufacture, especially when the drug substance and product are manufactured in the intended launch facilities and supported by validated methods. In this scenario, it may be possible to propose filing the BLA and support the PAI concurrent with stage 2 PPQ manufacture.

This type of scenario calls into question the rigidity of modality-specific validation requirements. Traditionally, sponsors preparing a BLA and/or MAA filing for biological/biotechnological products have considered the completion of at least three PPQ batches to be a required component of process validation for successful market authorization. In contrast, for small molecule products, it has long been considered acceptable to develop PPQ data during review or as a postapproval commitment; although in the EU, validation data for "nonstandard" products also must be provided in the MAA. This difference in expectations is perhaps owing to the difference in the risk-profiles between the two modalities, and the fact that the small molecule products can often be fully characterized using a relatively small set of validated analytical techniques. In decades past, the inherent molecular heterogeneity of biotechnological products led to the now-outdated common wisdom that the "product is the process." As analytical techniques have significantly improved understanding of the structure-function relationship of some biotechnological products, understanding of the effect of product-related variants on the mechanism of action of a proposed therapy has also expanded. Because of this in-depth characterization, coupled with more extensive experimental design within a quality-by-design (QbD) framework and expanding adoption of platform processes (which may include process analytical technology, where possible), the robustness of well-defined end-to-end control strategies has improved, and the predictive ability related to process variability on critical quality attributes has become more precise.

This is all part of the overall process validation strategy, and the life-cycle approach itself refutes the idea that validation is solely based on a small, discrete number of batches manufactured under protocol; instead, validation relies on a continually expanding body of process understanding. Industry case studies demonstrate that in certain circumstances, which are partially determined by the severity of a disease and the degree of unmet medical need, regulators are willing to consider, and indeed approve, market authorization without a full complement of PPQ data or other components previously considered requirements. Instead, sponsors and authorities are jointly reviewing the body of evidence of process control understanding and product quality and making risk-based decisions to determine the point at which the sponsor has, or will have, gathered adequate evidence to warrant market authorization and meet the postapproval obligations necessary to demonstrate that the product is in a continual state of validated control and suitable for administration to patients.

### Global Review of CMC Expectations

The database of approvals of accelerated programs in which sponsors and authorities have used science- and risk-based approaches to submit and review drug product submissions is expanding. From these data, we can identify lessons more broadly applicable to a wider range of drug development programs. A starting point could be the process validation topic, especially as applied to well-characterized biotechnological molecules. Other opportunities could be stability requirements for small molecule drug substances and products, and acceptance criteria for impurities in specifications for small molecule drug substances. These topics could fall under the ICH umbrella, because all except process validation are current ICH topics.

### Harmonized Guidelines for Advanced Therapies

The expanding number of approvals globally of advanced therapies also may present opportunities, again potentially under the ICH umbrella, to develop helpful guidelines for the CMC-equivalent parts of development and submission. ICH topic M6, Guideline on Virus and Gene Therapy Vector Shedding and Transmission, was started in 2009; however, it ceased in 2011 because of issues related to the state of science and resource allocation at that time.

Notably, the EMA Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products [15] contains a section on quality aspects. This could be a starting point for a global harmonization initiative.

## SUMMARY: EVOLVING FROM MODALITY-SPECIFIC TO RISK-SPECIFIC REQUIREMENTS

The industry may be evolving toward a scenario in which the decisions regarding the specific requirements to be included at the time of file should be risk specific, not modality specific. Rather than using a lexicon of categorically defined requirements for a biological/biotechnological product or a small chemical molecule, the discussions surrounding the development of a therapy for an unmet medical need should progress quickly to the best strategy of balancing patient needs with the process and product understanding at the time of file and a strategy of sequential discharge of both clinical and CMC risk. This concept of jointly owned decision-making responsibility between the sponsor and regulatory authority could enable acceleration of process development and unique, collaborative approaches to the validation and filing strategy.

## CONCLUSION

Drawing from the lessons learned from case studies of approvals of drug products developed and approved using accelerated pathways, the ISPE team has produced key considerations and themes

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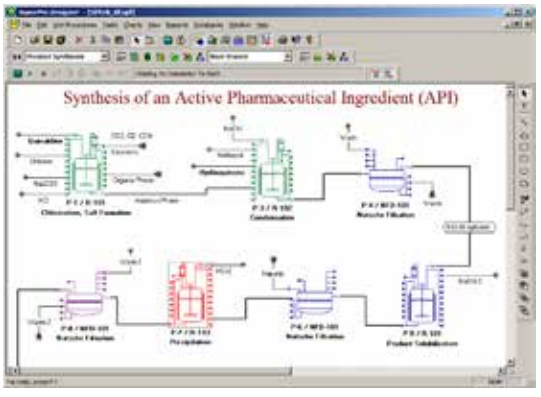


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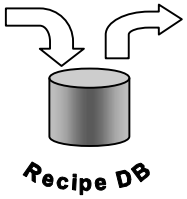


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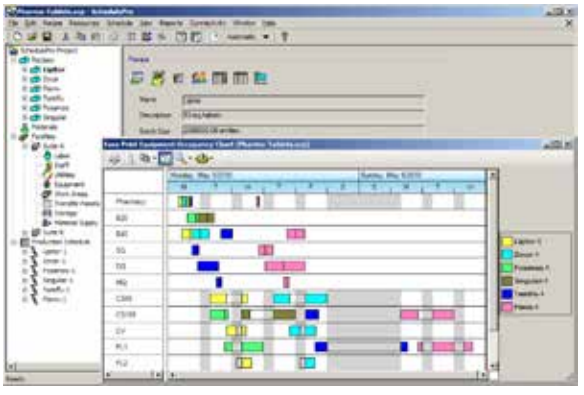

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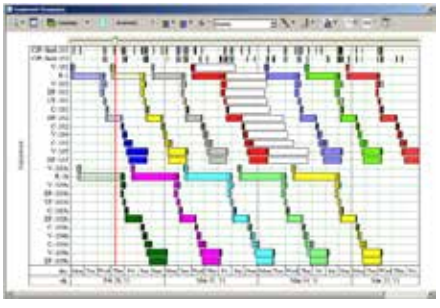

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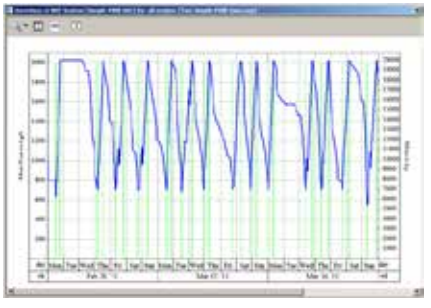

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regarding CMC challenges of accelerated development, which should be of benefit to other practitioners and CMC teams. These lessons and the key considerations apply to both small molecule and biological/biotechnological developments and may be applicable to advanced therapy programs.

At a high level, current model drug development paradigms and associated regulatory pathways may be inadequate to accommodate the rapid advances in personalized medicine and the ever-expanding array of diverse modalities, which show great clinical promise in addressing a variety of unmet medical needs. CMC regulatory flexibility in these types of submissions is therefore warranted to expedite global availability of these medicines to patients.

From these lessons, future opportunities have been identified, including some that could be applied specifically to accelerated development programs and some that could be applied to all drug development programs. Examples are:

- Review of current CMC regulatory requirements for submission (for example, process development requirements at time of submission for well-characterized biotechnological molecules; stability requirements for small molecules; and acceptance criteria, particularly impurities, for small molecule in specifications).
- More use of regulatory pathways based on approvals in Stringent Regulatory Authorities, as proposed by WHO, EFPIA, and others.
- Improved communication between regulatory authorities to ensure that CMC development programs are applicable globally.
- Review of postapproval regulations to improve efficiency and certainty relating to planned postapproval changes.

## References


1. Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144 (2012).
2. US Food and Drug Administration. "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics." Published May 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics
3. European Medicines Agency Committee for Medicinal Products for Human Use. "Enhanced Early Dialogue to Facilitate Accelerated Assessment of PRIority MEdicines (PRIME)." EMA/CHMP/57760/2015, Rev. 1. Published May 2018. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf
4. European Federation of Pharmaceutical Industries and Associations. "White Paper on Reliance and Expedited Registration Pathways in Emerging Markets." Published November 2017. https://www.efpia.eu/media/288590/white-paper-on-reliance-and-expedited-registration-pathways-in-emerging-markets.docx
5. Japanese Ministry of Health, Labour and Welfare. "Strategy of SAKIGAKE." Published June 2014. https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html
6. Australian Department of Health, Therapeutic Goods Administration. "Priority Review Pathway: Prescription Medicines." Published 2 August 2018. https://www.tga.gov.au/priority-review-pathway-prescription-medicines
7. Australian Department of Health, Therapeutic Goods Administration. "Priority Determination." Published 3 August 2018. https://www.tga.gov.au/publication/priority-determination
8. Health Canada Bureau of Policy Sciences and International Programs, Therapeutic Products Directorate. "Guidance for Industry—Priority Review of Drug Submissions." Updated 6 February 2009. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/priority-review/drug-submissions.html
9. Yao, X., J. Ding, Y. Liu, and P. Li. "The New Drug Conditional Approval Process in China: Challenges and Opportunities." *Clinical Therapeutics* 39, no. 5 (2017):1040–51. doi:10.1016/j.clinthera.2017.03.016
10. World Health Organization. "Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products and Vaccines Approved by Stringent Regulatory Authorities." WHO Technical Report Series, No. 1010, 2018, Annex 11. http://apps.who.int/medicinedocs/en/m/abstract/Js23456en
11. da Silva, Jarbas Barbosa. "Regulatory Advances in Drug Regulation Accelerated Pathways of Approval." Brazilian Health Regulatory Agency—ANVISA. Published 2018. http://portal.anvisa.gov.br/documents/219201/219401/ANVISA+JB+DIA+2018+Annual+Meeting+INGL%C3%8AS/4bea5429-ef3c-4b6a-9bb3-324896228c9e
12. Saudi Arabia Food and Drug Authority. "Guidance for Priority Review of Product Registration, Version 2." Published 24 October 2013. https://www.sfda.gov.sa/ar/drug/resources/DocLib2/ProrityReviewV2.pdf
13. US Food and Drug Administration Center for Devices and Radiological Health. "Breakthrough Devices Program, Guidance for Industry and Food and Drug Administration Staff." Published December 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program
14. US Food and Drug Administration Center for Biologics Evaluation and Research. "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry." Published February 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions
15. European Medicines Agency Committee for Advanced Therapies. "Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products." EMA/CAT/80183/2014. Published 22 March 2018. https://www.ema.europa.eu/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-gene-therapy-medicinal-products_en.pdf
16. "Stakeholder Workshop on Support to Quality Development in Early Access Approaches, such as PRIME and Breakthrough Therapies." European Medicines Agency. 11 November 2018. https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough
17. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Q6A." Published 6 October 1999. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf
18. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, Q6B." Published 10 March 1999. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf
19. Dye, E. S., J. Groskoph, B. Kelley, G. Millili, M. Nasr, C. J. Potter, E. Thostesen, and H. Vermeersch. "CMC Considerations when a Drug Development Project Is Assigned Breakthrough Therapy Status." *Pharmaceutical Engineering* 35, no. 1 (2015): 22–36.
20. US Food and Drug Administration. "CDER Breakthrough Therapy Designation Approval as of December 31, 2018." https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM494010.pdf
21. US Food and Drug Administration. "CBER Breakthrough Therapy Designation Approvals." Updated 28 March 2018. https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm413991.htm
22. European Medicines Agency. "Data for Entry into PRIME Scheme." Updated 16 May 2019.https://www.ema.europa.eu/documents/report/list-products-granted-eligibility-prime_en-0.xlsx
23. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Step 2." Published 16 November 2017. https://www.ich.org/products/guidelines/quality/quality-single/article/technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-management.html
24. US Food and Drug Administration. "Guidance for Industry—Process Validation: General Principles and Practices." Published January 2011. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/process-validation-general-principles-and-practices


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ISPE's Core Members are pharmaceutical professionals who use expert knowledge to create high-quality, cost-effective GMP solutions. ISPE delivers technical and operational solutions to support our Members across the global pharmaceutical and biopharmaceutical industry in the manufacture of quality medicines for patients. **Attend one of our conferences, and find out what you've been missing.**

# ISPE SCHEDULE OF EVENTS

## NORTH AMERICA

**2019 ANNUAL MEETING & EXPO**
27–30 October | Las Vegas, NV USA

**2019 Regulatory Conference**
5–6 December | North Bethesda, MD USA

**2020 Facilities of the Future Conference**
30–31 January | California USA

**2020 Aseptic Conference**
2–3 March | North Bethesda, MD USA

## EUROPE AND ASIA

**2019 Europe Biotech Conference**
25–26 September | Brussels, Belgium

**2019 South Asia Pharmaceutical Manufacturing Conference**
25–27 September | Bangalore, India

**2019 Asia Pacific Pharmaceutical Manufacturing Conference Singapore**
30 September–1 October | Singapore, Asia

**2019 Europe Pharma 4.0 Conference**
20–21 November | Manchester, United Kingdom

**2020 Europe Annual Conference**
30 March-1 April | Madrid, Spain

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# ISPE EUROPE ANNUAL CONFERENCE:

## Digitization, Technologies, and More

By Thomas Zimmer

More than 800 attendees met in Dublin, Ireland, on 1–4 April for the 2019 ISPE Europe Annual Conference—a new record attendance for this conference! Participants at ISPE's sixth Europe conference learned about how manufacturers, key suppliers, functional peer groups, and regulators expect the pharmaceutical industry to be affected by digitization, new products, changing portfolios, disruptive technologies, and other factors.

The speakers and others at the conference demonstrated an enthusiastic commitment to finding answers to the industry's challenges. Impressive case studies represented a range of perspectives. Presenters emphasized that pharmaceutical products deserve special attention because no other products affect health and safety as much as pharmaceutical products. Increasingly, health and disease management is managed by the patients themselves, so patients are partners with other stakeholders in the pharmaceutical network, and they can be empowered by new technologies, such as apps, as well as direct communication.

Innovation, at all levels and for all stakeholders, is key to success. The conference attendees made it clear that taking an active role in changes is better than simply following trends.

### EXECUTIVE FORUM

A highlight of the conference's first day was the Executive Forum, in which speakers offered the audience a high-level perspective, including discussions of major developments in the political boundaries in Europe as well as important regulatory developments related to product life-cycle management.

#### Pam Cheng, AstraZeneca

Pam Cheng, Executive Vice President of Global Operations and IT at AstraZeneca, stressed that digital technology will change everything in pharma. Driven by rising costs and new demands for innovation in health systems worldwide, stakeholders will increase their scrutiny of value. Therefore, the industry needs to invest in new digital solutions to solve research, development, and access challenges and drive differentiation in the market. Cheng noted that breakthroughs in digital technology are redefining society and the practice of medicine and explained that AstraZeneca is putting greater emphasis on advancing ever-more innovative science, being more patient-centered, and doing more with digital technology and data. Among the company's areas of technological focus are three-dimensional printing, virtual reality, voice-directed technology, artificial intelligence (AI), digital twins, connected drones, machine learning, and the internet of things (IoT). Figure 1 illustrates the company's view of the factory of the future.

