PHARMACEUTICAL ENGINEERING®

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The Transition to Digitalization

Validation of Clinical Trial–Related Systems in Smaller Enterprises

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14

TECHNOLOGY TRENDS: THE TRANSITION TO DIGITALIZATION

In the pharmaceutical industry, digitalization involves developing and implementing digital technologies at all levels of pharmaceutical operations. The aim is to transform the industry by capturing, analyzing, and using vast amounts of data collected from a wide range of sources to support research and development, clinical development, drug manufacturing, supply chain management, patient engagement, quality assurance and quality control, product safety monitoring, and other objectives.

Despite the transformational potential of digitalization, the pharma industry has historically been slower than other sectors to adopt digital tools, such as cloud storage, artificial intelligence, machine learning, blockchain, and remote communication technologies, and make associated changes in workplace culture and strategic priorities. Now, however, the COVID-19 pandemic may be accelerating the pace of change.

CORRECTION: In the July-August *Pharmaceutical Engineering* article "Case Study: Facilitating Efficient Life-Cycle Management Via ICH Q12," information was incorrectly stated on page 51 in Table 1. Under the European Union filing category, the first piece of information for "critical" should be Type II, not Type I.

ON THE COVER An artist's rendering illustrates the complexities and possibilities inherent in the pharmaceutical industry's transition to digitalization.

FEATURES

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

ISPE Headquarters
6110 Executive Blvd., Suite 600
North Bethesda, MD 20852 US
Tel: +1 301-364-9201
Fax: +1 240-204-6024

ISPE Operations
600 N. Westshore Blvd., Suite 900
Tampa, FL 33609 US
Tel: +1 813-960-2105
Fax: +1 813-264-2816

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

Alisa Pachella, Sales Account Manager
+1 813-739-2274 apachella@ispe.org

Doug Whittemore, Sales Account Manager
+1 813-739-2300 dwhittemore@ispe.org

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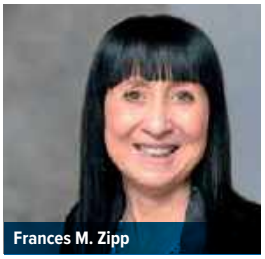
By Frances M. Zipp


Frances M. Zipp

Pandemic
Problem or Solution Opportunity?

How many times have you heard phrases like these over the last several months: unprecedented marketplace disruptions, staggering economic conditions, or maybe insurmountable business challenges? If you're like me, probably more than you can count.

Their endless repetition can be depressing and disheartening. But despite all the current harbingers of doom, there are agile, visionary, forward-leaning companies that not only survive and thrive under these conditions, they see them as opportunities to create and innovate while helping society. Solving the problems currently at hand *and* affecting positive change within their respective organizations and across our industry are motivational forces to them, not obstacles.

As part of my industry-related role at Lachman Consultants, I am part of a team that tracks trends and closely monitors shifts in the economic and regulatory landscape to provide real-time guidance and insights to clients across the various sectors of the life sciences. Today, I am spotlighting the medical device industry and share some examples with you. And, by the way, a nod of appreciation to Ricki Chase, a senior member of our team and former FDA Medical Device Specialist and Director of Investigations, for her greatly appreciated contributions to this month's column; we all support ISPE as we support our industry.

NEW TECHNOLOGIES

Here are highlights of some of the newest, most exciting technologies on the forefront of modern therapies that are actively seeking to keep pace with the rapidly changing ecosystem.

In Vitro Diagnostics (IVD). The COVID-19 emergency has driven fast development of new IVD for the diagnosis of COVID-19 as well as IVD to detect the presence of antibodies. The development of IVDs has been growing in recent years and the FDA Center for Devices and Radiological Health has released guidance on the new expectations for dual 510(k)/Clinical Laboratory Improvement Amendments (CLIA) clearance [1]. Currently, some of the most exciting growth is being seen in the form of total genome sequencing technologies that strive to quickly sequence the total genome within hours as opposed to days, identifying any mutations or nuances not known by a genus-species identification made through standard diagnostic procedures. This allows healthcare providers to almost immediately choose the most effective therapies available and more rapidly defeat the infection.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). This technology seeks to cut or remove the defective or mutated genomic sequence associated with certain disease states from the patient's cells to defeat the disorder. CRISPR technology is being developed for use as a diagnostic tool, where CRISPR proteins can be used to hunt matching sequences of diseased cell DNA/RNA sequences and provide a signal for detection. This presents a potentially powerful tool to aid in very specific disease diagnosis.

Artificial Intelligence. We have also noted a recent increase in the growth and development of Artifical Intelligence (AI). The most promising and closest to approval use of AI is in diagnostics and its role in detecting diseased tissue early, before symptoms manifest or disease spreads. In this regard, AI is the device. It is Software as a

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Medical Device (SaMD) and serves to analyze images produced by mammography to assist in early detection of breast cancer. Specifically, the software can learn to recognize previously undetectable patterns and nuances in the diagnostic image, allowing opportunities for greater accuracy in the diagnosis.

3D Printing. Also pushing the envelope is production of 3D-printed whole organs for transplant using compatible tissues and ensuring vascular structures are in place to support blood flow and viability upon transplantation. Microrobots are being designed to target cell specific delivery of chemotherapies to diseased cells using natural magnetic fields along the body's blood vessels. Fully dissolvable devices, such as wireless brain sensors, are now possible, allowing physicians to see inside the patient's brain and understand the disease state without having to perform additional surgeries for retrieval.

Bionic Eye. Amazingly, ophthalmic devices are being designed to create an eye to restore not just vision, but vision with a wider range of wavelength detection than the "natural" human eye, using nanowires that mimic the function of the retina.

With these examples, I am sure you know that we are just scratching the surface, metaphorically speaking, of the amazing advancements that are here today or just over the horizon. From my perspective, there appears to be no limit to the rapid development of these and many other pioneering technologies. Opportunities and challenges abound. For the biopharmaceutical industry, the new device technologies present even more prospects for combination products, such as AI-integrated inhalers that help teach patients to effectively administer a historically difficult to use treatment.

This is truly an exciting time to be part of the life sciences industry bringing creative new solutions to some of the world's greatest medical challenges. I encourage you to remain strong. To be positive and optimistic. And most of all, look for solution opportunities whenever and wherever you can.

Reference

1. US FDA. Recommendations for Dual 510(k) and CLIA Waiver by Application Studies. February 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-dual-510k-and-clia-waiver-application-studies

Frances M. Zipp is the 2020 ISPE International Board of Directors Chair and President and CEO of Lachman Consultant Services, Inc.

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By Vivianne Arencibia


Vivianne Arencibia

PANDEMIC COPING STRATEGIES

Because of the global pandemic, we have experienced unexpected joys, learned new skills, adjusted to long days of video conferencing, and dealt with drops in income and potential job losses. At the same time, we have also experienced an increased sense of urgency, collaboration, and pride because we are a part of the industry that has been tapped to heal all our nations from this unexpected virus.

If you are like me, you are not getting a break from the influx of work meetings, family stressors, feelings of isolation, and the media outlets. Quarantine fatigue affects us all and can distract us from what we need to accomplish. In order to bring some sense of normalcy into your routine, there are a few things to remember.

GIVE YOURSELF A BREAK

It is ok to set boundaries. Make sure you know when it is time to shut off the phone or computer and stop taking phone calls. Also, if a child, adult, or pet interrupts a meeting or distracts you, it is ok. It is happening to all of us around the world. Just mute or turn your video off, and text or chat your team that you will return shortly but need to tend to your family for a moment.

TAKE YOUR TEMPERATURE AT HOME

Not just your physical temperature, but the pulse of your family before you leave the house. If you are going into work, you are likely feeling like you have unsettled household duties as well as unsettled tasks at the site or office. That is ok. Again, we are all in the same situation. Do your best to make a list to get the unresolved tasks off your mind and then set your plan for what you can realistically accomplish today and for the rest of the week.

Our new normal is to have our temperature checked at the door, be quizzed on how we are feeling, put on our mask, and live under a constant fear that we may contract, or transmit, coronavirus to someone else. We know that this is a temporary situation and we are a part of the solution.

I challenge you to do one thing for you today that does not involve work, your phone, or your computer.

TURN OFF THE NEWS STREAM

We live in a world where we are always tuned in to the media, the news; it is a constant stream of communication. In order to not drive yourself crazy, it is ok to limit your news time. Make a commitment to yourself that you will not check email until you have had your first cup of coffee, or at the very least until your feet have hit the floor!

My family is blessed with a talent for music. We take time to enjoy those talents and listen to each other sing, play an instrument, showcase the latest video, or rehearse for virtual auditions. This situation has brought us closer and taught me to appreciate the time we spend together.

I also like to sit outside and enjoy the sunshine on my deck. I enjoy nature and taking a moment away from a busy schedule to reflect on my workday and disconnect—this helps me maintain my best self.

I challenge you to do one thing for you today that does not involve work, your phone, or your computer. I cannot guarantee it will make you feel better, but I know stepping away from the new normal even for 10 minutes a day gives me the energy and breather that I need to be the best I can be for my family and my colleagues.

Vivianne Arencibia is President of Arencibia Quality and Compliance Associates, LLC, and a member of the ISPE International Board of Directors. She has been an ISPE member since 1991.

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TIMES ARE CHANGING

As many of you read this, I am sure your social and work life have been turned upside down, flipped around, and now are possibly settling into "the new normal." I personally cringed when I wrote that—I was so tired of hearing that phrase about three weeks into the pandemic.