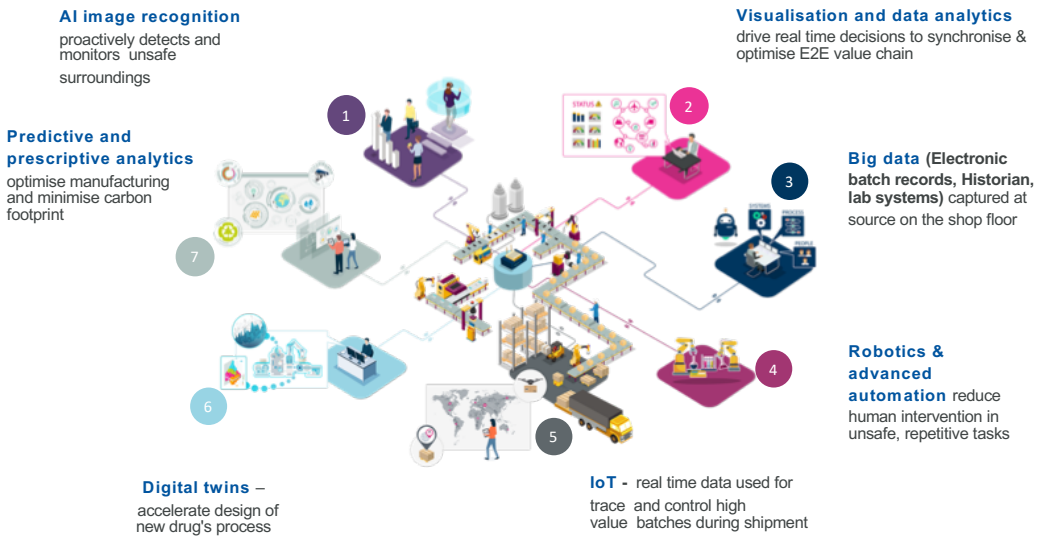
#### Olivier Loeillot, GE Healthcare

Olivier Loeillot, General Manager of Bioprocess at GE Healthcare, presented on biopharma of tomorrow and rethinking efficiency. He addressed the challenges involved in bioprocessing, emphasizing that considerable investment is required while a molecule's likelihood of success is still low. Only 5% of oncology and 12% of nononcology drugs successfully make it to market.

He further noted that it takes an average of 12 years for a drug to go from concept to market. Small batch sizes are becoming more common, driven by biosimilar production, personalized medicine, and higher monoclonal antibody titers.

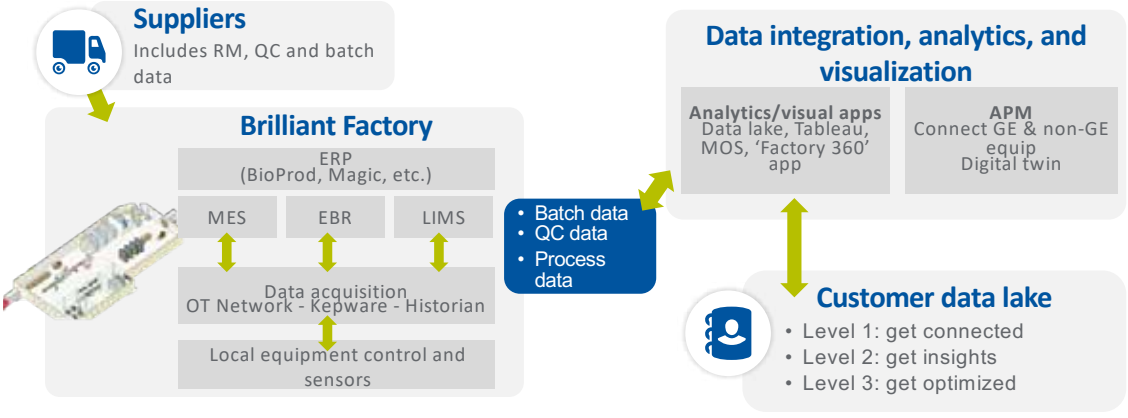
In production, it is expected that there will be no downtime and quality will meet the highest standards. For example, in cell therapy, there is zero tolerance for production failures. Therefore, real-time preventive alerts and a process-monitoring dashboard are essential for 100% assurance that every patient batch is correct.

Figure 1: AstraZeneca's view of the factory of the future.




Source: Pam Cheng, AstraZeneca

Figure 2: Main enablers for moving biopharma forward.




Source: Olivier Loeillot, GE Healthcare

In procurement, manufacturers need to address errors and events rapidly and remotely to isolate the root causes of failure. Loeillot stated that the main enabler for moving biopharma forward is interconnected digital platforms to integrate, analyze, and visualize data for suppliers, factories, and customers (Figure 2).

## Chris Chen, WuXi Biologics

Chris Chen, Chief Executive Officer of WuXi Biologics, reported that his company will have a state-of-the-art biologics production facility established in Ireland within the next two years. WuXi Biologics' strategy is to use disposable bioreactors as disruptive technology and to consider the merits of scale-out (numbering up) versus the scale-up (sizing up) principles in production. Furthermore, drivers and enablers for continuous bioprocessing have been considered.

Chen noted that the challenges of using disposable bioreactors are the current limitation in size, with 4,000 liters being the maximum, and the need for manual installation, which involves tough training requirements. Some cell lines are sensitive to extractables and leachables and require selecting clones that perform well in bags. WuXi Biologics has selected a scale-out strategy based on 2,000 liters to help the company rapidly adjust production to vari-

Innovation, at all levels and for all stakeholders, is key to success.

ous stages in the life cycle and meet unpredictable market demands. The risks associated with cell culture scale-up are eliminated by this approach. Furthermore, the risk of market supply interruption can be minimized by a dual sourcing for supplies. Technology transfer will be much easier, too.

Chen stated that there are limits for bioreactor scale-up to very large scales (from 10,000 to 25,000 liters). He also explained that the forces driving continuous processing include the need for flexibility and speed to market, the demand for more low-volume biologics, business competition, and the desire to restrain the cost of goods.

### Mary Harney, Former Irish Government Official

Mary Harney shared her perspective as a long-time government leader. Over 18 years, she held several ministerial positions in the Irish government, including in the areas of environmental protection, industry, trade, research and innovation, and health. She was deputy prime minister for 10 years and was both the longest-serving woman in the Irish Parliament and the longest-serving female minister.

Harney pointed out that the presence of pharmaceutical plants and technical operations in Ireland is considered a real asset for the country. In general, industry should be proud of driving innovation and creating value for patients in health and disease management, she said.

### Thomas Friedli, University of St. Gallen, Switzerland

Thomas Friedli, Associate Professor and Senior Lecturer of Management at the University of St. Gallen, Switzerland, explained that in recent history, all major pharmaceutical companies have established their own production systems based on the groundbreaking Toyota production system. Nevertheless, companies still face difficulties when they try to quantify the influence of the different system elements on overall performance.

In growing numbers, companies are interested in research on this issue to determine their strongest strategies for their production systems and assign resources accordingly. Using data to further accelerate continuous improvements is essential. In a digitalized industry, more and better data are available for such analysis.

Friedli noted that 94% of companies don't believe that digitalization will make Lean-style management redundant. Also, although digitalization seems easy in theory (and in consulting practice), there are many conceptual challenges to overcome. Therefore, real success stories depend on careful consideration of where "digital" can make a difference. One prerequisite for a successful transformation to industry 4.0 is a plant technology competence framework model, which includes three basic qualifiers: access to skills and knowledge, access to low-cost production, and proximity to market. Decisive factors in this model are automation and manufacturing; human-machine interfaces; data analysis and information and communication technology (ICT); embedded systems; and assurance that activity regarding technology X is also performed for other sites in the manufacturing network.

In conclusion, Friedli recommended that digitalization should be understood to be an opportunity to increase efficiency and improve quality while also taking its complexity into consideration. After having spent some time on an emergent approach, the pharmaceutical industry should move toward the deliberate planning and implementation of digital technologies.

### Graham Cook, Pfizer, EFPIA Topic Lead for ICH Q12

In his presentation, Graham Cook, Senior Director of Process Knowledge/Quality by Design at Pfizer and European Federation of Pharmaceutical Industries and Associations (EFPIA) topic lead for the International Conference on Harmonisation (ICH) Q12 standard answered the question, "Why cover ICH standards in an executive forum?"

He explained that the pharmaceutical industry is the most regulated industry globally, and regulatory standards are essential to ensure health and safety and form a strong foundation for regulatory oversight. To uphold the ICH Q12 pharmaceutical standard, company management is responsible for knowing the principles in the standard and allocating adequate resources to uphold them.

The product life-cycle management components of ICH Q12 can be considered an innovation in regulatory standards with regard to the following elements of postapproval changes (PACs), which can be used for new and existing products:

- Established conditions
- PAC management protocol
- PACs for marketed products, including a structured approach to analytical procedure changes and stability data approaches to support the evaluation of changes in chemistry, manufacturing, and controls

Cook emphasized that ICH Q12 is already serving as an agent for change within regulatory agencies to simplify PAC management and encouraged management and senior experts to "learn by doing."

A positive surprise came when Cook asked the audience, "Did you read the ICH Q12 draft?" and a considerably large number of attendees raised their hands.

## KEYNOTES

The keynote addresses on Tuesday, 2 April, were given by high-level representatives of large manufacturers. These speakers shared their companies' approaches to innovation in the small molecule and biopharma business.

As an introduction, John Bournas, ISPE President and CEO, noted positive developments in ISPE's conferences, membership, training, and publications. In particular, Bournas said attendance at the Europe Annual Conference has grown significantly since the first conference in 2014.

### Brendan O'Callaghan, Sanofi

In his keynote address, Brendan O'Callaghan, Senior Vice President and Global Head, Biologics Platform, at Sanofi, noted that Sanofi's manufacturing strategy is evolving to meet the needs of a growing and increasingly divergent biologics pipeline. The company's overall goals are speed to market, flexible/agile and reliable supply solutions, competitive costs of goods, and better service to the needs of patients. Digital technology is expected to transform the way that therapies are discovered, developed, and delivered to patients, providers, and payers.

The company's operational strategies are focused on large-scale cell culture (microbial and mammalian). Strategic partnerships will provide additional capacity and optionalities as well as a future platform for smaller scale, single-use, and digitally enabled technology. Furthermore, this platform should be "product agnostic" to enable a diverse pipeline.

For some time now, 70% of portfolios have been represented by biologics. Research in a broad range of sciences is being conducted to select the right tool for the right target. Areas of investigation include antibody conjugates, peptides, enzymes, fusion proteins, multispecific antibodies, small molecules, nanobodies, gene therapy, gene editing, and mRNA and siRNA conjugates.

### Jim Breen, Johnson & Johnson

Jim Breen, Vice President, Lead Biologic Expansion, Janssen Pharmaceutical, and 2019 ISPE International Board of Directors Chair, discussed trends and disruptors that Johnson & Johnson is following in healthcare. In particular, the company is focused on consumers and patients seeking personalized and on-demand experiences, marketplace consolidations, middle-class expansion in emerging markets, and the growth of an aging population.

Breen emphasized the challenge of creating "intelligent" manufacturing systems in which the production system is able to predict quality, output, service, and maintenance via self-learning and self-correcting mechanisms. Meeting this challenge will require connecting the manufacturing infrastructure, equipment, materials, and people through data systems.

Small batch sizes are becoming more common, driven by biosimilar production, personalized medicine, and higher monoclonal antibody titers.

### Rick Friedman, US FDA

Rick Friedman, Deputy Director, Science and Regulatory Policy, Office of Manufacturing Quality, FDA/Center for Drug Evaluation and Research (CDER), focused on recent regulatory findings and sustainable solutions in the context of Pharma 4.0. He pointed out that quality risk management (QRM) is not sustainable or effective if it is static. The QRM program should support continual improvement because QRM is an iterative, life-cycle endeavor. Notably more information is available after product launch and through extensive batch production experience than was available in early experiments. This new knowledge inevitably identifies new QRM opportunities. The links between QRM and knowledge management (KM) involve many factors such as complaints, rejections, and feedback from the shop floor; maintenance issues; deviations; returned goods; out-of-specification and stability results; current staff competencies; raw material data; results of audits; and process trending.

Pharma 4.0 approaches will help to connect the dots between these factors to present a holistic view on product life cycles. Data integration and pattern recognition are critical for managing quality risks, he said. Human-factor risks during production can be effectively reduced.

In summary, the current pharmaceutical quality system drives sound life-cycle decision-making, which is based on a strong QRM and KM foundation. Furthermore, it establishes and maintains a state of process control; sources robust materials from qualified vendors; designs reliable tests, processes, and products; monitors process performance and product quality; and manages risks effectively. It creates real, long-term, and systemic solutions for problems.

### Joydeep Ganguly, Gilead

Joydeep Ganguly, Senior Vice President of Operations at Gilead, focused on execution of Pharma 4.0 from a practitioner's perspective, using the following elements to describe its realization:

- Collaboration
  - Foster communities with research and development
  - Reimagine the notion of technology transfer
  - Link space plans to scientific flow
  - Implement a socialized collective vision throughout the value chain
  - Create an open space that can be adjusted to fit different purposes
  - Create technology-enabled collaboration zones within a campus to allow for an academic campus atmosphere
  - Create laboratories with a greater digital footprint
- Connection
  - Shift to cloud computing
  - Introduce and assimilate social tools
  - Increase and enhance web and video conferencing
  - Leverage technology to drive a culture of co-creation
- Control
  - Implement an automation concept to drive a disciplined approach to data governance and structure
  - Increase point-of-use analytics to put data in the hands of users and automate a multitude of reports
  - Develop a life-cycle approach
  - Use analytics cases to increase predictive power within facilities
- Safety
  - Conduct risk assessments to guide safety constructs within facilities
  - Increase technology footprint to reduce risks in processing and operations
  - Employ advanced analytics to drive a reshaping of campus pathways, signage, lighting, and vehicular flow, thereby promoting a new culture of safety-by-design
  - Harness the power of robotics and predictive analytics to create more sophisticated near-miss surrogates
- Security
  - Implement a sophisticated security system that leverages the combination of people analytics, social media, and ecosystem changes to assess and track risk
  - Collect real-time analytics on campus risk
  - Pilot all-based tools to create robust investigations and assessments
  - Automate an overall crisis management plan to enable a mobile solution for the overall risk and emergency process
- Sustainability
  - Prioritize energy-efficient operations
  - Encourage eco-friendly behaviors
  - Conserve resources, such as using wind, solar, and fuel cells to provide 100% of power

Figure 3: Industry trends related to changing technologies: Different modalities require different approaches.

| | Plasma & Biologics | Small molecule dosage forms |
|---|---|---|
| **Dose regimen** | Daily to (bi)weekly | Daily |
| **DP Size (# Packs)** | Medium to low (thousands) | High (millions) |
| **Batches of 1 Product /year** | < 50 Batches | > 100 Batches |
| **Products per Line/ year** | 2-3 | > 10 |
| **Target DP Stability** | 2 years | 3- 5 years |
| **Flexibility** | Low | High |
| **Disposables Steps** | High | Low |
| **Capex** | High | Low to medium |

Source: Thomas Wozniewski, Takeda

### ISPE's Women in Pharma® Initiative

ISPE's Women in Pharma® Initiative delivered a panel discussion on emerging innovations in the pharma industry. The panel was led by Susan Hynes, Vice President and Site Lead for Takeda Dunboyne Biologics; Bernadette Doyle, Vice President of GSK corporate technical and NPI pharma supply chain; and Amy White, Janssen Sciences UC Senior Operations Manager.

The discussion focused on agile principles for team design, showing all elements of Pharma 4.0 in a holistic manner. This approach is a structured one, starting with strategy and a roadmap, followed by organization and governance, leadership and culture, and needed capabilities, and closing with enterprise business processes. The panel members emphasized that Pharma 4.0 is far more than a technology project driven by digitization.

Hynes noted that digital enables agile. Doyle highlighted digital enterprise skill sets and tools such as agile learning, thinking in systems and from the enterprise point of view, and breaking away from silos. White discussed the operations perspective by addressing needs for process intensification, modularization, automation, and patient-centered solutions.

### Thomas Wozniewski, Takeda

Thomas Wozniewski, Global Manufacturing and Supply Officer at Takeda, presented on the Transformation of Corporate Manufacturing and Supply at Takeda. This was a highlight of the conference. Using the example of the gene and cell therapy product Alofisel, he demonstrated the high complexity of manufacturing and supply of this new generation of products.

The main stages in the end-to-end supply chain are mobilized blood cell collection, selected stem cells, which are transduced with the selected gene, harvested, and cryopreserved, and application by infusion to the patient.

Several factors make the production and delivery of the product challenging, including the 48-hour shelf life, which requires tracking the expiry time as well as the expiry date; storage conditions of between 15°C and 25°C; and the need for direct distribution from the plant in Madrid to about 150 treatment centers in Europe, Israel, and Canada, with transit times of up to 22 hours. In addition, production of the treatment starts seven days prior to surgery, and one batch of four vials is designated for only one patient.

Clearly, time is of the essence, and only digitalized supply chains can solve such a complex delivery challenge. The goal is to match the treatment day with the delivery day on a platform that all stakeholders in the supply chain can use to collaborate. The availability of daily production capacity is disclosed to nurses. Dedicated and specialized logistics service providers and qualified transport lanes and shippers are utilized. Everything is supported by a strict GxP protocol for treatment receipt and checks. As a result, customer service levels higher than 99% have been achieved.

Wozniewski also highlighted the following major industry trends:

- **Changing technologies:** Different modalities require different approaches (see Figure 3).
- **Drug product and medical device combinations:** For example, Factor VIII treatment is being optimized and personalized through these types of products.
- **Changes in the regulatory framework that result in shorter development time:** For example, certain innovative drugs for rare diseases, oncology products, and personalized medicines are being fast-tracked for approval.
- **Environmental sustainability:** Consumers, governments, investors, and others are increasing the momentum for environmental protection measures. As a consequence, company commitments to sustainability and public positions on related social and political issues are expanding.

## OTHER EVENTS

After the keynote session, the conference was divided into four tracks: Facilities of the Future, Pharma 4.0, Quality and Regulatory, and Project Engineering. The speakers (about 70 in all) delivered high-quality presentations and engaged audiences in question-and-answer sessions and panel discussions. Attendees appreciated the opportunity to interact with several actively involved regulators from various countries, and the exhibit halls were filled with 76 tabletops and booths sponsored by machine, equipment, infrastructure, digital technology, and consultancy companies, and supply chain management providers.

Overall, the feedback on the conference was extremely positive. Many participants have already committed to attend ISPE's 2020 Europe Annual Conference, which will be held 30 March through 1 April in Madrid, Spain.


### About the author

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# ISPE YOUNG PROFESSIONALS HACKATHON:

## Networking and Learning

By Aisling Judge and Sam Andrews

Judging the teams' spaghetti towers during the icebreaker activity.

The ISPE Young Professionals (YPs) Hackathon, which has become an annual event run in conjunction with the ISPE Europe Annual Conference, brings together some of the brightest, most inquisitive young engineers from across Europe for a two-day networking and learning event.

This year's event was organized by the ISPE Ireland Affiliate YPs. Special thanks to John Clarke, Emer Somers, and Elaine Clarke, as well as Marta Malo de Molina of the ISPE Spain Affiliate and the many others who assisted.

On 30–31 March 2019, more than 25 YPs gathered at the Clayton Hotel Dublin and were posed a simple challenge:

> *"It's 2030 and you have been employed at Jigsaw Inc., an innovative pharmaceutical manufacturer. Develop a strategy for a new multiproduct Dublin-based facility."*

### HACKATHON RULES

The YPs were divided into four groups, and each group was given a separate theme for the challenge. These themes mirrored many of the topics covered in the ISPE Europe Conference over the subsequent days: Pharma 4.0, process analytic technology (PAT), next-generation therapeutics, and single-use technology. Under the guidance of senior ISPE mentors (Damian Greene, HiTech Health; Christian Wölbeling, Werum IT Solutions; Ursula Busse, Novartis; Gert Moelgaard, Moelgaard Consulting; and Eamon Judge, Eli Lilly), the groups explored and brainstormed potential ideas and solutions to the challenges the pharmaceutical industry may face in 2030.

Each group was tasked with scoping the topic, developing a project charter, and assessing the financial implications of their proposed solutions, with the ultimate goal of pitching to a panel of expert judges at the culmination of the Hackathon.

In conjunction with the core topics, and in keeping with the ISPE Communities of Practice (CoPs), representatives from each of the four groups broke out on the first afternoon to form mini-CoPs and discuss a number of challenges faced across all themes. CoP topics included data integrity, supply chain management, regulatory issues, and sustainability—all pertinent topics for the pharmaceutical industry as a whole. When groups reconvened, each member shared the lessons and challenges they had gathered while participating in their CoP. During this exercise, participants immediately noted the significant overlap among the Hackathon themes and how no one topic was independent from the others.

### NETWORKING OPPORTUNITIES

Of course, the event wasn't all work and no play! After a challenging first day, the true networking began in earnest with an evening meal attended by ISPE International Board members and staff at Medley in Dublin. The meal, sponsored by Novo Nordisk, was an opportunity for the YPs to let their hair down, learn more about their new colleagues and friends in an informal setting, and converse and network with more experienced members of the ISPE community. The dinner proved to be a huge success and one of the highlights of the two-day event.

Sunday morning dawned bright and early for the YPs. While there were some bleary eyes, all groups were busy putting the finishing touches on their presentations. Each group then had the opportunity to make a 15-minute pitch to the panel of expert judges regarding their initiatives and suggestions: LeAnna Pearson Marcum, Manager, QA Validation, bluebird bio, and 2019 International YP Committee Chair; Michael Rutherford, Executive Director, Computer Systems Quality and Data Integrity, Syneos

Health, and a member of the ISPE International Board of Directors; and Paul Gerhard Heiden, Senior Vice President, Corporate Quality, Bayer AG.

## FUTURE VIEWS

So, what does manufacturing in 2030 look like according to the YPs? They imagined a future of three-dimensional printing of consumables, ballroom manufacturing suites, drone delivery of medicines to and from patients, and novel methods for integrated real-time data collection and cloud storage. Each team was quizzed on their proposals by both the judges and the audience of fellow YPs, with team Pharma 4.0 chosen as the overall winner. Each member of that team received a year of complimentary membership to ISPE.

Overall, the YP Hackathon proved an outstanding success, allowing participants to share ideas and experiences across a wide network of peers. Teamwork and communication skills were developed by all, as groups learned how to harness the unique expertise of each individual contributor to arrive at the best solutions. Friendships were formed and relationships were built, with everyone looking forward to the opportunity to reconvene at the 2020 ISPE Europe Annual Conference in Madrid.


### About the authors

**Aisling Judge** is a Bioprocess Engineer at Eli Lilly's API Manufacturing Facility in County Cork, Ireland. She graduated in 2014 with distinction as a chemical and bioprocess engineer from University College Dublin and subsequently attended University College London, where she completed a master's degree in biochemical engineering, graduating top of her class. In 2015, Aisling joined Eli Lilly as a bioprocess engineer and was actively involved in the startup of the site's IE43 Train 1 large-volume mAbs facility. She has since overseen process engineering aspects of two new products' introductions, including additional purification unit operations. Aisling is an Eli Lilly Outreach University Ambassador, working with Irish universities to promote engineering and advise on curricula to meet the Irish pharmaceutical sector's needs. She became an ISPE member in 2019.

**Sam Andrews** is Global eCompliance Manager for Commercial IT at Novartis and is based in Dublin, Ireland. He previously spent six years within the life science industry consulting with Integrity Solutions Ltd., working in the United Kingdom and Ireland. He has been an ISPE member since 2016 and is the Secretary of the ISPE GAMP UK Community of Practice. He is an active member of numerous Special Interest Groups, including Data Integrity and Agile. Sam has a bachelor's degree from the University of Sheffield and a distinction class MSc in information systems from the University of Brighton. He is also accredited with the PRINCE2, ITIL, and BCS software testing certifications, and is an Agile Project Management practitioner.


## HACKATHON Q&A

### What is a Hackathon?

The word "hackathon" is taken from the words "hack" and "marathon," where "hack" is used in the sense of exploratory efforts. Hackathons typically start with one or more presentations about the event and the specific subject. Then participants form teams based on their individual skills and interests. The work can last anywhere from several hours to several days. At the end of the Hackathon, there is usually a series of demonstrations in which each group presents their results.

### What will happen at the Student & YP Hackathon at the 2019 ISPE Annual Meeting & Expo?

The Student & YP Hackathon will bring ISPE Student and YP members together for a weekend of networking, collaboration, education, and innovation. All participants will receive a real-world, industry-relevant case study prior to the Hackathon. At the Hackathon, participants will be put into teams. Each team will receive a challenge based on the case study and work together through the weekend to develop a solution. More experienced YPs will be on hand throughout the Hackathon to coach the teams, and industry professionals from the United States and Europe will judge each teams' presentations on the last day. The Hackathon will be held Saturday, 26 October 2019 from 0900–1700; and Sunday morning, 27 October 2019, ending at 1100, when the judging will be held along with a celebratory brunch.

### Will there still be an International Student Poster Competition?

Students who win local poster competitions and are sent to Annual Meeting by their Chapters/Affiliates will display their posters in the foyer outside of the Exhibit Hall. A specific time will be scheduled for them to discuss their posters with interested conference attendees. These students, along with other ISPE Student and YP members, will also participate in the Student & YP Hackathon.

### Who is eligible for the Student & YP Hackathon?

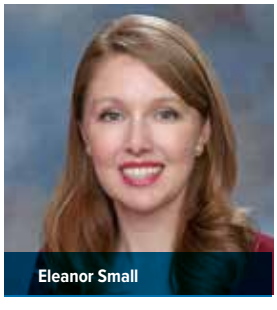
Students who win their local Student Poster Competition are automatically enrolled in the program, which is also open to all ISPE Student members in undergraduate or graduate programs, along with ISPE YP members.

*—Debbie Kaufmann, ISPE Membership Coordinator*

Member Profile

# AWARD-WINNING YP MAKES A BIG PROFESSIONAL IMPACT

By Mike McGrath


Eleanor Small

Delaware Valley Chapter Executive Vice President Eleanor Small, 34, is a woman with a passion for science and technology. Although still early in her career, she has already accomplished a lot, including being awarded the prestigious Delaware Valley Young Engineer of the Year award for 2019.

Small is the daughter of an active-duty US Air Force father. Her mother is a registered nurse midwife, and her father is a medical doctor. Small was born in the United Kingdom and spent her formative years in the United States. As is common for military families, the family moved frequently and lived around the country, including in Alaska. Because of this, Small attended three elementary schools, three junior high schools, and two high schools.

Small's love for physics and chemistry began in high school, and she carried that passion for science with her to Johns Hopkins University in Baltimore, Maryland, where she completed her bachelor of science in chemical and biomolecular engineering in 2006. She then earned her doctorate in chemical and biological engineering at Drexel University in Philadelphia, Pennsylvania, in 2012.

## BUILDING A CAREER

Small started her career as a product development scientist in a postdoctoral position at the global oral care business unit of Johnson & Johnson Consumer Inc. in Skillman, New Jersey. Two years later, she was hired full time as Senior Scientist in Oral Care Product Development, where she was responsible for the formulation, claims support, and global launch of the first clinically validated peroxide-free whitening mouthwash for the Listerine brand.

After working in oral care products for five years, she moved to the wound care product development team as a Senior Scientist in support of the company's Band-Aid brand adhesive bandages and Neosporin brands. In July 2018, Small was promoted to Principal Scientist, where she is the global technical lead in charge of development, claims support, scale-up, and launch of new products. She also leads one of the department's early-stage research platforms focusing on incorporation of new technologies into adhesive bandages to address consumer needs.

"I have the opportunity to work on an array of technologies and biological models to address the needs of individuals with minor wounds," Small explained. "We're looking at what we can do in terms of true science to ensure that the healing process is comfortable and worry-free. It's a great opportunity for me engage my scientific and engineering background for practical applications in the wound care space. What is most exciting is that some of the approaches we are exploring have never been commercialized and studied in great detail for the issues relevant to our consumers."

The immediate and significant impact of consumer health products on the everyday lives of patients is an important aspect of healthcare that is often overlooked. "It's interesting that even

> "You never get rid of a good idea—you figure out how to repurpose it."

a minor wound can influence our behaviors," Small said. "For example, when you have a cut on your finger, you'll wash your hair with only four fingers so that you don't get shampoo on the wound. So, a cool aspect of what we do is help people get back to normal again. And with the skin being the largest organ of our body and our main defense against the world, it's important to keep it intact and healthy. Whenever there is a breach, it's important to get it healed in the right way."

## CONTRIBUTING OUTSIDE OF WORK

Small is actively involved in multiple professional organizations, such as the Engineers Club of Philadelphia, which brings together people working in different engineering fields from various industries. Small joined the club in 2012 and was active in the Delaware Valley Engineers Week planning committee, including helping plan the Young Engineers Social and leading the Undergraduate Student Paper Award selection through 2017. In February 2019, she received the club's 2019 Young Engineer of the Year award, which recognizes engineers under 35 for their professional accomplishments and contributions to the community.

"It's a real honor for me to be up there representing myself but also my field of engineering on behalf of ISPE, showing a unique career path for a chemical engineer," Small said, adding that the ISPE Delaware Valley Chapter submitted her name for the award. "And it is awe-inspiring because I know some of the previous winners of the award, and these people have been mentors to me."

In fact, it was one of those mentors, Alan Levy, who first encouraged Small to become involved with ISPE. She joined the Delaware Valley Chapter in 2013 and was elected to the board as Vice President of Communities of Practice (CoPs) the following year. In that role, she helped design a fully integrated, subject matter expert–monitored digital discussion board to strengthen the local CoPs. The design was beta tested but ultimately was not moved forward because members are already digitally well served through ISPE's international CoPs.

That did not deter Small. "You never get rid of a good idea—you figure out how to repurpose it," she said. "We are taking our digital platform and utilizing it to expand our educational program. Just recently, we tested an educational session for people who were not able to attend in person. Being able to see both the slides and the speaker created a different level of engagement." She said the Delaware Valley Chapter will continue to evaluate how to move forward with the digital platform.

In addition, Small is actively involved with her sorority's alumnae association. She was a member of the Kappa Kappa Gamma sorority while at Johns Hopkins and has been the Philadelphia Alumnae Association Foundation of Kappa Kappa Gamma president for the last four years. The association has an independent charitable arm that supports local and international philanthropy. She has also been a chapter adviser to the sorority's chapter at Princeton University since 2014. "The mentorship side of that is really important to me," she said. "I really love working with these young women, being there as a voice of guidance as they work their way through to becoming tomorrow's leaders."

Small lives in Philadelphia with her husband, whom she met in college. In their spare time, they are competitive ballroom dancers.

### About the author

**Mike McGrath** is a freelance writer and corporate communications consultant. For the past 15 years, he has helped organizations in the aerospace, transportation, telecommunications, and pharmaceutical industries develop their digital and print communications strategies. He has been a regular contributor to *Pharmaceutical Engineering* since 2015.

## ISPE Briefs

# ISPE Launches Complimentary Webinar Series

ISPE launched its complimentary Pharma Best Practices Webinar Series in April. The debut was outstanding, drawing more than 850 registrants and over 500 real-time participants representing 62 countries and six regulatory agencies from around the world.

The first webinar on 29 April 2019 was "Water for Injection Using Non-Distillative Methods—ISPE D/A/CH Approach," presented by Fritz Röder, Senior QA Manager Validation, Qualification, and Engineering at Merck KGaA, Darmstadt, Germany. Röder shared collective insights from the ISPE D/A/CH (Germany/Austria/Switzerland) Affiliate's Regional Community of Practice, Water and Steam, and provided answers to questions such as ,"What are suitable technologies for the final treatment step of a cold water-for-injection system?"