I am sure you all have calendars that are now packed with meetings, calls, and video chats; honestly, I think my calendar has never been this full!

I realized this about a month in and have worked with my team to ensure they are still carving out time for professional development and personal time. Both are super important and should not be overlooked, even when we are in a virtual working world. The biggest mistake we can all make is putting this off until "things resume" because you have missed out on months of development and opportunities!

VIRTUAL PROFESSIONAL DEVELOPMENT

The obvious one is sign up for a webinar. They are all over now, and most have some great breakout sessions!

Schedule some time with your mentor or someone in your company. This could be to have a virtual lunch, cup of coffee, or even a glass of wine. Ask them what they are doing to stay up to date on professional training, and have a relaxed conversation with them.

Now is the time for online training. There is a plethora of online training, and now more than ever, it is easier to work into a schedule.

Attend a virtual conference. Have you ever gotten pushback on attending a conference due to the high cost of travel? That is not an issue with virtual conferences!

I love to listen to an audio book when I walk at lunch. This was once something I did on my commute. Now with working from home, I make sure to step away at lunch and give myself some work/life balance by taking walk with my audio book.

Many are participating in virtual hackathons. These are sessions scheduled on weekends or after work hours to help "hack" or solve a problem pressing on the industry. The ISPE Young Professionals of North America recently hosted the first virtual Hackathon with a problem statement provided by AveXis. It took place over three weeks and combined teams from the East Coast and West Coast to battle it out for the overall winner.

LeAnna Pearson Marcum is a Senior Project Manager at PharmEng Technology and the 2019–2020 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

YP Opportunities to Connect and Learn

Now that you are inspired to recommit to professional development, here are some options to consider:

- **ISPE Young Professionals (ispe.org/membership/young-professionals): Explore news, events, and resources for YP members.**
- **ISPE Community Connection (cop.ispe.org/home; access from ispe.org/membership/communities-practice): Use this enhanced networking platform to participate in discussion threads for Communities of Practice (CoPs), Chapters, Affiliates, and Special Interest Groups. Check out the YP CoP page!**
- **ISPE Conferences (ispe.org/conferences) and Webinars (ispe.org/webinars): Broaden your knowledge and get to know your colleagues by attending upcoming virtual conferences and webinars.**
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Technology Trends: THE TRANSITION TO DIGITALIZATION

By Scott Fotheringham, PhD

In the pharmaceutical industry, digitalization involves developing and implementing digital technologies at all levels of pharmaceutical operations. The aim is to transform the industry by capturing, analyzing, and using vast amounts of data collected from a wide range of sources to support research and development (R&D), clinical development, drug manufacturing, supply chain management, patient engagement, quality assurance (QA) and quality control (QC), product safety monitoring, and other objectives.

Despite the transformational potential of digitalization, the pharma industry has historically been slower than other sectors to adopt digital tools, such as cloud storage, artificial intelligence (AI), machine learning (ML), blockchain, and remote communication technologies, and make associated changes in workplace culture and strategic priorities. Now, however, the COVID-19 pandemic may be accelerating the pace of change.

What are the digitalization trends in the industry? What is the business case to develop and implement digital tools and digitalization strategies? And how can organizations introduce and use them? *Pharmaceutical Engineering*® spoke with industry experts with a wide range of experience in these areas to explore these questions and related topics.

DIGITAL MATURITY

According to Christian Wölbeling, Senior Director, Global Accounts at Werum IT Solutions GmbH, when the Pharma 4.0™ Special Interest Group (SIG) surveyed industry representatives about digital maturity in late 2019, only 16% of respondents said that their organization was involved in systematic, ongoing action to digitalize operations. Another 28% of organizations were engaged in pilot projects. These data suggest that more than half of organizations had either not yet started or were just starting to digitalize operations. This aligns with findings from an earlier (2018) survey report from Deloitte Insights, which found that only 20% of companies consider that they are maturing digitally [1].

"The Pharma 4.0™ operating model is interconnected, meaning that the digital tools allow for a fully connected network to allow direct communication between all levels in an organization," said Wölbeling. When the operating model is deployed, digitalization provides connection and results in full transparency, with data used for improved decision-making.

Wölbeling noted that the digitalization adoption rate depends on the industry segment. Large pharmaceutical manufacturers tend to have greater digital maturity than companies in the generics sector because the larger operations (e.g., Merck, Pfizer, and Johnson & Johnson) have more financial resources, superior data storage and collection assets, and greater access to digitalization experts. In contrast, he explained, generics companies are lagging, in part because budget constraints limit their ability to adopt digital innovations.

Advanced therapy medicinal product and cell and gene therapy manufacturers are the frontrunners in digitalization, Wölbeling said. "They have been highly digitalized from the beginning with all their processes, including a holistic control strategy for the end-to-end process that collects a patient's blood, modifies cells, and reintroduces them to the patient. Everything is still done manually but uses high-tech equipment and, in the end, the data are captured and analyzed by highly sophisticated machinery. The technology guides the operator through the manufacturing process."

AI- AND ML-DRIVEN INNOVATIONS

"AI and machine learning are being used in two distinct ways by biopharma," said Eric Staib, Vice President, PVAI QA/Compliance, at Genpact. They can serve to automate heavily resource-burdened or repetitive activities and as decision-support systems to accelerate the handling of vast amounts of data.

Virtual clinical trials are a potential application of AI/ML to overcome some weaknesses of traditional clinical trials, which tend to be slow, costly, and inefficient. Virtual trials can harness the power of digital health technologies—such as mobile apps and remote health tracking devices—to collect patient data regardless of location, thus increasing the potential for wider recruitment and participation [2].

"AI and machine learning can help analyze data to determine the best, most effective and efficient ways to virtualize clinical trials for a given target population," said Staib. Such systems can help industry stakeholders understand the relevant data in a much more comprehensive and extensive way than was previously possible.

In addition, "many companies are using these technologies to enhance the efficiency of processing, analyzing, and reporting adverse events (AEs)," he said. "With the vast growth in AE case volumes, the expanding number of reporting sources, and the complexity of therapies, such pharmacovigilance systems are sure to be game-changers—and a necessity—within the industry over the next few years."

FACILITY DESIGN

"Digitalization will change how facilities are designed and built," said Robert Guenard, Senior Director, Product and Technology Development, at Biogen. "There is a movement toward building digital twins to virtually model how the operation will function even before plant construction begins." (A digital twin is a digital replica of physical object/entity that can be used to run scenarios and simulate or predict outcomes [3].)

"In the digital world, we'll have a better understanding of what the need is and the likelihood of the need," Guenard said. "Often, we're building plants based on some level of risk and we don't know exactly what's going to happen with them, which leads to costly retrofits. The ability to predict the actual need using simulation will be better and will help inform the design specifications of the plant."

Successful facility design thoroughly anticipates needs related to automation levels and optimal data flow across the product life cycle, including how data from plants, labs, products, and supply chains fit together. "We have to think about how this [the facility and its network] meshes with vertical and horizontal integration using standards such as ISA-88 [4] and ISA-95 [5]," Guenard said.

This focus on increased digital integration should stretch "from the physical layer of the plant to how the sensing, controls, and automation work, all the way up to enterprise management and the supply chain," he emphasized.

Using Data for Predictive Drug Processing

Christian Wölbeling sees the opportunity to use a combination of methods to transition from continuous manufacturing to Pharma 4.0™ intelligent manufacturing.

"In continuous manufacturing, we have data capture, but now we can use it in the manufacturing process in a predictive way," he explained. "You're not just learning about the past and reacting to it, you're using it for decision-making and preventive actions in the present. This uses analytics and predictive algorithms. AI and machine learning can add on to this but aren't necessary.

"The huge data sets that used to be captured on paper and have been digitized over the past 5 to 10 years were stored but not leveraged to make predictions," Wölbeling continued. Those data are now accessible, and there are affordable tools to capture and distribute them. "You can dig into data pools, structure the data, distribute them, and use them to predict.

"An excellent business case for using digital tools during drug processing is the popular current application of these data to predict the optimal harvesting point of a bioreaction. We take data from batches, create algorithms that can use data from a running batch to predict how that batch will develop, and then predict the harvesting time that optimizes titer. Even a small improvement (1%) in harvesting point calculation can lead to a huge increase in profit—as much as $100,000. There's a huge amount of money sleeping there. An electronic system makes this accurate and repeatable."

—Scott Fotheringham

"We have the opportunity to evolve from a culture of compliance to a culture of quality."

BLOCKCHAIN

Blockchain can be used for data security—and more. "Decentralized ledger technologies such as blockchain record data in a time series (i.e., the order of transactions)," explained James Canterbury, Principal at Ernst & Young LLP.

"The combination of the transactions (the events) and the time between transactions creates a pattern that is prime training material for machine learning and predictive analytics. This in turn can be used by artificial intelligence algorithms to suggest optimized business decisions. For example, we can use a blockchain to track the movement of drugs through various distribution channels.

"We are moving from centralized systems that require trust to decentralized systems that generate proof," Canterbury continued. "At the same time, we are shifting from process-oriented data structures to product-oriented data structures. In a decentralized system, the data can follow the product as it moves through its life cycle without needing to integrate all of the systems that govern it along its way. Cryptography plays a really important role in all of this, being able to provide proof that you know something, without actually revealing what you know. It opens up a whole new realm of information exchange. This will change the way we rely on systems, which in turn will change the way we manufacture drugs and devices."