ISPE will be hosting monthly webinars featuring leading subject matter experts covering critical and relevant topics in pharmaceutical manufacturing.

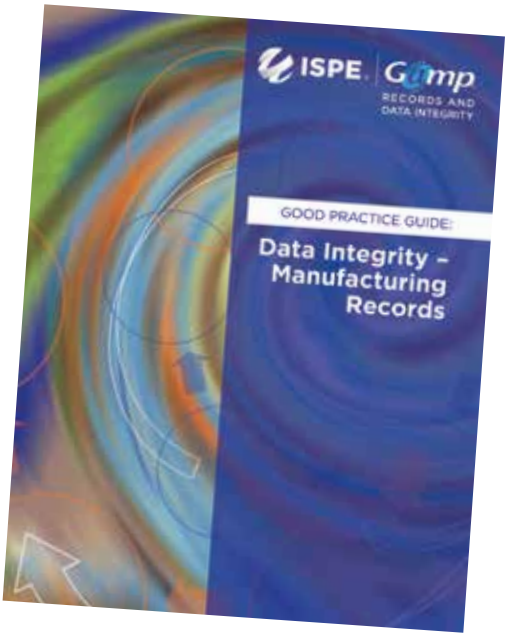
Upcoming topics include:

- New GAMP® Data Integrity Good Practice Guidance and Experience from the Field
- GAMP® *Good Practice Guide for GxP Compliant Lab Computerized Systems*
- Polishing an Old Gem: Commissioning & Qualification Baseline Guide Update

ISPE members will have access to the recorded webinars on the ISPE website. Visit https://ispe.org/webinars to learn more and to sign up to be notified when registration opens for each webinar.

### NEWEST GOOD PRACTICE GUIDE: DATA INTEGRITY–MANUFACTURING RECORDS

The newly released *ISPE GAMP® Records and Data Integrity Good Practice Guide: Data Integrity—Manufacturing Records* addresses the expectations for data integrity in a GMP environment to aid companies in meeting regulatory requirements.




This guide provides a manufacturing business process framework to:

- Facilitate interpretation of regulatory requirements and expectations based on industry best practices
- Define the data integrity approach for planning and project activities
- Apply risk management to all aspects of the data life cycle
- Identify roles and responsibilities to manage the data within the data life cycle
- Develop an appropriate data strategy for manufacturing IT systems

For more information and to purchase the guide, go to https://ispe.org/gamp-good-practice-guide-data-integrity-manufacturing-records.

### CALL FOR ARTICLES: SUBMIT YOUR ARTICLE TO PE

PE is always looking for great technical articles, features, and editorials on topics of interest to ISPE members. Find the Author Guidelines and more information about submissions at https://ispe.org/pharmaceutical-engineering/about/submit-article. Your article does not have to be related to an issue's theme, although we welcome submissions on theme. Questions about submitting? Contact Susan Sandler, Editorial Director, at ssandler@ispe.org.

**We'd like to feature your chapter, affiliate, or other ISPE group in an upcoming ISPE Briefs! Share highlights from training programs, conferences, social events, or other activities with ISPE members in an article of 250 to 400 words. We welcome photos, too; these should be 300 dpi or >1 MB. Send your submissions to Susan Sandler, Editorial Director, at ssandler@ispe.org.**

# A STRATEGY FOR THE ANALYSIS OF DISSOLUTION PROFILES

By Ronald D. Snee


Ronald D. Snee

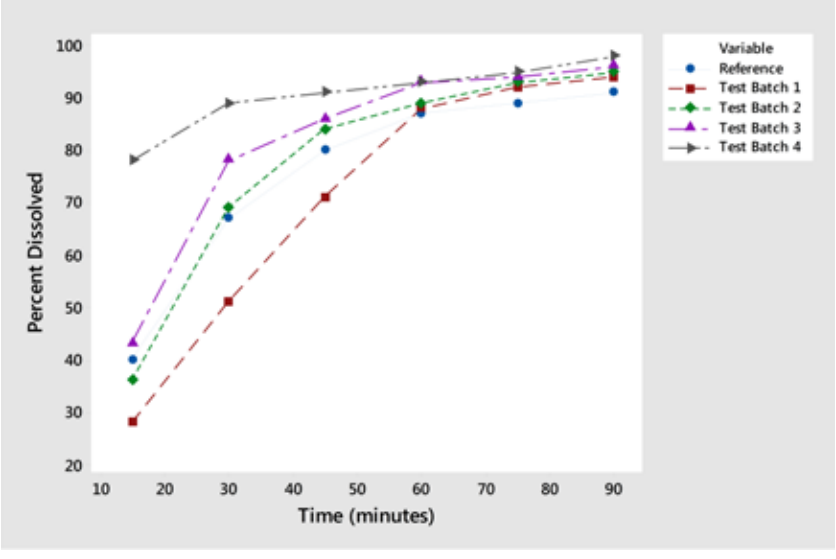
In this article, a new method for the analysis and comparison of dissolution profiles (DPs) is proposed and illustrated with case studies. This useful strategy makes effective use of DP data by using all data in each profile to create two statistics: profile level and profile shape. The profile level relates to the area under the profile and reflects the "exposure" of the patient to the drug. The shape statistic is related to the rate of increase of the drug dissolution over time. These characteristics enable practical interpretations regarding the factors studied in the experiment. The method is easy to use, requiring only straight-line regression and design of experiments analysis procedures. A modified principal component analysis (MPCA) is recommended as an alternative approach when the proposed model does not give an adequate description of the data.

## DISSOLUTION PROFILE BEHAVIOR

Rate of dissolution is a critical quality attribute of a pharmaceutical tablet. Tablet dissolution is typically studied by examining the form of the DP, which is the percentage of the tablet dissolved at various points in time. Figure 1 shows five such DPs—the reference plus four test batches—generated in a study reported by Shah et al [1]. Figure 1 shows a typical variety of a DP. Some start at low dissolution levels (e.g., 25%–40% at 15 minutes), whereas others start at approximately 75% at 15 minutes. The result is a collection of DPs with a variety of response patterns.

Experiments are commonly conducted to study the effects of various factors on the DP. The complicating issue in the analysis of dissolution is that the response is a "profile" involving several data points rather than a single response metric. This article describes a new approach that reduces the profile to two statistics: one measuring the profile level and the other measuring the profile shape. Note in Figure 1 that the batch 4 profile has a high average value (level) and a low slope (shape). Batch 1 has a low average value (level) and a high slope (shape). The other DPs (reference, batch 2, and batch 3) are in between the DPs of test batches 1 and 4 and are very similar. These observations are supported by the profile average and slope statistics shown in Table 3, presented later in this article.

Figure 1: Dissolution profiles plotted vs. time.




Several methods have been proposed to analyze DPs (see Table 1). After reviewing the available methods, the proposed approach is described and it is shown how the new approach overcomes the limitations of the existing procedures.

## AVAILABLE METHODS FOR ANALYZING DISSOLUTION EXPERIMENTS

Several univariate and multivariate methods have been proposed to study the effects of experimental factors on the DP. Seven

Table 1: Methods for studying the effects of factors on dissolution profiles.

| Method | Description | Comment |
|---|---|---|
| 1 | Pick a particular point in time and base results and conclusions on this data | Ignores results at other time points |
| 2 | Analyze results at each point in time separately—if the profile consists of *p* time points, then *p* analyses are performed | Interpretation may be complicated as the results of the *p* analyses have to be integrated to arrive at a conclusion |
| 3 | Similarity factor analysis [1] | Useful for comparing only two profiles |
| 4 | Fit a model to each profile separately and analyze the calculated model coefficients as the responses; for example, a three-coefficient model results in three analyses [2] | Number of analyses is reduced; a single model needs to be found that will describe all the curves |
| 5 | Repeated measures ANOVA [3] | Provides a single model for the analysis of the profiles; provides tests of significance for profile level and shape; does not provide a statistic to measure profile shape |
| 6 | Multivariate ANOVA [4] | Can require a large number or repeated dissolution profile experiments; does not provide a statistic to measure profile shape |
| 7 | MPCA [3] | Provides tests of significance for profile level and shape; level and shape statistics are analyzed to study effects of experimental factors |

Table 2: Example 1—Dissolution profiles from Shah [1].

| Time (minutes) | Reference Drug | Test Batch 1 | Test Batch 2 | Test Batch 3 | Test Batch 4 | Average Profile |
|---|---|---|---|---|---|---|
| 15 | 40 | 28 | 36 | 43 | 78 | 45.0 |
| 30 | 67 | 51 | 69 | 78 | 89 | 70.8 |
| 45 | 80 | 71 | 84 | 86 | 91 | 82.4 |
| 60 | 87 | 88 | 89 | 93 | 93 | 90.0 |
| 75 | 89 | 92 | 93 | 94 | 95 | 92.6 |
| 90 | 91 | 94 | 95 | 96 | 98 | 94.8 |
| Average | 75.7 | 70.7 | 77.7 | 81.7 | 90.7 | 79.3 |

such methods are summarized in Table 1. Each method can be useful given a particular set of circumstances.

These methods have the following general limitations:

- Methods 1 and 2 don't take advantage of all information in the DP.
- Method 4 requires a model to be fit to each DP. A single model that will be descriptive of all the DPs is often hard to find.
- Methods 5, 6, and 7 require the use of sophisticated statistical procedures such as repeated measures analysis of variance (ANOVA), principal component analysis, and multivariate ANOVA methods.
- With the exception of method 7 (MPCA), these methods do not directly address DP level and shape.

A method is needed that provides statistics that relate to DP level and shape. In the process, the number of points on the DP is reduced to these two statistics. For the associated analysis, it should be easy to understand, to interpret the results, and to perform the needed calculations. The goal is to find a strategy that works in a variety of situations.

## EXAMPLE 1: LINEARIZING DISSOLUTION PROFILES

As noted previously, the complicating issue in the analysis of dissolution experiments is that the response is a profile involving several data points rather than a single response metric. The methods proposed in the literature work to reduce this complexity by performing various types of univariate or multivariate statistical analyses. The univariate methods often ignore important information, whereas the multivariate methods can be complicated to perform and interpret.

The goal proposed here is to find a time-based metameter that will result in a straight line when the DP is plotted vs. the time metameter. The time metameter is a time-based quantity that conveys the magnitude and nature of the time effect. The result is the profile being reduced to two parameters: the slope and intercept of the linearized profile. The work of Rao [5] and Mandel [6] show that the overall average profile provides such a metameter in many cases.

Rao [5] comments: "The success then exists in replacing the various observations on growth (dissolution) by a few summary figures which lead to most efficient comparison between groups. ... If,

however, time can be transformed by a function r = G(t) in such a way that the growth rate is uniform with respect to chosen time metameter, then an adequate representation is available in terms of the initial value and the redefined uniform rate." In other words, a plot of DP vs. the time metameter is a straight line.

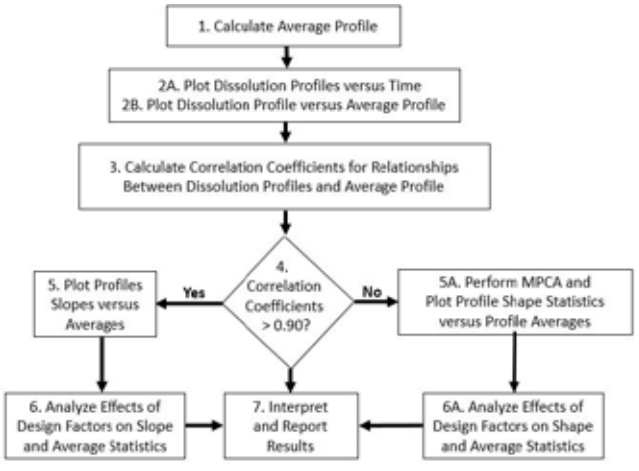
Mandel [6] shows for two-way tables of data that "we have already seen how the row-linear model can be understood as consisting of a bundle of straight lines, one for each row, when the rows are plotted against their common column averages." In Mandel's model, each "row" of the data table is a DP resulting from a set of experimental conditions.

DPs have two general properties: level and shape. The ideal approach would be to have a single statistic to measure level and a second statistic to quantify shape. If each DP can be described by a straight-line model of the form:

Table 3: Example 1—Summary statistics for linear relationships shown in Figure 2.

| Batch | Average (A) | Slope (B) | Correlation with Average Profile |
|---|---|---|---|
| Reference | 75.7 | 1.032 | 0.999 |
| Test Batch 1 | 70.7 | 1.376 | 0.983 |
| Test Batch 2 | 77.7 | 1.182 | 0.997 |
| Test Batch 3 | 81.7 | 1.049 | 0.989 |
| Test Batch 4 | 90.7 | 0.361 | 0.983 |

Figure 2: Strategic approach to analyzing dissolution profiles.




MPCA = modified principal component analysis.

$$Y_t = A + B^*(APt - AP_{avg})$$

where:
$Y_t$ = Dissolution of the tablet at time $_t$
A = Average of the profile (profile level)
B = Slope of the linear relationship (profile shape)
$AP_t$ = Average profile value at time *t*
$AP_{avg}$ = Average value of the average profile

In this model, the slope (B) and intercept (A) of the straight line summarize all the information in the profile. Without loss of generality, this straight-line model is constructed so that the intercept (A) is the average of the profile.

The intercept (A) and slope (B) have an important practical interpretation. The profile average (A) is the profile level statistic; it measures the area under the profile and reflects the patient exposure to the drug after dissolution begins. The slope statistic (B) reflects the profile shape and measures the rate of dissolution vs. the rate of the average profile. For example, a DP slope of B = 1.20 implies the associated profile has a dissolution rate that is 20% higher than that of the average profile.

## PROPOSED METHOD FOR DISSOLUTION PROFILE LINEARIZATION

The proposed method of DP linearization will be illustrated using the dissolution data shown in Figure 1 and Table 2 [1]. The data consist of a reference profile plus four test batches. Dissolution measurements are made at six time periods: 15, 30, 45, 60, 75, and 90 minutes. The analysis of these profiles proceeds as shown in Figure 2.

### Step 1

Compute the average profile curve found by averaging across the five batches at each time point. The resulting average profile for Example 1 is shown in the last column of Table 2.

### Step 2A

Plot DPs for each batch vs. time, as shown in Figure 1. In Figure 1, the typical DP shows a concave pattern of increasing response plateauing around 100%. The profiles show different levels and shapes. For example, the test batch 4 profile starts at a high level and increases slowly, whereas the test batch 1 profile starts at a low level and increases rapidly toward 100%.

### Step 2B

Plot the profiles for each batch vs. average profile, as shown in Figure 3. In Figure 3, we see all profiles show a strong linear relation when plotted vs. the average profile. This indicates that the average profile provides a useful metameter for time. The plot further shows that the profile average (level) and profile slope (shape) summarize the information in the profiles. As a result, we have the summarized the six points on the curve into two statistics.

### Step 3

Compute correlation coefficients for each profile vs. the average profile to check the adequacy of the fit of the linear relationship.

### Step 4

Examine the size of the correlation coefficients calculated in step 3.

The correlation coefficients are all larger than 0.983, confirming the strong relationship observed in Figure 3. Correlation coefficients greater than 0.90 are generally associated with strong positive relationships, suggesting that the results of the experiment can be evaluated using the slope and the average of each profile. When one or more of the correlation coefficients are less than 0.90, one should

Figure 3: Example 1—Dissolution profiles plotted vs. average profile.

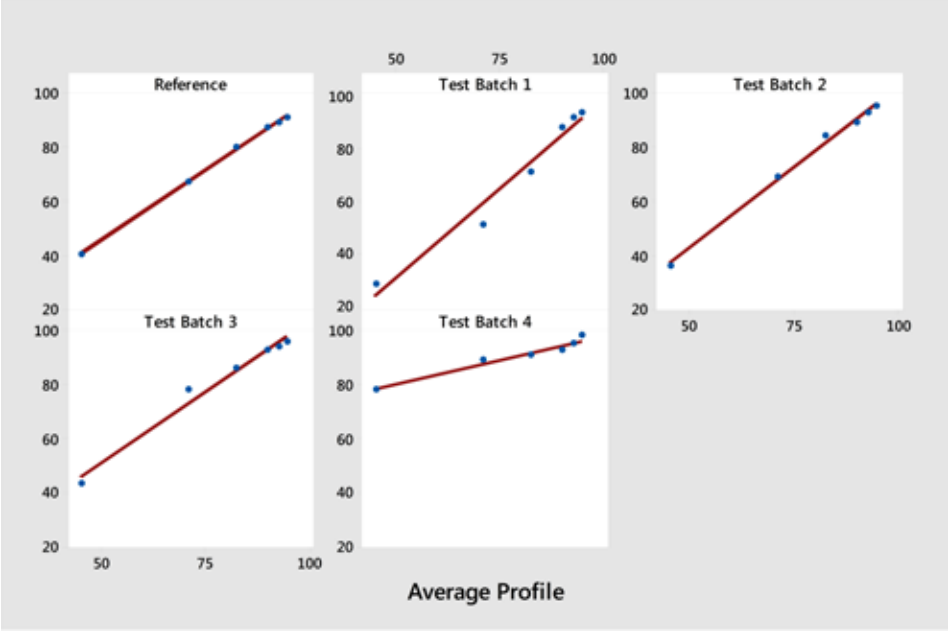



Figure 4: Example 1—Dissolution profile slopes vs. profile averages.

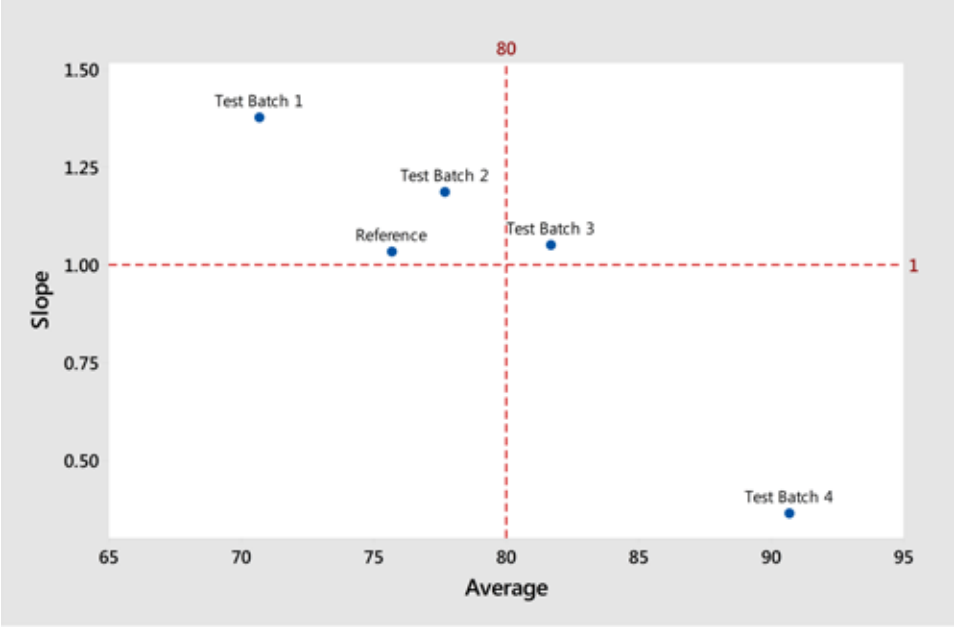


Table 4: Example 2—Fourteen dissolution profiles from a 3×3 factorial experiment.

| Time (minutes) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | Average Profile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 38 | 41 | 46 | 34 | 37 | 42 | 28 | 39 | 41 | 38 | 37 | 38 | 37 | 37 | 38.1 |
| 15 | 62 | 65 | 68 | 55 | 58 | 64 | 46 | 50 | 61 | 59 | 60 | 57 | 60 | 58 | 58.8 |
| 30 | 81 | 86 | 92 | 72 | 74 | 85 | 65 | 72 | 81 | 77 | 76 | 76 | 76 | 73 | 77.6 |
| 45 | 89 | 93 | 98 | 86 | 90 | 95 | 83 | 86 | 92 | 91 | 90 | 92 | 91 | 87 | 90.2 |
| 60 | 97 | 98 | 99 | 98 | 97 | 97 | 98 | 98 | 98 | 98 | 97 | 99 | 97 | 98 | 97.8 |
| Average | 73.4 | 76.6 | 80.6 | 69 | 71.2 | 76.6 | 64 | 69 | 74.6 | 72.6 | 72 | 72.4 | 72.2 | 70.6 | 72.5 |

Table 5: Example 2—Factorial experiment: Summary statistics for the linear relationships shown in Figure 5.

| Profile | Ac-Di-Sol | Klucel EXF | Average | Slope | Correlation with Average Profile |
|---|---|---|---|---|---|
| F1 | 60 | 25 | 73.4 | 0.972 | 0.996 |
| F2 | 60 | 20 | 76.6 | 0.962 | 0.991 |
| F3 | 60 | 15 | 80.6 | 0.933 | 0.981 |
| F4 | 50 | 25 | 69.0 | 1.040 | 0.997 |
| F5 | 50 | 20 | 71.2 | 1.002 | 0.999 |
| F6 | 50 | 15 | 76.6 | 0.956 | 0.993 |
| F7 | 40 | 25 | 64.0 | 1.143 | 0.989 |
| F8 | 40 | 20 | 69.0 | 0.996 | 0.986 |
| F9 | 40 | 15 | 74.6 | 0.967 | 0.999 |
| F10 | 50 | 20 | 72.6 | 1.007 | 1.000 |
| F11 | 50 | 20 | 72.0 | 0.995 | 0.999 |
| F12 | 50 | 20 | 72.4 | 1.035 | 0.999 |
| F13 | 50 | 20 | 72.2 | 1.003 | 0.999 |
| F14 | 50 | 20 | 70.6 | 0.988 | 0.997 |

consider using MPCA as suggested by Wang and colleagues [3]. This method can describe a wide variety of profile shapes in the same set of experimental results.

## Step 5

Compute the coefficients for the linear relationship between each profile and the average profile. The resulting A (level) and B (slope) statistics for the five profiles shown in Table 3 indicate the following:

- Test batch 4 and test batch 1 profiles have the highest and lowest averages (levels) at 90.7 and 70.7, respectively.
- Test batch 4 and test batch 1 profiles have the lowest and highest slope (shape) values at 0.361 and 1.376, respectively. This indicates that, because the slope of the average profile is 1.0, the test batch 4 slope is 36.1% of the average profile and the test batch 1 slope is 37.6% more than the slope of the average profile.

## Step 5A

Using the results of step 5, plot the slope (shape) vs. the average (level) statistics for all profiles to see graphically how they relate to each other. For guidance, dashed lines can be plotted for slope = 1 (slope of the average profile) and average = average of the average profile, as shown in Figure 4.

In Figure 4, we see several important patterns:

- There is a strong negative correlation between the shape and level statistics because the profiles have a high dissolution at the minimum time period of 15 minutes.
- More important, the strong correlation indicates that we need only analyze the profile average (level), as the analysis of the

Figure 5: Example 2—Factorial experiment: Dissolution profiles plotted vs. time.

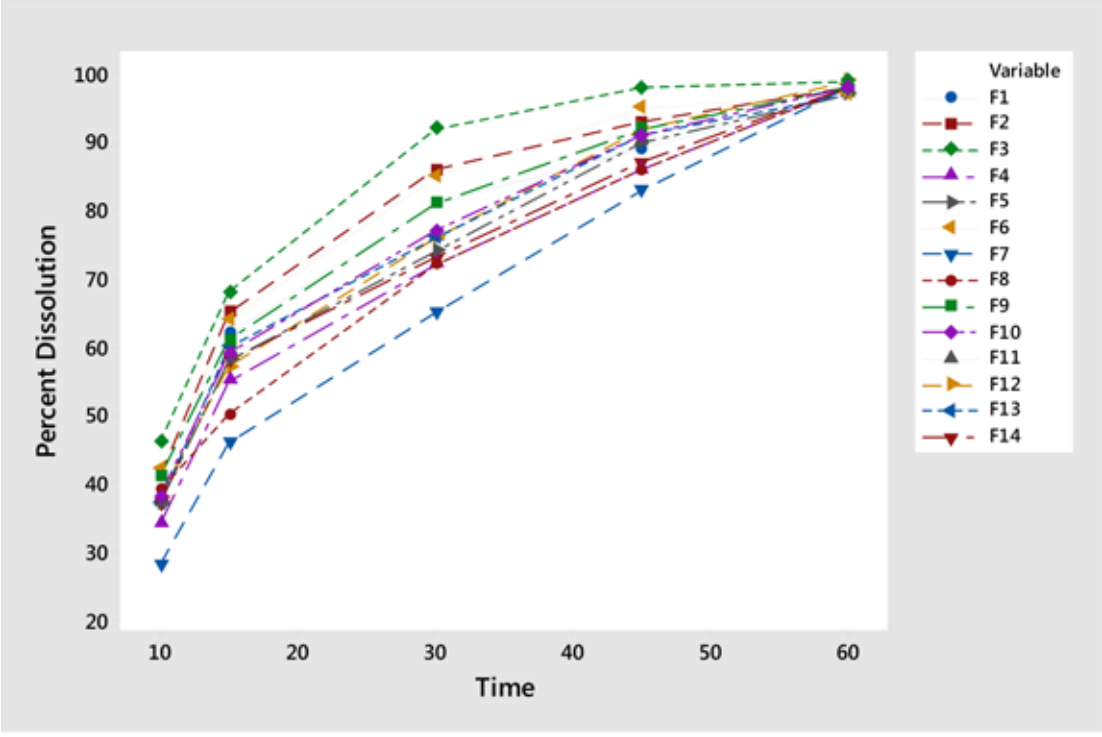



Figure 6: Example 2—Factorial experiment: Dissolution profiles plotted vs. average profile.

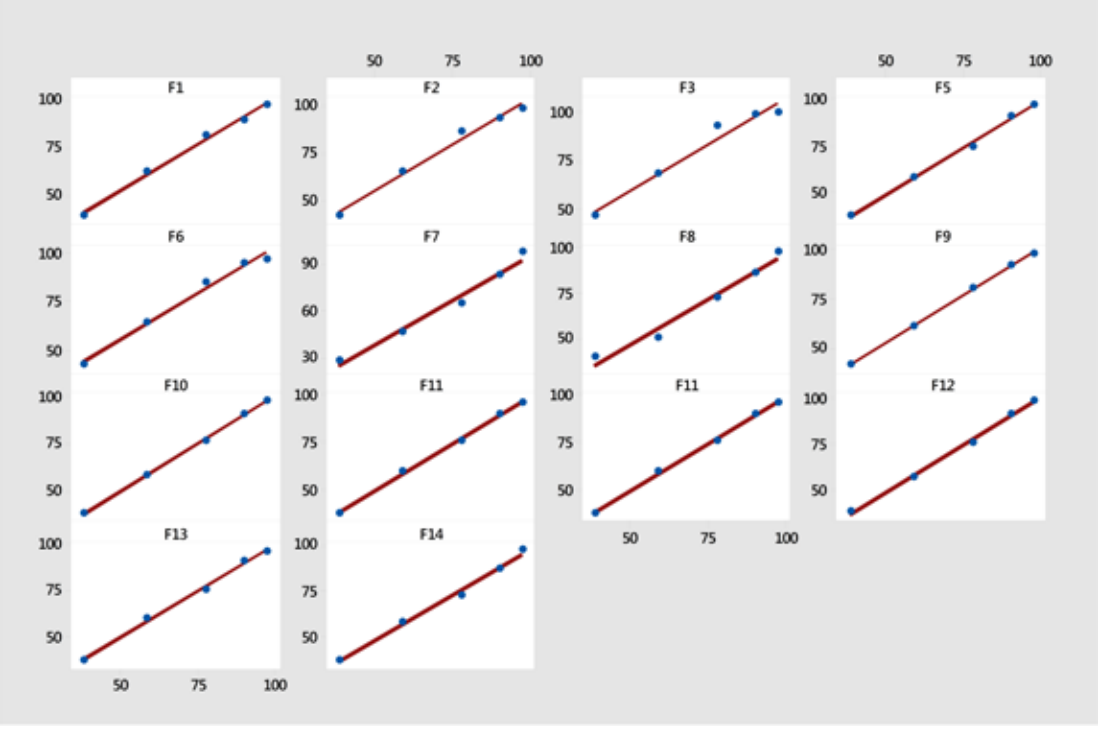


Figure 7: Example 2—Factorial experiment: Dissolution profile slopes vs. average.

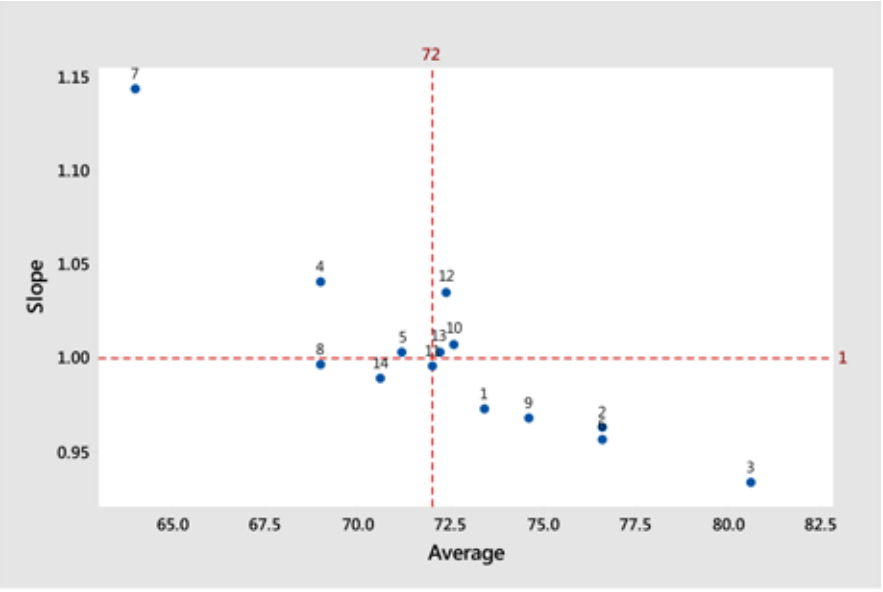
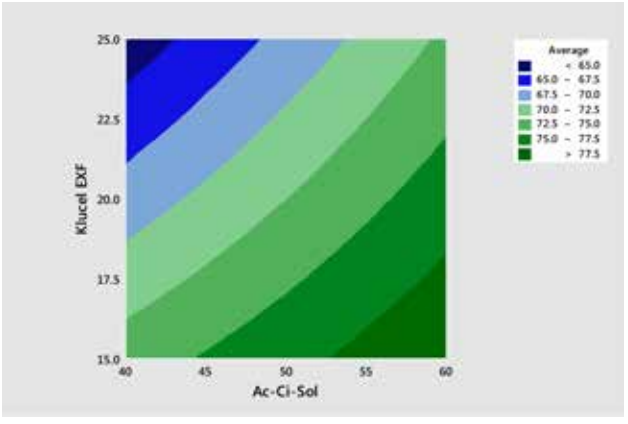
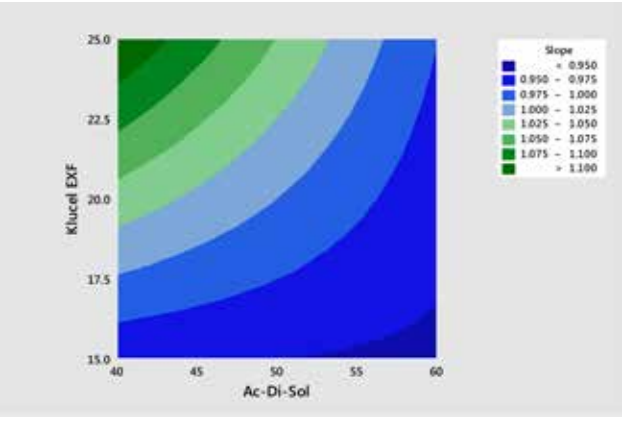



Figure 8: Example 2—Factorial experiment: Contour plots for dissolution profile average (left) and slope (right).




shape will produce the same results due to the correlation between the level and shape statistics.