QA AND QC

"We have the opportunity to evolve from a culture of compliance to a culture of quality," said Georg Singewald, PhD, Vice President for Global Quality Control at Roche/Genentech. Improved QA and QC can be accelerated by the ability to analyze data made available from sensors and connected networks. This affords "a degree of freedom within the tightly regulated environment to allow good decision-making and can be used over time to change processes and control systems," he explained. "We can eventually to understand root causes and analyze them. Digitalization helps identify and even predict clusters that we might not be able to see today," and will help us be more accurate.

Another benefit of digitalization is the ability to make accurate predictions. "Before these technologies were available, the quality team was looking at historical deviations that happened in a batch," Singewald said. "What we want to achieve for QA and QC is to use data for predictive models. This allows us to have more in-line technologies on the floor to provide analytical readouts, faster methods that can pick up trends in real time, and having elements that identify those trends and feed them into the quality system to compare with previous experience. In this way, the quality team moves away from being focused on records of batches that have already been produced to becoming a business partner to improve processes, as is seen in other industries."

He added, "These technologies need not interfere with the regulatory compliance requirements for release testing. We can bring in these new methodologies running in parallel and learn to use them as preventive measures, even if they are not giving us the final readout of a lot release."

Singewald foresees additional changes from digital technologies. "Once a company has reached a certain level of automation, including computer system validation, then the need for oversight can be reduced. Then you have a culture of quality that truly builds quality into the process. This will enable an organization that makes informed and consistent decisions at the lowest level possible, further fostering accountability and quality culture."

WORKFORCE EFFECTS

"New product modalities and manufacturing technologies require the existing workforce to settle into a mode of lifelong learning," said John Balchunas, Workforce Director at the National Institute for Innovation in Manufacturing Biopharmaceuticals. Workers will need to constantly advance their subject matter expertise and awareness of technologies.

"This is critical because companies are going to be hiring an increasingly diverse workforce to meet needs and grow into new areas such as continuous manufacturing, digitization, big data, and automation, as well as new product modalities like gene and cell-based therapies," Balchunas said.

"Employees need to take professional development into their own hands and think creatively about where to find opportunities to continue their lifelong learning," he said, noting that there is tremendous capacity for online and hands-on training available through universities, community and technical colleges, professional societies, and specialized industry training centers. In addition, because technological innovation often starts with suppliers and vendors, pharmaceutical manufacturing employees should view them not just as not just transactional partners but also as knowledge resources.

"From senior leadership down to technicians and operators, the fundamental need will be the same," Balchunas said. Everyone will need to learn how to collaborate with colleagues across a complex multidisciplinary workforce. "While everyone does not need to become a subject matter expert, they will need foundational awareness of new technologies to communicate effectively."

Singewald agreed. "Competition for skilled IT and data specialists will be strong," he said. "We need to think about the mindset and skills that will build a robust operating model of continuous embedded change to processes within an organization."

COVID-19 IMPACT

The COVID-19 pandemic is shaping the industry's transition to digitalization in multiple ways. Notably, social distancing measures have prompted substantial changes to how and where work is done. "Companies are being forced to be more flexible and consider remote options, including having a qualified person working from home," Wölbeling said. "Having workers who are essential for business continuity unable to be onsite brings a business case to digitalization."

Speed to market for essential medicines is another driver of change. "Digital technologies will be 'must haves' for companies that want to bring new medicines to market quicker and safer," Staib said. "As a result of COVID-19, we can no longer rely on traditional means of conducting clinical trials and gathering pharmacovigilance data. We must know much quicker whether a given drug or therapy is a viable option. This can only be done through a mix of scientific disciplines, all of which involve, and rely heavily upon, technology, data, and best practices."

The pandemic is making it clear that "organizations can delay digitalization no longer," Canterbury declared. "Supply chains need to be more agile to account for better business continuity. Relevant data must be available—and trusted—so manufacturers can switch suppliers easily. In some cases, we cannot afford the time to do traditional, manually exhaustive, supplier qualifications. Even some of the most basic processes, like physically signing a document that requires people to be co-located, will need to change."

Singewald noted specific examples of digital technologies that have been key to effective operations during the pandemic, including digital signature systems and remote access to chromatograms or batch protocols; the latter allows offsite personnel to assess deviations and maintain supply and quality metrics. However, he said that "as long as we are in a hybrid state, where some parts of a process are electronic and some are not, or a whole workflow of a batch is not covered in an electronic way, you will have this challenge of needing to be onsite for some processes."

WHAT'S NEXT?

"The future is here now—it's just not evenly distributed or fully embedded in our industry," Guenard said. "Since I joined the pharma industry in 2003, I've wondered why this transformation

"The best way to get started is to talk with your business partners and industry groups."

[i.e., digitalization] is not happening more quickly. There are many reasons for this. Yes, this is a conservative industry in many ways, but we do incredible things in medical science, so innovation is really happening." Although he said innovative digitalization efforts in manufacturing are making progress, he also observed that companies often do not consider these efforts to have strategic value, which means they tend to be lower priorities than other work to run or improve the business.

Additional challenges, Guenard said, include perceived regulatory and quality barriers. However, "the regulators I've talked to want to see these digital innovations implemented because of the large opportunity to improve patient outcomes and ensure supply continuity."

Guenard noted that the pace of digitalization in the pharma industry relative to other industries may be slower because the incentives are not the same. "We don't talk about margins and cost of goods to the extent that it pushes us to innovate. In the chemical industry, a very small improvement in efficiency can determine whether you remain competitive. Contrast this to our industry, in which the competitive advantage is in efficacy, safety, product performance, and the experience of the customer, and generally not in manufacturing."

According to Guenard, the complexity of the pharma manufacturing industry also makes digitalization especially challenging. "We've seen studies about how other industries are more advanced, but some of our processes are highly complex and the way we manage those plants should be commensurate with the complexity of the process. There's a step change that we have to go through to be able to deliver products in a low-cost, reliable, highly agile manner. There's a significant opportunity here." Efficient digitalization, he emphasized, "is best done by designing it in and being strategic."

Wölbeling pointed out that AI and ML are not new to the industry. "The key trend is how to make a business case and apply them. The main challenges to implementing digitalization are having the right people choosing where and how to use it, developing the systems, analyzing the data, and, of course, the cost." Large pharmaceutical companies have large amounts of data, he said. "Now we have good data in a format that can be fed into AI, as well as interoperability of data sources across geographies and technologies."

However, Wölbeling believes that simply developing and implementing technology is insufficient. "You have to transform the culture," he said. A culture of digital maturity will encourage the mindset to accept, use, and benefit from these technologies and not see them as a burden.

"Decentralized systems are a team sport, and nearly all of the really good development work is being done on public, open-source networks," he said. It's important to play a role in those communities now, and to invest the time to understand the foundations of these technologies and how they will impact your business, he added. "For example, blockchains were originally intended as public utilities and if they're going to reach their full potential, they need to be thought of as such."

Canterbury suggested that industry stakeholders reach out to colleagues as they explore new options. "When you design an experiment or participate in a pilot, you need to consider the ecosystem and account for the right level of privacy versus transparency," he said. "The best way to get started is to talk about it with your business partners and industry groups, such as the ISPE GAMP® Blockchain or AI/ML Special Interest Groups."

Trust in data science is key to moving forward as an industry, Staib said. He also noted that stakeholders need trust in "the rigorous IT controls framework that ensures the quality of such technologies, and the integrity of data they rely upon." In addition, "the successful application of these digital innovations requires investment in the appropriate technology as well as collaboration with tech companies. The pharma and biotech industries need to invest heavily in the understanding and processing of data that are already available to them, both within their organizations and external to their companies, including publicly available information. They also need to embrace partnerships with large and small tech entities to create mutually rewarding codevelopment scenarios."

References

1. Deloitte Insights. "Survey Finds Biopharma Companies Lag in Digital Transformation." 2018. https://www2.deloitte.com/cn/en/pages/life-sciences-and-healthcare/articles/survey-finds-biopharma-companies-lag-in-digital-transformation.html

2. Shore, C., E. Khandekar, and J. Alper, eds. *Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop.* National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation. Washington, DC: National Academies Press, 2019. doi:10.17226/25502

3. Whytock, A. "The Digital Twin: Creating Efficiencies in a Virtual World." *Pharmaceutical Engineering* 39, no. 4 (2019): 21–22.

4. International Society of Automation. *ISA-88: Batch Control.* Research Triangle Park, NC: International Society of Automation, 2001–2010.

5. International Society of Automation. *ANSI/ISA-95: Enterprise-Control System Integration.* Research Triangle Park, NC: International Society of Automation, 2010–2018.

About the author

Scott Fotheringham, PhD, is a freelance medical writer with interests that span fields as diverse as medical cannabis, pharmaceuticals, biotechnology, and molecular genetics. Most recently, he was Senior Medical Writer at Spectrum Therapeutics.

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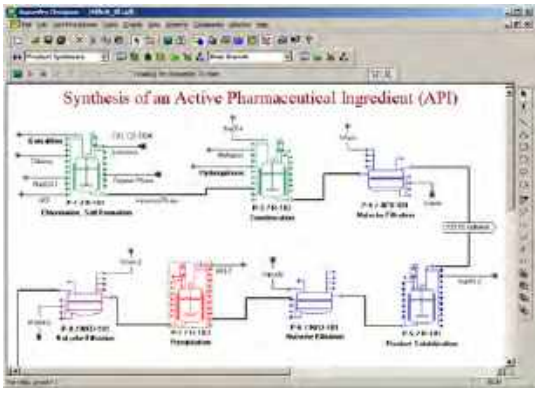

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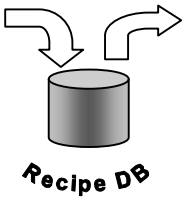

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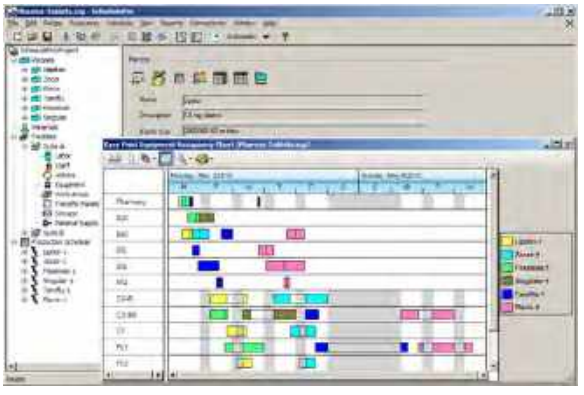

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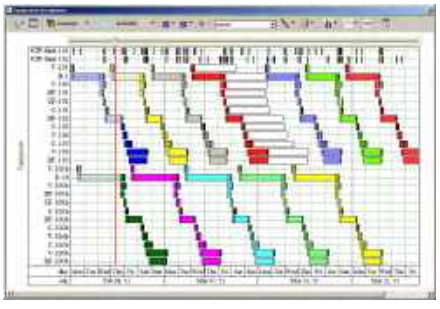

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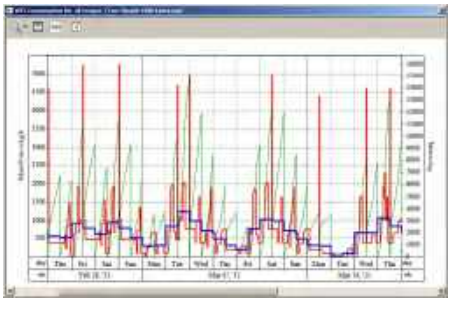

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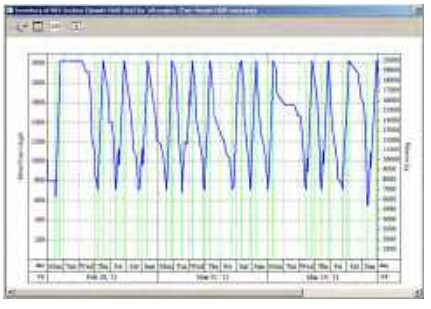

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VALIDATION OF CLINICAL TRIAL–RELATED SYSTEMS in Smaller Enterprises

By Frank Henrichmann and Oliver Herrmann

Existing risk-based approaches to computerized system compliance and validation as outlined in *GAMP® 5* [1] are applicable to a variety of life sciences organizations supporting or performing GxP-relevant activities. However, specific guidance on how to implement all the necessary measures and what to prioritize in small- and medium-sized enterprises is scarce.

The need for such guidance is significant. For example, there are approximately 26,000 medical technology companies in Europe, and 95% of them are small- or medium-sized companies, meaning each of these companies employs fewer than 250 persons and has an annual turnover not exceeding €50 million [2].

Despite the importance of these companies to the pharma industry, the adoption or use of tailored validation approaches in small- and medium-sized enterprises is currently not addressed or described in any guidance or literature. As a result, small- and medium-sized enterprises continue to face the challenge of selecting and applying a suitable process for computerized system compliance and validation [3].

The need for robust computerized system validation as the basis for the integrity, reliability, and robustness of data generated in clinical trials has recently been highlighted in the "Notice to Sponsors on Validation and Qualification of Computerised Systems Used in Clinical Trials" issued by the EMA in April 2020 [4]. This notice specifically states:

> *Failure to document and therefore demonstrate the validated state of a computerised system is likely to pose a risk to data integrity, reliability and robustness, which depending on the criticality of the affected data may result in a recommendation from the GCP [good clinical practices] inspectors to the CHMP [Committee for Medicinal Products for Human Use] not to use the data within the context of an MAA [marketing authorization application].*

Therefore, small- and medium-sized enterprises supporting GCP-relevant activities by providing services and/or technology need to be ready to support their clients with documentation and evidence generated by a robust, reliable, but also right-sized quality management system (QMS).

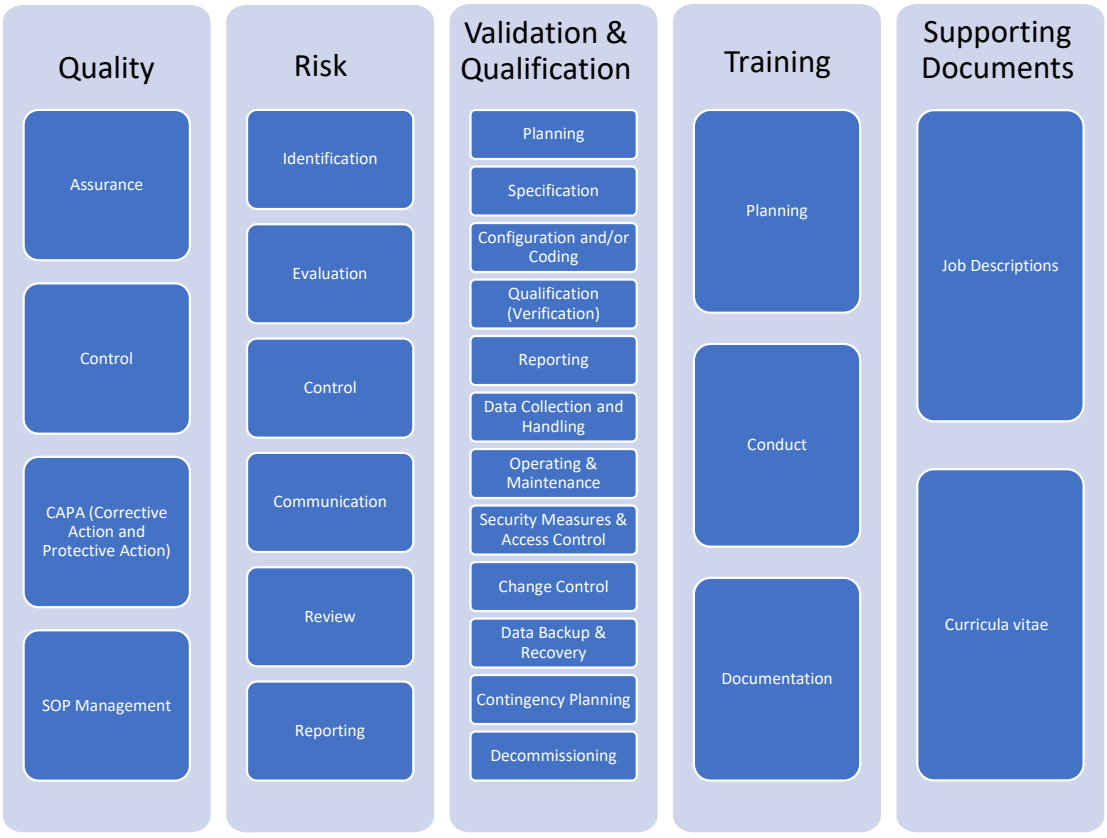
POTENTIAL QMS IMPLEMENTATION CHALLENGES

As Welsh and White have observed, "A small business is not a little big business" [5]. In the pharma industry, this quote is especially true with regard to quality and validation. This becomes obvious in the resourcing of quality and IT departments. Whereas large organizations may have hundreds of people working on sometimes very specialized tasks and a dedicated sizable budget for quality and IT, small- and medium-sized enterprises often have less than a handful of experts, whose efforts may be limited by financial constraints. In the context of quality and validation, this may lead to issues around separation of duties in some organizations.

At the same time, small- and medium-sized enterprises often provide a single or very few specialized services or software and therefore may not need the entire set of processes, checks, and balances that are often implemented and seen as "the standard" in larger organizations. Larger companies often must develop and maintain an extensive QMS that covers all GxP areas to ensure appropriate standards are applied across the entire organization. It may start with high-level quality policies that are then detailed in underlying standard operating procedures (SOPs), work instructions, manuals, and other documentation for the various aspects and areas to be covered. In contrast, small- and medium-sized enterprises should be able to develop and maintain a much smaller QMS that is focused on and tailored to the business and regulatory compliance aspects that are relevant to the services they provide. This QMS may not require as many levels as a large enterprise's QMS.

ICH E6(R2), Guideline for Good Clinical Practice, [6] states that "the sponsor should implement a system to manage quality throughout all stages of the trial process." Although "a sponsor

Figure 1: QMS expectations for detailed processes.



may transfer any or all of the sponsor's trial-related duties and functions to a CRO [contract research organization]," the sponsor needs to ensure oversight of "trial-related duties and functions that are subcontracted to another party." Furthermore, "the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor."

The 2020 EMA notice mentioned previously [2] provides further clarification, stating "sponsors shall be able to provide the GCP inspectors of the EU/EEA authorities with access to the requested documentation regarding the qualification and validation of computerised systems irrespective of who performed these activities." If a small- or medium-sized enterprise (or even a larger company) cannot support the sponsors by providing, for example, system requirement specifications or documentation and system access for GCP inspectors, "systems from such a vendor shall not be used in clinical trials" [2]. This is often interpreted to mean that service and technology providers need to implement a QMS similar to that of sponsor organizations, which are often large pharma companies. Figure 1 illustrates the QMS expectations for detailed processes.