- The strong correlation between the level and shape statistics is not uncommon for DPs. In this example, the correlation is negative. In instances where the profiles start at low dissolution levels, the correlation will be positive. The important consideration is the correlation strength rather than its direction. A strong correlation, positive or negative, indicates the profiles can be compared by analyzing their level statistics.

### Step 6

Analyze the level and shape statistics according to the sources of variation in the experiment design. This step will be illustrated in the analysis of a 3×3 factorial experiment discussed in Example 2.

### Step 7

Interpret and report the results of the experiment.

## EXAMPLE 2: DISSOLUTION EXPERIMENT USING A 3×3 FACTORIAL DESIGN

Example 2 involves an experiment that uses a 3×3 factorial design to study the effects of two ingredients on the dissolution of efavirenz tablets [7]. The design consisted of the nine factorial points with five replicate points at the center point (Formulations 5, 10–14) for 14 formulations. The resulting DPs are shown in Table 4. The ingredients that make up each of the 14 formulations are provided in Table 5.

For Example 2, steps 1–5 of the analysis described previously and in Figure 2 produced the following results:

**Table 6: Example 2—Factorial experiment: Results of fitting response surface models separately for the average and slopes summarized in Table 5.**

| | Model for Average | | | | Model for Slope | | | |
|---|---|---|---|---|---|---|---|---|
| **Term** | **Coef** | **SE Coef** | **T-Value** | **P-Value** | **Coef** | **SE Coef** | **T-Value** | **P-Value** |
| Constant | 71.9 | 0.265 | 271.05 | 0.000 | 1.0013 | 0.0083 | 121.23 | 0.000 |
| $X_1$ = Ac-Di-Sol | 3.83 | 0.282 | 13.57 | 0.000 | –0.0397 | 0.0088 | –4.51 | 0.002 |
| $X_2$ = Klucel EXF | –4.23 | 0.282 | –14.99 | 0.000 | 0.0497 | 0.0088 | 5.65 | 0.000 |
| $X_1$ SQ | 0.68 | 0.411 | 1.65 | 0.138 | –0.0109 | 0.0128 | –0.85 | 0.421 |
| $X_2$ SQ | 0.68 | 0.411 | 1.65 | 0.138 | 0.0078 | 0.0128 | 0.61 | 0.557 |
| $X_1$*$X_2$ | 0.85 | 0.346 | 2.46 | 0.039 | –0.0341 | 0.0108 | –3.16 | 0.013 |
| Residual Std. Dev. | 0.69 | | | | 0.022 | | | |
| Adjusted $R_2$ value | 97 | | | | 82 | | | |

**Coef: Model regression coefficient**
**SE Coef: Coefficient standard error**
**T-Value: Student's T statistic = Coef/SE Coef**
**P-Value: Probability level associated with T statistic**

**Table 7: Example 3—Comparing dissolution profiles using different apparatuses.**

| Time (minutes) | A-2 | B-2 | C-2 | A-4 | B-4 | C-4 | Average Profile |
|---|---|---|---|---|---|---|---|
| 6 | 62 | 48 | 25 | 16 | 9 | 4 | 27.3 |
| 12 | 88 | 68 | 46 | 38 | 18 | 12 | 45.0 |
| 20 | 94 | 80 | 63 | 63 | 30 | 22 | 58.7 |
| 30 | 95 | 86 | 74 | 80 | 41 | 30 | 67.7 |
| 45 | 96 | 88 | 80 | 92 | 55 | 43 | 75.7 |
| 60 | 95 | 90 | 82 | 95 | 64 | 52 | 79.7 |
| Average | 88.3 | 76.7 | 61.7 | 64.0 | 36.2 | 27.2 | 59.0 |

- Plotting the profiles vs. time showed a family of concave curves typical of DPs (Figure 5).
- Plotting each profile vs. the average profile showed that the linear model provided a good fit to the data (Table 4, Figure 6). The linear model correlation coefficients for the 14 profiles ranged from 0.981 to 1.000 (Table 5).
- A plot of the linear model coefficients (slope vs. average) showed a strong negative correlation (Figure 7), indicating that as the level of the profile increased, the slope decreased.

Step 6 in the analysis is to study the effects of the two ingredients ($X_1$ = Ac-Di-Sol and $X_2$ = Klucel EXF) on the average (level) and slope (shape) of the DP. A quadratic response surface model [8] of the following form was developed separately for average and slope values:

$$Y = b_o + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

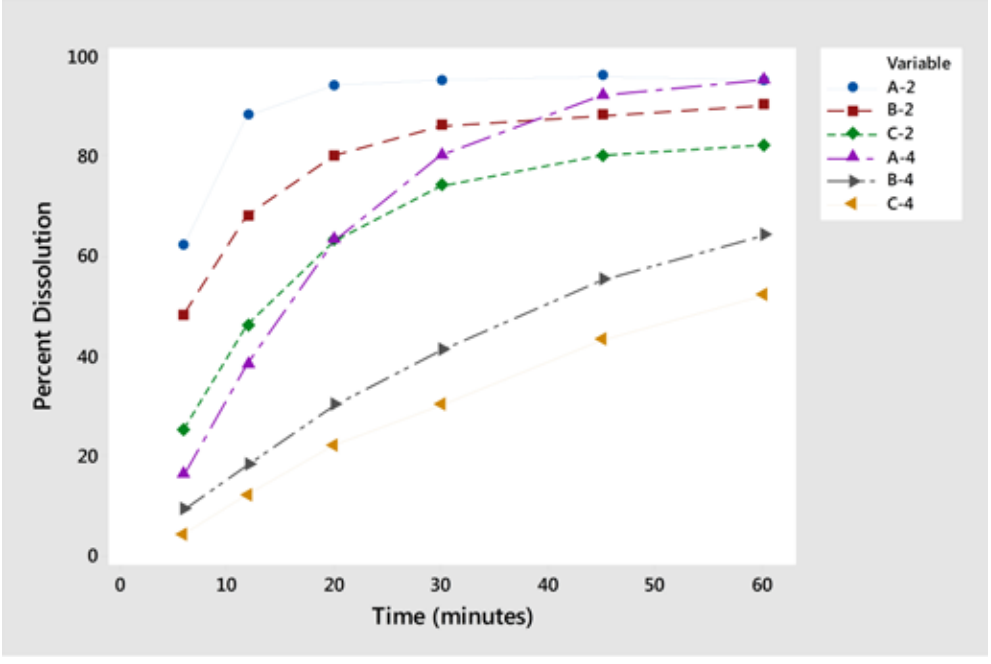
where:
Y is the profile average or slope
b represents coefficients to be estimated from the data
$X_1$ is the amount of Ac-Di-Sol
$X_2$ is the amount of Klucel EXF

The results of fitting these models in standardized form are shown in Table 6. It is shown that there are statistically significant linear and interaction effects for both variables. The linear terms dominate. The quadratic terms are not statistically significant. The models give a good fit to the data; the adjusted $R_2$ values for the average and slope are 97% and 82%, respectively.

Table 8: Example 3—Dissolution profiles using different apparatuses: Summary statistics.

| Code | Product | Apparatus | Average | Slope | Correlation with Average Profile |
|---|---|---|---|---|---|
| A-2 | A | USP 2 | 88.3 | 0.586 | 0.918 |
| B-2 | B | USP 2 | 76.7 | 0.795 | 0.981 |
| C-2 | C | USP 2 | 61.7 | 1.118 | 0.997 |
| A-4 | A | USP 4 | 64.0 | 1.582 | 0.998 |
| B-4 | B | USP 4 | 36.2 | 1.035 | 0.973 |
| C-4 | C | USP 4 | 27.2 | 0.884 | 0.968 |

Figure 9: Example 3—Comparing dissolution profiles using different apparatuses.




The best way to see these effects is to examine response surface contour plots for the average and slope shown in Figure 8. The negative relationship between the profile average and slope that we saw in Figure 6 is evident in Figure 8, in which high average profile values are at low $X_1$ – high $X_2$ and high slope values are at high $X_1$ – low $X_2$ values.

## EXAMPLE 3: COMPARING DISSOLUTION PROFILES USING DIFFERENT USP APPARATUSES

Plotting DPs vs. the average profile sometimes doesn't fit all the profiles equally well. This is particularly true when the collection of profiles covers a wide range of levels and shapes, such as shown in Example 3 (Table 7). In Figure 9, we see profiles ranging from small curvature (profiles B-4 and C-4) to large curvature (profiles A-4 and A-2). The data in Table 7 and Figure 9 are from a study involving three products, A, B, and C, analyzed by two apparatuses, USP 2 and USP 4 [9].

In Figure 10 and Table 8, we see that the linear fit is very good for all the profiles except the first, Profile A-2, where the correlation with the average profile is a respectable 0.918. All the other correlation coefficients range from 0.968 to 0.998 (Table 8). Even for DP A-2, the average profile metameter captures 84% ($R_2$ = 0.918 × 0.918 = 0.843) of the variation in the profile.

In the plot of the DP slopes vs. the level shown in Figure 11, we

Figure 10: Example 3—Dissolution profiles using different apparatuses vs. average profile.

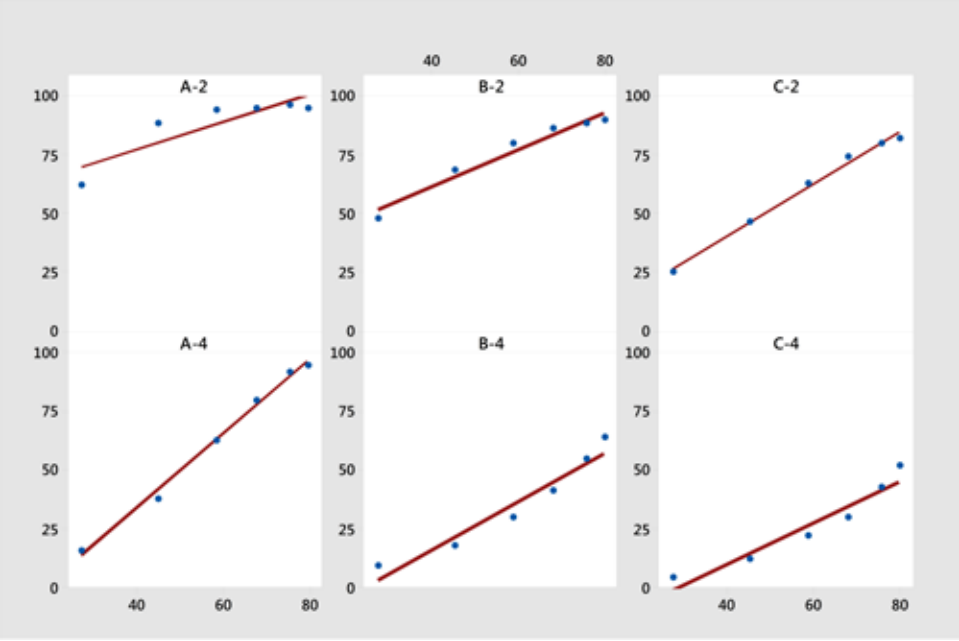
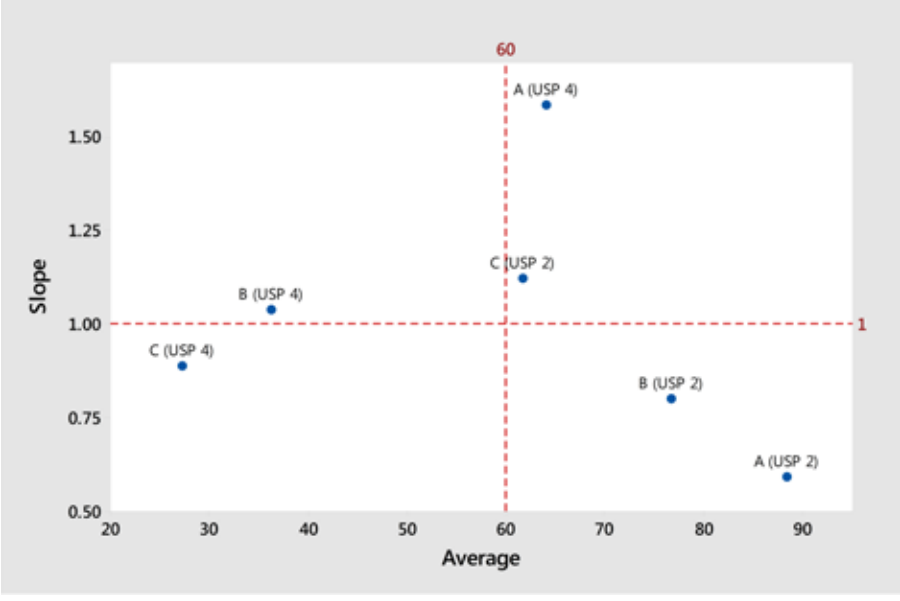



Figure 11: Example 3—Dissolution profiles using different apparatuses: Profile shape vs. level.

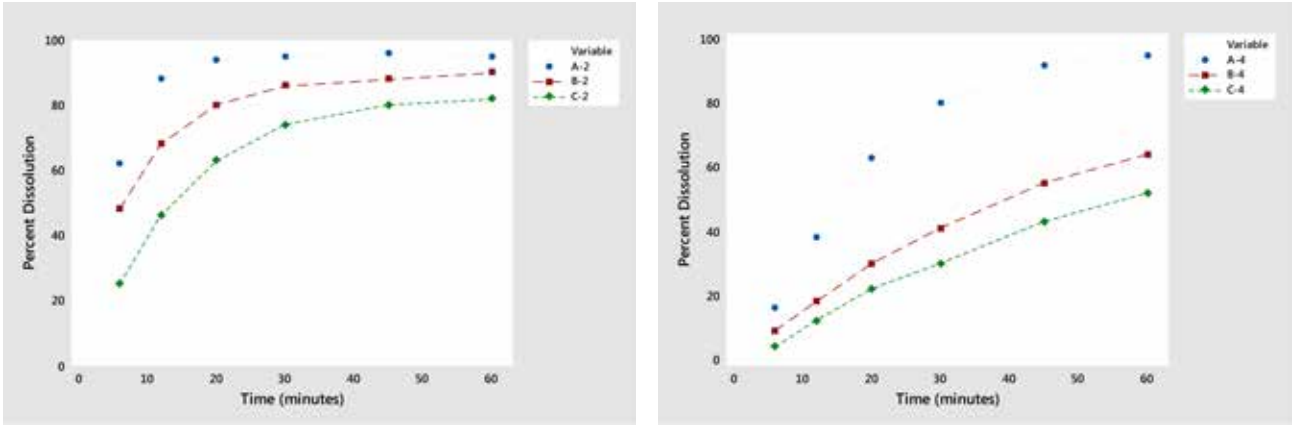



see that the two apparatuses produce different DPs. We see linear relationships between the level and slope statistics, but the relationship is different for the two apparatuses. The differences in the DP for the two apparatuses are apparent in Figure 12, where the DPs of the two apparatuses are plotted separately.

We also see in Figure 11 that the Product A (USP 4) profile is different from all the other profiles. This different DP for Product A is apparent in both Figures 11 and 12.