At the same time, the quality approach should avoid unnecessary complexity, procedures, and data collection and follow the application of science- and risk-based methodologies. But how can one determine what is required? And how can enterprises implement the quality approach in an efficient, cost-effective, and justifiable way?

QUALITY

Among the biggest advantages of small- and medium-sized enterprises are the personalized management and flat hierarchies that make them agile and nimble in the market and allow them to address their clients' needs quickly. This advantage should also be reflected in the enterprise's basic quality approach.

This basic quality approach should ideally be documented in a single document that describes the following:

- The basic roles and responsibilities as they are required for the services provided: Even though auditors are very familiar with roles like "process owner" or "system owner" that are distinct from job titles, it may be more suitable in small organizations to use job titles and job descriptions to document the roles and responsibilities and reference those in the quality process descriptions. It should also be understood that the often-granular roles used by large organizations are not feasible for small- and medium-sized enterprises. The adequate separation of duties should be the guiding principle for the design of roles and responsibilities. Even though the *GAMP® 5 Guide* [1] suggests a number of roles including, but not limited

to, process owner, system owner, quality unit, corporate quality, operational quality, and subject matter experts, this does not mean that these roles cannot be combined and covered by very few individuals (in the extreme, by one individual covering process/system owner and subject matter expert and another individual covering all quality roles).

- The overall process for generating and maintaining the QMS, including versioning and document control: Many companies use electronic document management systems to establish access control and versioning, but small companies can be compliant by maintaining a master SOP binder or storing the final documents in a protected area to which most employees are restricted to read-only access. Regardless of the approach chosen, the superseded or retired processes need to be retained. The process for generating and maintaining the QMS can be quite short and lean, focusing on:
  - Steps to request a new process or update to an existing process
  - Approval of processes before they become effective
  - Communication and training of new or changed processes
  - Maintenance and storage of all processes that ever became effective

  Larger organizations often require detailed reviews by a significant number of stakeholders to maintain the internal integrity of their QMS. Small- and medium-size enterprises—with their flat hierarchies, smaller number of SOP authors, and smaller business focus—may be able to reduce or even eliminate these reviews.
- The internal and (if needed) external audit approach, planning, and documentation: This information can be recorded in a document or spreadsheet. Controls similar to those used for SOPs need to be in place to prevent manipulation. This is especially important if the small- or medium-sized enterprise outsources some aspects of the provided services (e.g., to cloud service providers).
- An approach for continuous improvement and corrective/preventive actions: This information may also be stored in a document or spreadsheet; however, most technology providers have systems in place for service desk activities. This system can potentially be configured to support corrective action and protective action (CAPA) activities as well. The overall number of incidents and CAPAs should drive the approach to management review and key performance indicators (KPIs). Smaller companies may not have a need to implement detailed processes for this if there are only few CAPAs and every CAPA is discussed within the entire management team. Whichever methodology is used should be documented as such in the process description.

RISK MANAGEMENT

Risk management activities are fundamental to all attempts to build an efficient, cost-effective, and defensible QMS and validation framework. Protecting patient safety, data integrity, and regulatory compliance needs to be at the heart of all risk evaluations.

A similar approach to the one outlined previously for the continuous improvement and corrective/preventive actions may be utilized for risk assessment and management. Risk may be assessed and managed for each individual project or product; however, an extensive approach to aggregate the risks and have them reviewed by management may not be necessary in small organizations.

Key questions to be addressed in risk assessment activities are:

- What parts of the provided services can directly or indirectly impact patient safety or data integrity?
- Do the services contribute to or directly perform drug safety activities (e.g., collection or processing of serious adverse events)?
- Do the services contribute to the collection or processing of clinical trial data that support a clinical end point?
- Do the services contribute to the storage or distribution of investigational products?
- Do the services contribute to the protection of patient rights (e.g., informed consent)?
- What parts of the provided services contribute to a regulatory submission?

The detailed answers to questions such as those outlined here allow the small- or medium-sized enterprise to focus on critical areas in all aspects of quality. It is critically important that experts in the organization have in-depth knowledge of the process and the system and a robust understanding of the regulatory framework and data integrity expectations. This knowledge enables the risk management activities to find and document the appropriate validation approach. Also, it is important to carefully align the risk assessment with the needs of clients. Understanding how the customer intendeds to use the product or service is important for the small- or medium-sized enterprise's risk evaluation. The risk mitigation activities may be included in quality agreements or service-level agreements.

For example, an electronic data capture (EDC) provider will significantly contribute to the collection and processing of clinical trial data that support a clinical end point. Depending on the trial design and the data to be collected, system downtimes of one or even more days may be acceptable. However, if the EDC system is also used by the customer to collect serious adverse events that need to be processed and reported within tight regulatory timelines, such downtimes may not be acceptable.

Small- and medium-sized enterprises may need to invest significant resources in risk management activities because they are crucial for reducing effort in a justified and compliant manner. The risk management methodology itself should be scaled for purpose; for example, it may not be necessary to document risks and corresponding mitigation actions or acceptance for every individual user requirement associated with a computerized system. Instead, a clear, structured, and detailed description of the intended use, the associated system functions, relevant procedural and technical controls, and the associated risks may be sufficient in a number of cases.

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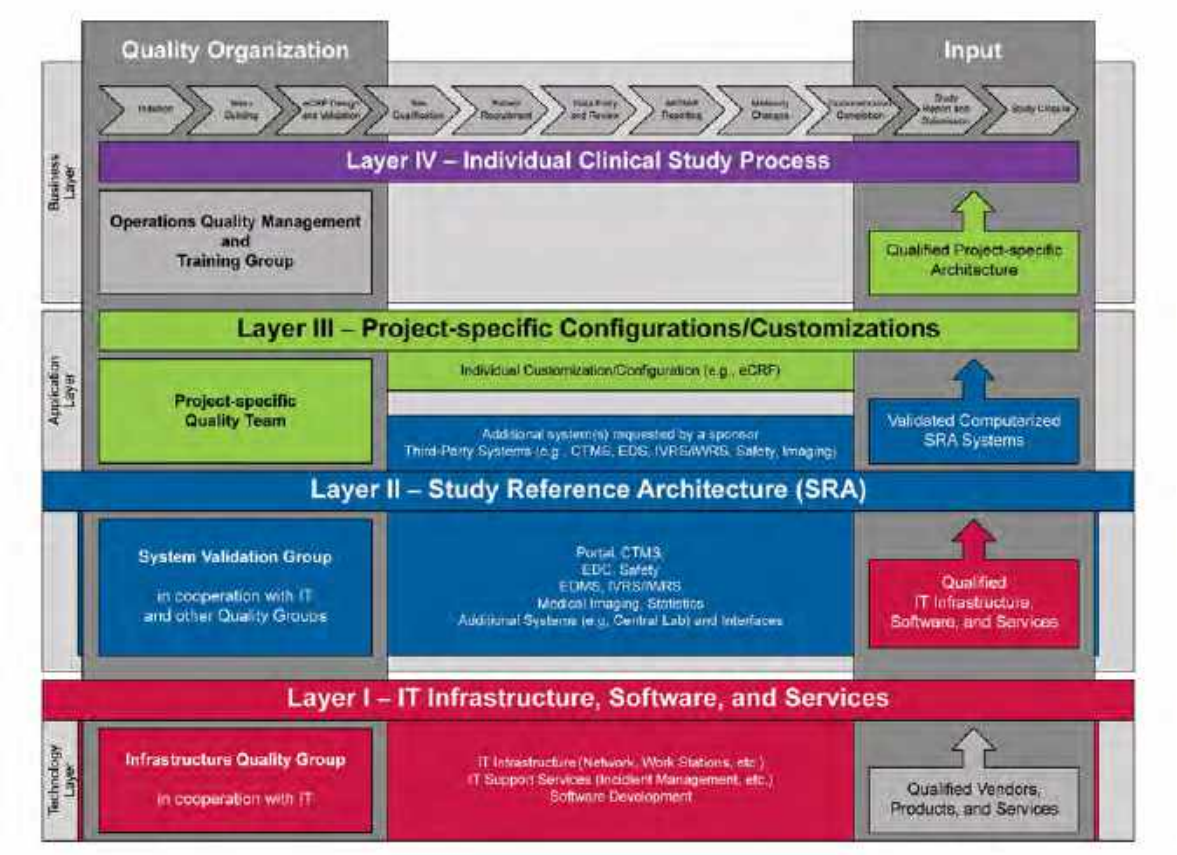
Figure 2: The validation layer model. (Reprinted from reference 7.)



VALIDATION

The validation of GCP systems and data has been described in the *GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data* [7]. In particular, the guide's validation layer model (Figure 2) and the risk assessment and validation guidance for tools that support GCP processes support a lean, efficient validation approach for small- and medium-sized enterprises.

Layer I

Layer I (qualified IT infrastructure, software, and services) establishes the foundation for the validation of computerized systems. The small- or medium-sized enterprise needs to establish a lean set of processes that focuses on qualification of the relevant IT infrastructure, security and data protection, software development, and IT support services.

Qualification of the relevant IT infrastructure

Qualification of the IT infrastructure may include:

- Servers for relevant software and data storage: Qualification can be achieved by a set of templates that capture the relevant data for hardware and the steps required to install operating systems and other software components (e.g., drivers, viewers, frameworks).
- Systems that support the core business but do not hold or process clinical data: Examples include help desk systems, incident management systems, and office applications. Capturing the installation and configuration details as well as the version(s) and release dates of the installed system is critical.

Generally, the need for IT infrastructure qualification is higher if the small- or medium-sized enterprise directly hosts systems that process or store regulated data. Enterprises that develop software that is implemented and operated on the customer's premises may not need to qualify all of their infrastructure. In such organizations, the qualification activities should focus on systems that directly support software development and testing of regulated software or important support services (e.g., a support hotline).

Security and data protection

The following aspects of security and data protection need to be considered:

- Patch management (operating system, browser, applications)
- Classification of data (e.g., sensitive, confidential, public, personal identifiable information)
- Physical and logical security (e.g., virus protection, hardening of systems, intrusion detection)

Obviously, some of these items (e.g., virus protection) are essential to protect the core business of the small- or medium-sized enterprise as well as the client. The relevance of other items may depend on the type of services offered. For example, a software as a service (SaaS) provider typically needs to have an intrusion detection system and process in place, whereas a software provider whose software is installed and operated on the client's premises often does not require this.

Software development

At minimum, software development validation concerns include:

- Specification
- Development and testing
- Deployment and release

For small- and medium-sized enterprises that develop software, this is an area of critical (quality) activities. First, validation is required to ensure that the software is working as designed and has no critical bugs. Second, documentation is essential to enable teams to organize their work during development. Third, a robust approach to software development and documentation enables the small- or medium-sized enterprise's customers to build on that documentation and limit their validation efforts to verifying that the system is fit for the intended use and supports the business process, rather than verifying that all required individual functionalities are working as designed. For this reason, a robust software development approach and documentation can be a market differentiator for the vendor.

Table 1 describes the most important aspects to keep under control. These aspects need to be covered regardless of the development methodology and organizational setup (waterfall, agile, DevOps, etc.). Small- and medium-sized enterprises should try to build a robust end-to-end solution that is suitably integrated to allow team members to answer the key questions. A strong, documented connection between requirements and testing is especially important. To achieve this, the quality requirements and aspects should be considered—along with programing, development, and business needs—when a software development platform is selected and implemented.

IT support services

Generally, the following scenarios are relevant to layer I validation:

- Service/help desk
- Incident management
- Disaster recovery/business continuity

Table 1: Aspects of software development to control.

Aspect	Key Questions to Address
Requirements management	Which requirement was implemented/released in which version?
Version management	Which versions of the software are in development, released, and in use with support?
Test management	How and when was the functionality tested? How can this be traced back to the requirements?
Release management	When was a version of the software released/implemented?
Bug fixing	How and when have bugs been fixed? How is bug fixing integrated into the overall development and release processes?

These are very important concerns if the technology provider offers software products in infrastructure as a service (IaaS), platform as a service (PaaS), or SaaS. This type of offering often requires significant investments in hardware, software, services, processes, and people to establish:

- Service/help desk coverage
- Backup and restore services
- Incident management process and Incident tracking
- Disaster recovery sites, plans, and exercises
- Business continuity plans and exercises

For small- and medium-sized enterprises, it may be more cost-effective to outsource some of these activities to specialized third parties such as cloud service providers. However, the adequacy of these specialized third parties needs to be verified via qualification activities such as audits or questionnaires.

Layer II

Layer II (study reference architecture) of the validation layer model addresses the validation of computerized systems that support the processes to conduct a clinical trial. Small- and medium-sized enterprises that offer services to support clinical trials need to establish a lean set of processes focused on implementing compliant systems that outline the generation of the required documentation and evidence and can also be easily adapted to each customer's requirements. Customers often expect that the small- or medium-sized enterprise will follow the customer's processes in the implementation and integration effort.

Generally, the following scenarios are of concern:

- Systems that support clinical trials directly or as a central, cross-study application: For example, clinical trial management systems (CTMS) that manage all trials in a central database often require significant validation efforts during their implementation because configuration/customization and testing activities on a study-by-study basis are not done or are very limited. An analysis of the supported business process that considers business intent, patient safety, and data

integrity will reveal the critical steps, actions, and data. This analysis needs to be the nucleus of the risk-based validation focused on the identified critical aspects. Small- and medium-sized enterprises that provide such technology solutions should have robust software development documentation that allows the elimination of functional testing on the customer side in this phase. The validation should focus on verifying that the configuration of the system is supporting the business process of the customer as expected.

- Systems that provide a platform and need to be significantly configured/customized to support individual clinical trials (e.g., EDC systems): Typically, such systems require a very limited validation approach focused on functionalities used across all clinical trials, and a significant risk (as outlined previously) is associated with these systems. In an EDC system, the functionality could be the general query functionality. See layer III for more details.

Layer III

The validated systems and platforms are then configured or customized in layer III to build the trial-specific solutions required. The small- and medium-sized enterprise needs to establish a lean set of processes that focus on efficiently building these solutions, often based on customer requirements, in a compliant way.

Generally, the following scenarios are of concern:

- Configuration of systems for specific trials: As outlined previously, the configuration efforts may vary greatly depending on the type of system and/or the complexity of the study. Whereas a CTMS system may simply require a setup of the study through the user interface, an activity that, of course, does not require validation, the setup of an EDC system is significantly more complex and requires programming-like skills. Additionally, data collected via the EDC systems are often directly related to the safety of the participants and the end points of the clinical trial. Most of the validation activities need to be performed on a study-by-study basis to ensure the trial-specific needs—such as electronic case report form (eCRF) design and edit checks—are met. An analysis of the study processes and study protocol focused on patient safety and data integrity is required. Generally, it is advisable to organize such validations to enable a potential reuse of validated elements, if possible. For example, eCRFs capturing demographic data tend to be very similar across studies, so it may be possible to reuse an existing, already validated eCRF. Small- and medium-sized enterprises that provide services to set up technology solutions for individual clinical trials should focus on identifying the critical data points for the study and ensuring thorough testing of configured functionalities that capture and/or process these data.
- Development of interfaces, reports, or data analysis programs based on existing platforms (e.g., business intelligence solutions or specialized development platforms): These items usually require fewer validation efforts because they are based on qualified standard platforms. However, depending on the data that are processed or reported and the potential decisions that are made based on these data, a robust and significant validation effort may be required. For example, interfaces and reports for EDC or safety data are often critical in nature and should be validated. Small- and medium-sized enterprises should achieve an in-depth understanding of the data, data flows, and data usages. This will enable the enterprise to focus the validation effort to the data elements that matter most.
- Building secure and robust data exchange platforms with clients and third parties: Data integrity can also be at risk when data are transmitted between multiple parties. Based on agreements reached between these parties, a secure platform should be established to exchange data. Any required validation activities must focus on access control and security. Small- and medium-sized enterprises that offer such platforms as technology solutions need to focus their effort in these areas.

Layer IV

Layer IV (individual clinical study process) emphasizes that validated systems must be used according to the applicable business processes for the execution of the clinical trial. The high-level processes are usually applicable for all clinical trials; however, the details may differ greatly from one trial to another as study protocols differ with regard to indication, trial design, end points, target populations, and inclusion criteria. Established systems and platforms continue to evolve and improve, but new technologies may be needed to meet individual trial requirements.

The relationship between the business process and the supporting technology is often ignored or underestimated in its importance. Small- and medium-sized enterprises should proactively reach out to clients and gain a robust understanding of their business processes. The better the processes are understood, the better they can be supported by an agile and nimble small- or medium-sized enterprise.

TRAINING

Training has the following objectives:

- Staff are aware of the relevant processes and can follow them.
- Required competencies and skills are developed for the completion of tasks.

The second objective may be achieved via external training or through hiring already fully qualified personnel, but the first objective always requires an internal training program.

All training must be planned for the relevant roles, and the applicable syllabus/training plans should be documented. The training assignments for processes should be in line with the scope or audience descriptions in the process documentation. Also, after training has taken place, documentation must be completed and filed. To demonstrate compliance, organizations should be able to show:

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Table 2: Validation and quality approaches in larger and smaller enterprises.

Aspect	Larger Enterprises	Small- and Medium-Sized Enterprises
QMS	Extensive QMS is required to cover all multiple GxP areas and a wide range of services and activities. The QMS is often implemented as a multilayer document hierarchy with complex relationships and references.	QMS focuses on the services and activities performed. It may be single-layered with a limited number of SOPs focused on the business at hand (e.g., software development, system operation). Stakeholder reviews are shortened or eliminated. A master SOP binder may be maintained, or final documents may be stored in a protected area to which most employees have read-only access. The bare minimum to be covered by the QMS includes: • QMS maintenance • CAPA • Audits • Training and qualification (could include job descriptions) • Qualification and validation of computerized systems
Management review	Management review is often described in an SOP with details on frequency, participants, data to be reviewed, and documentation requirements.	Management review can be informal in small companies with few employees/managers; it requires appropriate documentation such as meeting minutes.
Roles and responsibilities	Problems with the segregation of duties are seldom encountered. Teams are often large, with very detailed division of responsibilities.	Maintaining the segregation of duties may be challenging because teams/departments may be very small. Segregation may be achieved by combining roles and responsibilities and very careful planning of resources and/or by outsourcing of certain tasks.
Job descriptions	Descriptions are often for very specialized roles but without details for specific products. These details are often included in project documentation.	Descriptions could be very detailed and eliminate the need for further specification in project documentation. However, roles may be combined (e.g., the software developer may also have support responsibilities).
Risk management	Risk management is often implemented hierarchically (e.g., moving from team/project risks to department risks, regional risks, and global risks).	A documented risk assessment and management approach on the team/project level may be sufficient.
Critical thinking	Critical thinking needs to be continuously promoted and reinforced as employees of large companies may tend to just follow the rules.	Critical thinking is more predominant in smaller enterprises because every employee is more directly contributing to the success (or lack of success) of the company.
Tools	Extensive tool sets that are interfaced and provide quality metrics are often used. Typically, larger enterprises can afford "best of breed" system implementations.	It is recommended that smaller enterprises carefully select tools that support the business purpose as well as the quality aspects. Quality aspects should be part of the requirements (e.g., in software development tools). However, clever usage of functionalities provided by office software utilizing automated exports of relevant data out of the business tool set can establish robust quality documentation.
Project management	Large teams, which may be distributed globally, often require extensive planning and management. Typically, teams follow the QMS strictly.	Smaller teams are often self-managed and use agile approaches. Unless they are well trained, these teams may value working services and products over quality documentation.
Change control	Change control needs to focus on the implemented changes to the computerized system (infrastructure, software and configuration, processes, training).	Change control needs to focus on version control and release of the software, including its validation/qualification documentation.
Documentation approach	Documentation is mostly electronic, in databases or electronic document management systems.	Documentation can be paper based or electronic. The paper-based approach may be more cost efficient when teams are small and in a single location.