As noted earlier in the discussion of step 4 of the proposed method for DP linearization, when there is a concern about the

Figure 12: Example 3—Dissolution profiles using different apparatuses: USP 2 (left) and USP 4 (right) vs. time.




ability of plotting vs. the average profile as a way to linearize the profiles, the MPCA discussed by Wang and coauthors [3] can be used. It was applied in this case. Although the MPCA gave a better fit, the conclusions were unchanged. This leads to the conjecture, which is supported by the analysis of other dissolution studies, that the average profile captures most of the variation in profile even when the linear fit is not perfect. In any event, we are led to the conclusion that a good strategy is to use the average profile as a first choice in modeling the DP. If a better fit is needed or desired, the MPCA approach should be used.

## AN EFFECTIVE STRATEGY

DP is a critical property of a pharmaceutical. This article presents a method that overcomes many, if not all, of the limitations of previously available methods. The method provides statistics that relate to DP level and shape. This is accomplished by finding a time metameter that linearizes the DP. The average DP is one such metameter that works in many different situations. This approach is not as statistically sophisticated as the MPCA method. However, it is very effective and has broad utility, and the associated computations are easier to perform.

When a metameter that more closely approximates the DP is desired, the MPCA method is recommended [3, 10]. Both approaches reduce the DP to two statistics: level and shape. These statistics are then analyzed using the methods appropriate to the experiment design used to generate the DP, as illustrated in Example 2. The needed calculations are available in most statistical software packages. The statistical analysis results are easy to understand and relate to the practical context of the experiment.

When the value of doing the MPCA is not clear, it is recommended that both methods be used and the overall conclusions compared. If little or no additional information is provided by the MPCA, one's confidence in the results of the analysis of the linearized profiles slope and profile average is increased.

## References


1. Shah, V. P., Y. Tsong, P. Sathe, and J. P. Liu. "In Vitro Dissolution Profile Comparison—Statistics and Analysis of the Similarity Factor, F2." *Pharmaceutical Research* 15, no. 6 (June 1998): 889–96.
2. Yuksel, N., A. E. Kanik, and T. Baykara. "Comparison of In Vitro Dissolution Profiles by ANOVA-Based, Model-Dependent and -Independent Methods." *International Journal of Pharmaceutics* 209, no. 1–2 (November 2000): 57–67.
3. Wang, Y., R. D. Snee, G. Keyvan, and F. J. Muzzio. "Statistical Comparison of Dissolution Profiles," *Drug Development and Industrial Pharmacy* 42, no. 5 (2016): 796–807.
4. Cole, J. W., and J. E. Grizzle. "Application of Multivariate Analysis of Variance to Repeated-Measurements Experiments." *Biometrics* 22, no. 4 (1966): 810–28.
5. Rao, C. R. "Some Statistical Methods for Comparison of Growth Curves." *Biometrics* 14, no. 1 (1958): 1–17.
6. Mandel, J. *Analysis of Two-Way Layouts*. New York: Chapman and Hall, 1995.
7. Majji, A., and A. S. Shewale. "Formulation and Optimization of Intermediate Release Dosage Form of Efavirenz Using Design of Experiments." *International Journal of Pharmaceutical Sciences Review and Research* 24, no. 2 (2014): 245–50.
8. Montgomery, D. C. *Design and Analysis of Experiments*. 8th ed. New York: John Wiley and Sons, 2013.
9. Hurtado y de la Peña, Marcela, Yolanda Vargas Alvarado, Adriana Miriam Domínguez-Ramírez, and Alma Rosa Cortés Arroyo. "Comparison of Dissolution Profiles for Albendazole Tablets Using USP Apparatus 2 and 4." *Drug Development and Industrial Pharmacy* 29, no. 7 (August 2003): 777–84.
10. Snee, R. D. "On the Analysis of Response Curve Data." *Technometrics* 14, no. 1 (1972): 47–62.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# A NEW QUALIFICATION APPROACH

## for Mobile Purified Water Systems

By Fritz Röder


Fritz Röder

The unavailability of a backup pharmaceutical water system has been a severe limitation for pharmaceutical manufacturers. Until recently, qualification concepts that adhered to current Good Manufacturing Practice (GMP) guidelines hindered the rapid setup of a water system. A new, tailor-made qualification concept for mobile water treatment has been developed to align with guidance from various health authorities and organizations. It is now possible to set up a temporary purified water source for pharmaceutical applications in less than 3 weeks.

Mobile water treatment is a widely used solution in power, chemical, and numerous other process industries. Depending on the product water specification, different water treatment technologies are installed on a rack or in a container. The water treatment unit is then transported by truck and set up at the point of use. After installing the media supplies and connecting the necessary interfaces, experienced technicians can perform a quick startup. The water treatment system is then ready to use, can be rented for several days or weeks, and is easy to remove. However, these solutions are not intended for GMP-relevant applications.

GMP regulations require an in-depth equipment qualification, which includes performance qualification (PQ), before the water can be used for pharmaceutical purposes. During PQ, the unit must perform over several weeks. In addition to all other onsite qualification activities that must be completed before starting PQ, the traditional qualification process may require up to 4 months. This is why mobile water solutions are not commonly used in the pharmaceutical industry.

### APPLICATION

A market for mobile water systems in the GMP sector exists: many people ask local water treatment manufacturers for mobile solutions. Possible industry needs include:

- A backup solution is needed during maintenance or repair of an existing system.
- A new water treatment unit must be placed where the old one is installed.
- An existing water treatment unit must be replaced without shutting down manufacturing.
- An existing purified water system has microbial issues and remediating the issues takes considerable time.
- Washing areas must be relocated temporarily and no purified water outlet is available.

Purified water systems must always be easily and regularly available in the facility. If a tablet press has a defect, another qualified one can be used and few, if any, other processes at a site are impacted by the breakdown. A water system, by contrast, supplies all pharmaceutical facility applications: dispensing, processing, filling, equipment and machine cleaning, and potentially even air humidification. A water system issue would even shut down packaging lines because their format sets could not be cleaned. In other words, a water system breakdown stops all facility operations.

How much does production interruption cost? This question cannot be answered easily, as many factors must be considered. Could downtime be used for other activities, such as maintenance? Another important factor is that if a company cannot ensure patients' medicine supply, the patent for that medicine may be temporarily negated [1].

### INVOLVED PARTIES

These factors result in the need for a highly reliable water system in a pharmaceutical facility. This was also why the author considered solutions that increase the availability of water. Until now, it was not possible to quickly set up and qualify a pharmaceutical water system. This situation provided the motivation to develop a new qualification concept and discuss it with different health authorities and organizations:

- Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (Germany's central authority for health protection with regard to medicinal products and medical devices)
- US Food and Drug Administration (FDA)
- US Pharmacopeia (USP) Chemical Analysis Expert Committee
- German-Austrian-Swiss ISPE Community of Practice "Water and Steam" (ISPE CoP D/A/CH)

Each organization offered valuable input that was used to refine the qualification strategy. Some of these ideas are discussed in the Qualification Risks section. Finally, a qualification concept could be created that was recognized by all parties and accepted for use, but it must be approved by pharmaceutical manufacturers. With this concept, the period from installation to release of the water for pharmaceutical use can be reduced to less than 3 weeks. In contrast, the traditional qualification approach before release of the water normally takes up to 4 months.

Through the existing mutual recognition agreements [2], a wide range of countries is covered by the involved parties. In addition, as many experts admitted, there is no existing law or guidance that prohibits the use of mobile water systems; the challenge is to provide a quick but sufficient qualification.

## QUALIFICATION RISKS

A typical mobile water treatment system may be installed inside a standard 20- or 40-foot container for truck transport or it can be placed on a rack with rollers. This type of unit is transportable and has defined interfaces for feed water, wastewater, power, product water, and further media as required. The subject of this article is mainly the purified water generation unit. Storage and distribution systems must be installed inside the manufacturing building, and the water purification unit is connected to an existing tank. Possible solutions are shown in the photos on.

The new qualification concept addresses numerous risks that only occur in mobile systems.

- Purified water is considered a medicine excipient. Consequently, the water must be released for manufacturing purposes by the head of quality control (QC). How does QC obtain the relevant data needed for the release of the raw material?
- Which feed water quality should system design be based on? Feed water quality is unknown when the unit is designed.
- While the mobile water unit is under construction, the equipment supplier does not yet have a customer to provide requirements. A user requirement specification (URS) for the equipment should be made prior to fabrication by the equipment supplier. This document can be provided to the user for approval or to be used in the development of the user's own URS.
- It is assumed that the unit will not be connected to the local TCP/IP network and must be secured according to data integrity guidelines. How can the data be stored and transferred in a secure manner? The data must also be deleted from the water system when it is subsequently uninstalled.

Mobile water systems are feasible for different GMP applications and can help avoid purified water shortages at the pharmaceutical site.

- What happens while the unit is in transport? Resins or filter gravel layers may become mixed if the unit vibrates. In addition, a softener cannot be entirely dried again after wetting. This must be considered because any remaining water in the softener might pose a risk to microbial proliferation in the vessels.
- The risk of microbial contamination is increased when the system is transported. Cleaning and disinfection tasks should be done.
- Maintenance tasks may be increased if the unit needs to be transported. In addition, ownership for all typical maintenance tasks must be established for the mobile unit.
- During transport, single parts or components might be damaged. Checks after transport and a decommissioning procedure are recommended.

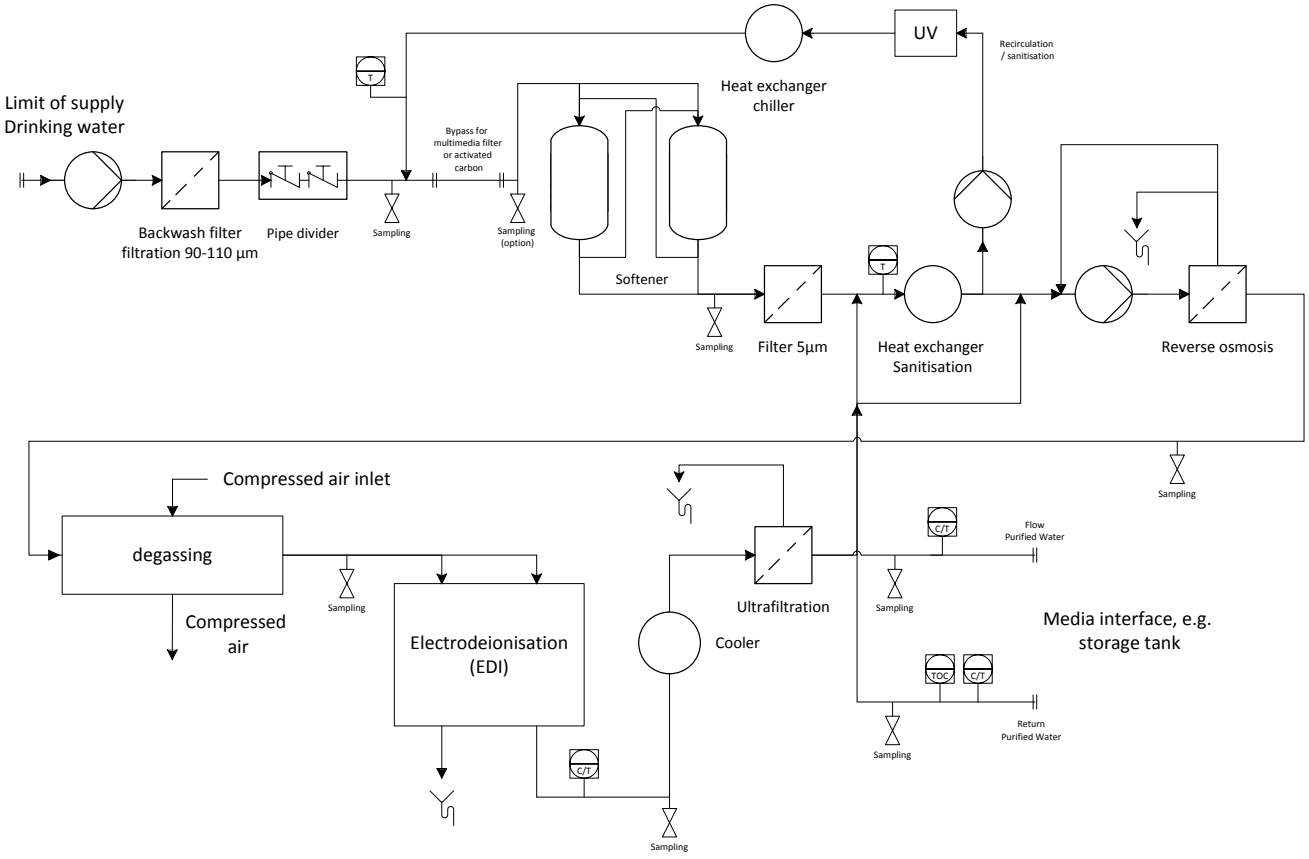
Most notably, the lack of specific requirements at the beginning of the project is of particular concern. The only possible solution seems to be selecting a custom water specification. However, drinking water regulations worldwide cover at least 50 compliance parameters. Which ones apply in a certain instance, and which specification range should be set in advance? The presented qualification concept provides a recommendation for a suitable feed water specification. A typical flow scheme for a mobile water treatment system is shown in Figure 1.

## QUALIFICATION CONCEPT

The typical qualification procedure for any GMP machinery consists of design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and PQ. To set up mobile water systems, two main aspects had to deviate from the common approach:

- An IQ/OQ process of a water system at the pharmaceutical site normally takes several weeks. Commissioning is performed in this period as well. To quickly have a portable purified water supply ready, this period had to be shortened.

**Figure 1:** Flowchart of a mobile water treatment system.




- Normally, under international PQ requirements, a water system will be in a test phase (Phases I and II) for 4 to 8 weeks before water can be released for pharmaceutical purposes. Furthermore, Phase III testing is conducted after release to take into account seasonal variations of feed water and verify the operation over a year. To ready a portable water system, this PQ step had to be modified.

To support these needs, the mobile system qualification strategy comprises two main elements: the qualification and the "prequalification," as shown in Figure 2. The first one is carried out at the supplier's site. Tests to verify adherence to ASTM E2500 [3] principles may be performed during commissioning activities. To fulfill "Good Documentation Practice," it is necessary to review and approve those test results as part of the qualification in the commissioning protocol/report.

The ASTM E2500 qualification approach strongly relies on subject matter expert knowledge and engineering documentation for any type of testing. This practical strategy is part of the mobile water system qualification plan.

The unit prequalification, including PQ, at the supplier's site justifies rapid qualification at the installation site. To compensate for the missing user experience at the site, several additional actions such as monitoring or training activities must be done. In total, a suitable process control strategy has been developed and is part of the tailor-made qualification concept (see Figure 2).

As Figure 2 illustrates, the entire unit qualification process is divided in two parts: one at the supplier's site, which is called prequalification, and one at the pharmaceutical site. After completing the prequalification phase, the unit is ready to be rented to the pharmaceutical customer.

In the next step, the mobile water system is transported to its destination next to or within the GMP site, where it is connected to the existing storage and distribution system. To complete this, a change request must be set up by the customer according to the site's pharmaceutical quality system. In case of outside placement, weather conditions must be assessed. Usually from the moment the system arrives at the site, all tasks must be performed rapidly, which is common in rental use. The author estimates 3–5 working days to locate the unit, connect all (prepared) interfaces, and per-

form the necessary IQ/OQ testing that could not be performed before delivery or that may have to be repeated onsite. After successful completion and approval of the OQ report, the water treatment unit must demonstrate robust operation in the scope of the PQ. Figure 3 shows how the timeline has been modified for the new approach.