- Training transcripts for individuals (e.g., individual training logs)
- Who has completed specific training (e.g., attendance lists for training sessions)

Organizations need to able to demonstrate that all staff have been trained in time for the roles they are to perform. This sounds simple, but the details can be quite challenging as circumstances change. For example:

- Staff may change roles or take on new responsibilities.
- Staff need to be retrained as processes evolve.
- Enterprises define new roles that require new training plans.

Very small enterprises may be able to manage training documentation with spreadsheets, but growing organizations may need a system to track trainings and processes. This system should describe:

- Training plan creation, review, and maintenance

- Assignment of training to individuals and control of timely training completion
- Documentation of training
- Training of new hires ("onboarding")

Whereas larger organizations may aim to become paperless in training documentation, small- and medium-sized enterprises may find it more cost effective to maintain paper records. Especially if the entire organization is in one location, generating paper records like sign-in sheets is easy and efficient.

SUPPORTING DOCUMENTS

The creation and maintenance of curricula vitae (CVs) and job descriptions is important to support training as well as various human resources and business development activities.

From a quality and compliance perspective, an accurate CV is evidence of staff qualification to perform a regulated activity. Additionally, clients typically request CVs of important staff working on their projects.

Job descriptions help identify the right resource for a specific role or position. Job descriptions should include an explanation of the responsibilities and tasks, the minimum qualifications, required levels of education and experience, and the organizational details. The CV of the person performing a role should demonstrate that they meet the job description requirements, or a justification for the assigned individual should be documented. If the justification entails improving the competencies and skills of the assigned individual through training, a detailed training plan with timelines should be included.

CONCLUSION

The regulatory expectations for computerized system validation do not differentiate between larger and smaller organizations. All organizations that support GxP-relevant processes have a responsibility to protect patient safety and data integrity. However, small- and medium-sized enterprises often have the advantage of flat hierarchies and personalized management, and the specialized services that these enterprises provide should be considered in the design and evaluation of their QMS.

Small- and medium-sized enterprises need to have a clear understanding of the services they provide, the GxP-relevance of these services, and the applicable regulatory framework. This knowledge is essential for risk assessments focusing on data integrity and patient safety, the determination of appropriate controls and validation approaches, and the creation of proper documentation that can be used in audits and inspections. There is no regulatory expectation that small- and medium-sized enterprises implement expensive tools and systems for quality-related

Small- and medium-sized enterprises often have the advantage of flat hierarchies and personalized management.

tasks, but all enterprises must follow validated processes and have adequate documentation to prove that the necessary controls are in place. In many cases, standard office software suites and/or trustworthy and reasonably priced cloud services can establish a robust QMS, if they are used correctly and embedded in the relevant processes. We cannot overstate the importance of risk assessment that is based on critical thinking, focuses on the business purpose, considers the organizational structure, and leads to effective controls.

Table 2 compares typical validation and quality approaches for larger and smaller enterprises but does not offer one-size-fits-all recommendations. Every organization needs to determine the appropriate approach by considering the nature or their services and products, the size and structure of their organization, the existing infrastructure and tool sets, and other factors. In some areas, potential customers will expect vendors to have QMS certification (e.g., ISO 9001). Such certification may require the enterprise to implement additional activities and controls.

There is a clear regulatory expectation that the sponsor can make evidence supporting validation available to inspectors. Given this expectation, the enterprise providing services may need to hand over copies of key validation documents to the sponsor during the initial system implementation or during later updates/upgrades. Depending on the nature of the outsourced services, robust contractual agreements with well-defined roles and responsibilities, a robust supplier assessment, and a quality agreement may suffice to establish regulatory compliance. However, if significant parts of the system implementation and validation are executed by the supplier, the contracts and quality agreements should include aspects of inspection support as required to provide additional supplier-generated documentation or explanation of the supplier's QMS that generated evidence and documents. Sponsors may not get approval of marketing authorization applications if the supporting data originate from a system that has not been adequately validated; therefore, a robust QMS that generates reliable validation evidence must be considered business critical.

References

1. International Society for Pharmaceutical Engineering. *GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2008.
2. Medtech Europe. "The European Medical Technology Industry—in Figures." 2017. https://www.medtecheurope.org/wp-content/uploads/2017/01/MedTech_FactsFigures2016_20160105.pdf
3. Schönberger, M., and T. Vasiljeva. "Towards Computer System Validation: An Overview and Evaluation of Existing Procedures." *Journal of Innovation Management in Small and Medium Enterprises* 2018 (2018): 512744. doi:10.5171/2018.512744
4. European Medicines Agency. "Notice to Sponsors on Validation and Qualification of Computerised Systems Used in Clinical Trials" 7 April 2020. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf
5. Welsh, J. A., and J. F. White. "A Small Business Is Not a Little Big Business." *Harvard Business Review* 59, no. 4 (1981): 18–27. https://hbr.org/1981/07/a-small-business-is-not-a-little-big-business
6. European Medicines Agency, Committee on Human Medicinal Products. "Guideline for Good Clinical Practice E6(R2) Step 5." 1 December 2016. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice
7. International Society for Pharmaceutical Engineering. *GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data (Good eClinical Practice)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2007.

About the authors

Frank Henrichmann, Senior Executive Consultant at Q-FINITY Quality Management, is an expert in quality management, computer system validation, and compliance, especially in the context of clinical trials and pharmacovigilance. Over the last 20 years, he has gained extensive experience in strategies, projects, and measures for GxP-regulated environments at a CRO as well as a major pharmaceutical company. In his current position, he helps life sciences companies and supports technology providers to find innovative answers to quality and validation challenges. Frank has been a member of the Clinical Systems Special Interest Group (SIG) and is a coauthor of the *GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data*. A member of the GAMP® Editorial Board, he has been an ISPE member since 2001.

Oliver Herrmann, Founder, CEO, and Senior Executive Consultant at Q-FINITY Quality Management, is an expert in quality management, computer system validation, data integrity, and compliance. In 2004, Oliver founded Q-FINITY to combine process management with the requirements for validation of computerized systems. Over the last 16 years he has gained extensive experience in planning, development, execution, documentation, and auditing of strategies, projects, and measures for GxP-regulated environments. He has supported projects with the focus on chromatography LIMS, PCS, and MES through ERP, pharmacovigilance, EDC, efficacy, DMS, and more. Oliver has been a Co-lead of the GAMP® SIG for the validation of clinical systems and is a coauthor of the *GAMP® Good Practice Guide on Clinical Systems*. Oliver is Co-chair of the GAMP® D/A/CH Steering Committee as well as a member of the ISPE GAMP® EU and Global Steering Committee. He has been an ISPE member since 2005.

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ISPE France Affiliate: LONG-TIME AFFILIATE CONTINUES TO SHINE

By Mike McGrath

The ISPE France Affiliate is fortunate in many ways. The pharmaceutical industry in France is world class, employing close to 100,000 people and generating €55.9 billion in annual revenue [1]. The Affiliate's membership runs the gamut from students and Young Professionals (YPs) to industry veterans with expertise in research and development, engineering, manufacturing, and regulatory guidelines. Additionally, the France Affiliate has a strong, dedicated leadership team and a well-established President, Jean-François Duliere.

Since he first joined the France Affiliate in 2002, Duliere has been an active member of ISPE, serving on multiple local and international committees. During his long career as a production manager in pharmaceutical manufacturing, he worked in quality control, oral solid dosage form manufacturing, packaging, raw materials production from bacteria growth, industrial development, and dual-compartment syringe aseptic filling and as a consultant for an engineering company involved in many pharmaceutical projects around the world. Now 68, Duliere recently retired from his day-to-day job, but he continues to serve as the France Affiliate President, a position he has held since 2012. In April 2020, he was appointed ISPE's European Regulatory Advisor.

KNOWLEDGE SHARING AND NETWORKING

Created in 1992 and established as a legal association in 2001, the France Affiliate is one of ISPE's older European Affiliates. It primarily communicates with members in French and counts several French-speaking participants from neighboring Belgium and Switzerland among its 220 members.

"We try to hold our events in French," said Duliere. "But when we have speakers from outside of France, our materials and presentations are in English. And while our work group meetings are in French, the groups produce written materials in English for publications such as *Pharmaceutical Engineering*®."

Most Affiliate members work and reside close to France's largest cities, Paris and Lyon. The Affiliate's events are therefore centered around those two cities.