Ensuring water safety is a critical aspect of using mobile water treatment systems. During the concept review, agency regulators specifically recognized that this accelerated approach to qualification involves more risks. In addition, neither the supplier nor the pharmaceutical manufacturer will have any significant experience with this water system combined with specific local feed water. The additional risks due to rapid startup procedure and lack of experience must be offset elsewhere. Especially in the first weeks, a high degree of control is needed until sufficient experience has been gained. After releasing the water for pharmaceutical purposes, PQ continues until 1 year of data has been acquired or until the unit is decommissioned.

Pharmaceutical manufacturing site technicians will also lack experience with the mobile water system. Although they will be trained how to operate the unit, the process of establishing standard operating procedures may take more time than is available at the site. Consequently, several tasks must be clearly described in the operator's manual or be automatically performed by the control system. In total, the new qualification strategy describes a suitable contamination control strategy for operation of a mobile water treatment system. Additionally, the new Annex 1 draft to the GMP guidelines [4] requires establishing a contamination control strategy for aseptic manufacturing. According to the new annex, affected companies will also have to develop a strategy for their stationary water for injection (WFI) or highly purified water (HPW) system (if still in use).

## MOBILE WATER SYSTEM DESIGNS

Mobile water treatment solutions can be designed in different ways to fit different needs and applications. They can be installed on rolling racks, in intermodal ISO containers, on trailers, or as decentralized small systems for the supply of single outlets (e.g., in a temporary washing area). Which process technology is used depends on the desired range of applications and how the unit is transported. The qualification concept is applicable for all design types. Examples of these designs are shown in the photos on pages 64 and 66. Additional technologies may be used to ensure safe operation and to compensate for additional risks associated with temporary use.

Figure 2: Mobile water purification system two-part qualification strategy.

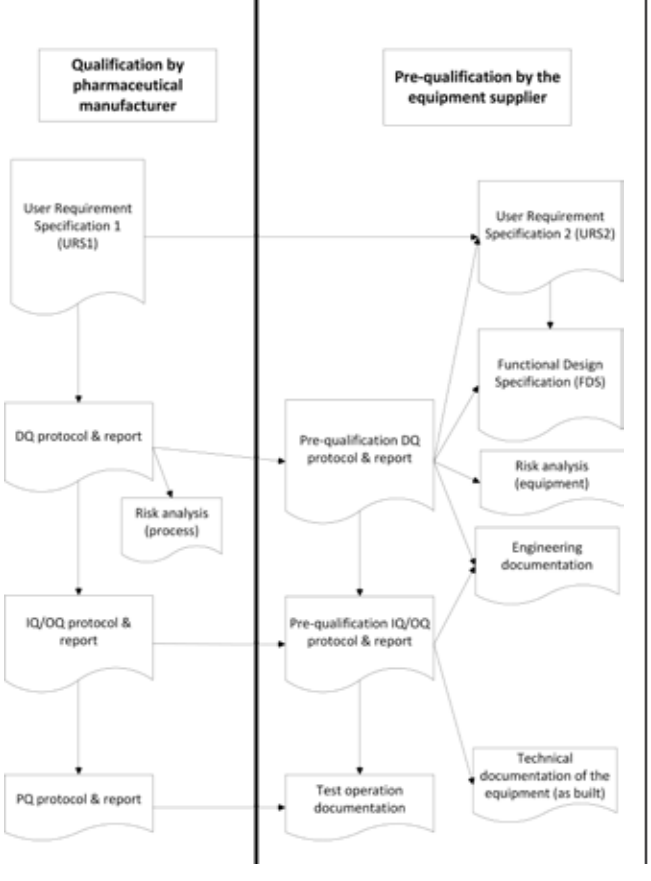
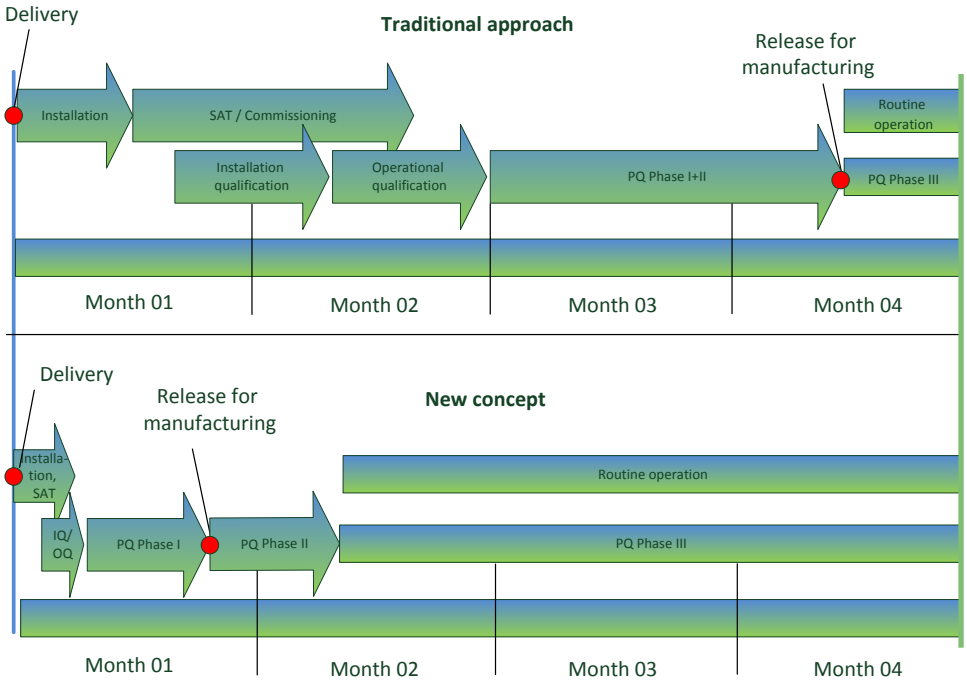


Figure 3: Timeline comparison of the traditional qualification approach and new concept.





Mobile water treatment in an ISO container; outside view.


Mobile water treatment in an ISO container; inside view.

## COST CALCULATIONS

The required amount of water and pharmaceutical site conditions must be considered before renting a water system. The following sections discuss a total cost calculation for a water treatment system supplier and a pharmaceutical manufacturer to provide basic economic information for both parties.

### Mobile Water System Supplier Example

The following calculation is based on a capacity of 1 cubic meter of purified water per hour (1 $m^3$/h) according to relevant worldwide pharmaceutical monographs. Estimated costs are based on experiences from European countries. Because all media are supplied (and paid for) by the pharmaceutical company, they are only included in the Pharmaceutical Manufacturer Cost Calculation, not here.

It is assumed that a pharmaceutical water treatment system including testing, setup, prequalification, documentation, and the additional requirements to make the system mobile would cost €250,000. (At the time of writing, €1 is approximately equal to $1.12 USD.) The typical rental cost for the water system is calculated as €7,000/week, with transport and fast-track qualification at the customer's site being charged separately (see the Pharmaceutical

Figure 4: Mobile water treatment system return on investment for the supplier. Supplier costs for the water system include maintenance costs (no media costs). Estimated supplier revenue is based on an annual rental of 20 weeks.

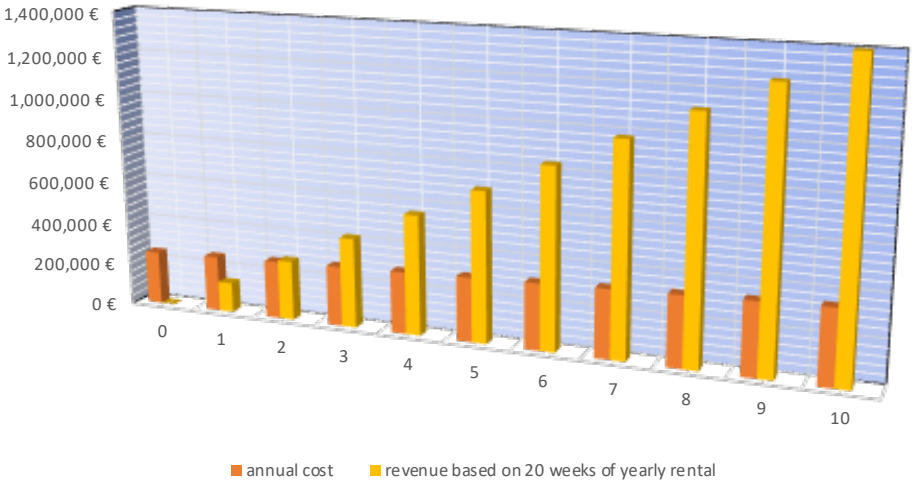



Table 1: Life-cycle cost calculation for the pharma manufacturer.

| Expense | Amount |
|---|---|
| Rental costs | €70,000 |
| Transport, commissioning, and qualification costs | €20,000 |
| Operating costs | €6,720 |
| **Total costs** | **€96,720** |

Manufacturer Cost Calculation). This would result in an amortization of the unit for the supplier after approximately 41 weeks of rental, including €10,000 of maintenance cost per year.

A typical rental period is assumed to be 10 weeks, including 2 weeks of PQ. If two customers rent the unit every year (20 weeks of rental per year in total), it would take approximately 2 years to cover the cost of the water treatment unit. Assuming a typical system lifetime of 10 years, the supplier would have approximately 8 years to earn profit with the mobile unit after amortization. Maintenance and repair costs of €10,000 per year can be assumed.

This calculation demonstrates that the supplier can earn a significant profit. As shown in Figure 4, the total return on investment for a mobile unit over its entire lifetime can reach more than €1 million.

## Pharmaceutical Manufacturer Example

Estimating all expenditures for the pharmaceutical manufacturer is more difficult and complex than for the supplier company. As discussed previously, the possible loss caused by unplanned downtimes can only be estimated as an opportunity cost, but the reputational damage and potential loss of business would be extremely high if the company's products go out of stock. Furthermore, a water system breakdown stops all GMP manufacturing activities across the entire site.

Calculations are based on data from the Water Treatment System Supplier example for easy comparison of both business cases. A daily consumption of 8 $m^3$ shall be met in the facility, for which the capacity of 1 $m^3/h$ described previously may be suitable. The facility operates 6 days a week, so the weekly amount of water is 48 $m^3$. As mentioned, the treatment plant rent is €7,000/week, which leads to rental costs of €70,000 for a 10-week lease.

The cost for transporting, installation, extra piping, commissioning, and fast-track qualification is calculated as €20,000 for a single event per customer.

The total water system operating costs have rarely been calculated in the past because many of the costs, including the following, are difficult to estimate:

- Monitoring
- Root cause investigations
- Electricity
- Feed water and waste water costs
- Compressed air
- Cooling energy
- Consumables, chemicals
- Spare parts
- Trending/product quality review activities
- Operational costs (trainings, daily inspection activities, etc.)

The author published a total life-cycle cost calculation [5] that is used for further consideration (Table 1). An average cost of €14 per cubic meter of produced purified water has been calculated to cover

Mobile water treatment on a rolling rack (source: Letzner Pharmawasseraufbereitung GmbH, Hückeswagen, Germany).

The only possible solution seems to be selecting a custom water specification. However, drinking water regulations worldwide cover at least 50 compliance parameters.

all mentioned expenses. Over the total term of the lease (10 weeks), 480 m³ purified water will be used, for a total cost of €6,720, and the total cost for the 10 weeks would be €96,720.

As an alternative to a mobile water treatment system, water may be bought in intermediate bulk container (IBC) totes (usually approximately 1 m³ volume) and filled manually into the existing storage tank. However, there are several risks to consider:

- Compared with a mobile water treatment system, use of water in containers requires regular sampling of a greater number of parameters (according to USP 1231).
- Raw materials in bulk must be sampled according EU GMP Annex 8 (statistically valid methods), which leads to very high monitoring costs.
- At least 60 m³ water would have to be transported to and through the facility every week.
- Purified water in containers is not always suitable for the preparation of solutions.

Assuming a price of €250 per cubic meter of water in an IBC container, €2,000/week transport costs, and €1,000/week sampling and testing costs, the total water supply price would be €15,000/week, or €150,000 over the entire period.

Clearly, a mobile water treatment unit is not only easier to handle but also the cheapest option for the pharmaceutical manufacturer to establish backup capacity in the facility.

## CONCLUSION

The new qualification strategy for mobile water systems has been discussed with experts and authorities from all around the world. Using it, the qualification procedure can be shortened to a duration of less than 3 weeks from installation to release of the water for pharmaceutical purposes. Mobile water systems are feasible for different GMP applications and can help avoid purified water shortages at the pharmaceutical site. In many cases, local quality assurance policies prohibit the use of a mobile system because the qualification time frame is abbreviated or simply because of a lack of experience. However, the concept offers advantages for the health authorities. Their mandate is to provide sufficient amounts of high-quality medicine for the public, and a mobile water system helps ensure the timely supply of medicine to the market.

### About the author

**Fritz Röder** has a diploma in environmental engineering and broad experience in the pharmaceutical industry. He has worked many roles in different companies such as Allergan, Bayer, and Merck KGaA. Currently, he is Senior QA Manager, Validation, Qualification, and Engineering, at Merck headquarters in Darmstadt, Germany, approving all facility and equipment qualification. In addition to his activities within ISPE as part of the Regional Community of Practice, Water and Steam, in the Germany/Austria/Switzerland (D/A/CH) region, Fritz is part of the European Directorate for the Quality of Medicines Working Group on Water and contributes to the European water monographs. He has been an ISPE member since 2015.

### References

1. Federal Ministry of Justice and Consumer Protection. "Medicinal Products Act. Section 79: Authority to Permit Exceptions in Times of Crisis." April 2016. http://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p1788
2. European Commission. Industry, Entrepreneurship and SMEs. Single Market and Standards. "Mutual Recognition Agreements." Accessed 11 February 2018. https://ec.europa.eu/growth/single-market/goods/international-aspects/mutual-recognition-agreements
3. American Society for Testing and Materials. "ASTM E2500-13: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment." West Conshohocken, PA: ASTM International, 2013. https://www.astm.org/Standards/E2500.htm
4. European Commission. Health and Consumers Directorate-General. EudraLex, Volume 4, Annex 1. "Manufacture of Sterile Medicinal Products." 20 December, 2017. https://ec.europa.eu/health/sites/health/files/files/gmp/2017_12_pc_annex1_consultation_document.pdf
5. Röder, F. Chapter 6.A. In *Pharmawassersysteme Wirtschaftlich Betreiben* (Pharmaceutical Water—Ingredients, Limits and System Concepts: Ultrapure Water for Manufacturing and Laboratory [GMP Expertise]). Schopfheim, Germany: Fritz, Maas & Peither Publishing, 2017.
6. European Commission. Health and Consumers Directorate-General. EudraLex, Volume 4, Annex 15. "Qualification and Validation." 20 March, 2015. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf

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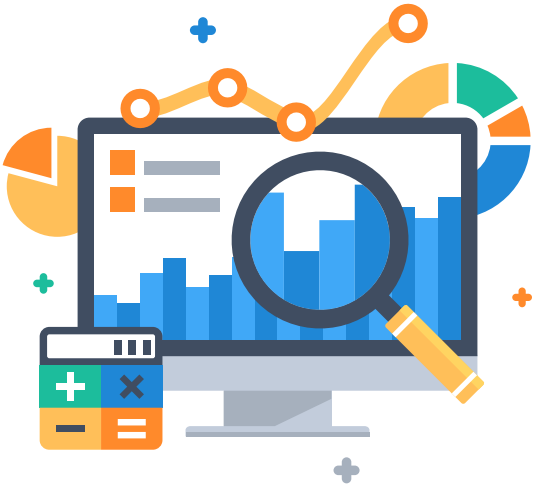

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**REFERENCE**

1. IQVIA Institute. "The Growing Value of Digital Health: Evidence and Impact on Human Health and the Healthcare System." Published 7 November 2017. https://www.iqvia.com/institute/reports/the-growing-value-of-digital-health

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