Duliere said the Affiliate strives to hold at least four events per year, typically in March, June, September, and November. The September event, he explained, is organized with Lyon University and held on the first day of the school year. Around 150 students come to see 30 industry professionals present on topics relevant to student interests, he said.

The other three events cover specific topics, such as GAMP®, computer systems, or serialization, and typically attract 30 to 40 attendees. "Through these events we try to grow the membership, but the main objectives are to share knowledge and have networking opportunities," said Duliere. These one-day events include presentations on the topic of the day followed by a workshop session where attendees are divided into groups to discuss the topic and share their experiences.

Given the ongoing COVID-19 pandemic confinement and physical distancing measures, the France Affiliate, like others around the world, has had to adjust its 2020 event calendar. The Affiliate postponed some 2020 events and converted others to virtual meetings. Fortunately, the Affiliate already had experience with virtual meetings, as many of its committee meetings are held that way.

COMMITTEES

In 2006, the Affiliate initiated the GAMP® Francophone Community of Practice (CoP), a group working on subjects related to IT systems and guidance. "Our GAMP® CoP is made up of a mix of experts and

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others with less experience who have come to be trained. In the last few years, they have been discussing topics like economic concerns, data centers, and agile methods," said Duliere.

The GAMP® CoP meets virtually every two months and usually holds two or three in-person workshops per year on current topics of interest.

In 2017, the Affiliate created a committee to address the impact of serialization on the organization of the supply chain and information systems. "For three years, the group published articles on best practices for serialization," said Duliere. "However, following trends in European regulations and FDA documentation, this group shifted last year to focus on the consequences of the implementation of unique device identifiers (UDIs) for medical devices."

The UDI committee meets virtually each month and face to face once or twice annually. "They hope to publish an article in *Pharmaceutical Engineering*® when they have finished their work," Duliere said. The plan was to complete the UDI project in 2021, but Duliere now anticipates that the work will wrap up in 2022.

CHALLENGES AND OPPORTUNITIES

Although the France Affiliate is running smoothly, Duliere acknowledges it faces some challenges, including member participation. "Members are not always involved in the life of the Affiliate, so we push to get them to attend our events," he said. "More and more facilities in France belong to contract manufacturing organizations, and this is a challenge because, in many of these companies, the people are often not allowed to travel to go to such events."

With that and other challenges in mind, Duliere welcomes opportunities to partner with other Affiliates. He participates in virtual meetings with other European Affiliates every two months, and the Affiliates get together in person each year at the ISPE Europe Conference and ISPE Annual Meeting. "We are sharing best practices, what is working in each of our Affiliates, which topics to address at conferences, and developing a strategy for Europe for the future."

Duliere also pointed out the Affiliate's commitment to students and YPs. In addition to the annual event at Lyon University, Affiliate board members participate in training sessions at pharmaceutical universities in Dijon, Lyon, and Paris, and the Affiliate has board members designated to the needs and activities of YPs.

Reference

1. LEEM. "French Pharmaceutical Industry—Key Data 2019." Accessed 9 July 2020. https://www.leem.org/sites/default/files/2019-09/BilanEco-GB-V2_7.pdf

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.

Quick facts about the ISPE France Affiliate

Founded: 1992 | **Region:** France | **Membership:** 220

Officers

- **President:** Jean-François Duliere
- **Vice President:** Philippe Lenglet , Servier Laboratories
- **Treasurer:** Philippe Robin
- **Vice Treasurer:** Cedric Lambert, Lourd'Innov
- **Secretary:** Michel Raschas, PROGMP SAS
- **Vice Secretary:** Marick Paris-Cadet, TechnipFMC
- **Young Professionals Chair:** Alexandra Yath, TechnipFMC
- **Young Professionals Secretary:** Ernstley Derisma, Curium Pharma
- **Communication:** Olivier Mary, COLCA Medical and Scientific
- **Membership:** Véronique Manigaut, Ekium, and Jean-Michel Blanc, Actemium Saint-Etienne
- **Directors:** Alain Cruset; Philippe Lenglet, Servier Monde; Jean-Pierre Jacquemier; Jérôme Keldenich, Immunic AG; Yves Samson, Kereon AG; Agnes Trouchaud, GSK

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2020 ISPE Annual Meeting & Expo: DRIVING THE FUTURE OF PHARMA

By Susan Sandler

The 2020 ISPE Annual Meeting & Expo will be ISPE's first completely virtual Annual Meeting. As always, there will be great learning and networking opportunities—in fact, the digital format offers greater flexibility for attendees.

The 2020 ISPE Annual Meeting & Expo will focus on steering the future of pharmaceutical science and manufacturing toward a more global, synchronized, and quality-driven industry. This signature event draws pharmaceutical and biopharmaceutical professionals at all levels of the industry, from Young Professionals to the most senior executives in drug manufacturing, supply chain, devices and equipment and services, and global regulatory agencies.

The theme for the Annual Meeting, "Driving the Future of Pharma," is especially appropriate in these times of tremendous challenge and change to the industry. The conference will take place over five days, from 2 to 6 November, maximizing participants' opportunities to attend the 41 education sessions featuring over 160 speakers in six tracks. In addition, the Annual Meeting will feature one plenary session, one global regulatory town hall, two FOYA sessions, and five postconference workshops, for a total of more than 75 hours of content.

The Annual Meeting will also include the new ISPE Partner Showcase, a platform providing access to a virtual exhibitor marketplace so you can filter, search, and browse the vendors serving the industry. You will be able to note your favorites among the exhibitors, and can reach out through the platform for appointment scheduling and live chats to learn more information.

Pharmaceutical Engineering® spoke with Jennifer Lauria Clark, Executive Director, Strategic Development, CAI, and 2020 ISPE Annual Meeting & Expo Conference Committee Chair, to hear her insights about the sessions and other conference experiences that you will not want to miss, and how this year's Annual Meeting will be different—and yet the same—as past meetings.

The theme of the 2020 ISPE Annual Meeting & Expo is "Driving the Future of Pharma." Why is this theme of such great importance right now? What knowledge will attendees take away related to this theme that will help them in their day to day work?

The Annual Meeting Planning Committee along with the ISPE staff was thoughtful in choosing our theme for the 2020 ISPE Annual Meeting & Expo. We discussed the importance of speed to market, cell and gene therapy, Pharma 4.0™, supply chain challenges, and the evolution of medications—all while maintaining compliance and meeting all global regulatory guidances. Little did we know the world would be literally laser-focused on many of our companies today due to the pandemic that has swept the globe! The time is now to participate in the 2020 ISPE Annual Meeting & Expo to learn more about what is happening around us, so you do not get left behind as we evolve together—quickly—in our current climate.

Educational topics will focus on subjects including advanced technologies, which we need now more than ever before to help us work together in delivering what may be the most important vaccine to reach the market. Decisions made by ISPE members who are leaders in the industry today will literally impact global economic and health for many years to come.

The focus on "Driving the Future of Pharma" allows attendees to participate in education and open discussions around:


Jennifer Lauria Clark

- Implications to current supply chain issues
- Fast-tracking molecules and medications to get patients the help they need faster
- The drive to modernize and transform our global industry
- Young Professionals
- Women in Pharma®

Alongside all the current challenges facing our industry, ISPE is leading the way to drive change and transform the way industry thinks about diversity, Women in Pharma®, Young Professionals, and this is truly shaping the next workforce of the future. The Annual Meeting is ISPE's largest event of the year, with more than 40 educational sessions and many opportunities for attendees to interact with global industry and regulatory experts and opinion leaders. It's a chance to learn about the current industry, technology, and regulatory trends and best practices so attendees can apply those learnings in their own companies. It's also a chance to interact with a wide variety of vendors and build a network of industry contacts and colleagues.

By going to a virtual platform for this year's Annual Meeting & Expo, we are afforded a bit more time to absorb the networking and educational aspects of the meeting.

The 2020 Annual Meeting will be virtual. Why will this be a great experience for attendees?

Evolution is essential in our business. Whether it is adapting to our new virtual technology by attending an education discussion of significant drivers of change related to supply chain, regulatory, or manufacturing issues, or learning how to video conference for the first time, the 2020 ISPE Annual Meeting & Expo has you covered.

By moving to a virtual platform, we have opened many new ways for more of our members to engage with and have access to fellow members and new ideas. All sessions are open to all attendees and will be recorded. We have also scheduled all committee meetings outside of the education sessions. In this way, you will not face competing sessions and committee meetings in the same time slots.

This schedule design gives each of us the flexibility to hear the relevant and timely information from all the sessions, on our own time. If you have a meeting come up halfway through a session, you will not have to miss any valuable content. Each attendee will be able to build their own itinerary and be alerted when their sessions are coming up in their tracks that best suit their current role and future desires, without having to run across a conference center to grab a seat for the next session.

We have over 160 speakers this year presenting on topics that include supply chain issues, facilities and workforce of the future, quality, and regulatory deep dives.

The ISPE Annual Meeting brings together both new members and more seasoned industry experts. How can both new and expert members make the most of the opportunity to interact at the Annual Meeting?

Having a blend of seasoned and new members is always a great way for new ideas and relationships to flourish. This year will be a little different with the virtual platform, but there are still plenty of ways to virtually network. There will be 24 hours of Women in Pharma® activities the week before the educational sessions. Communities of Practice (CoPs) and international committees that help the Society grow will also be meeting at times scheduled outside of educational sessions. This provides the opportunity to attend and participate, and also gives you the time to attend as many educational meetings as you would like.

If you have not joined a CoP yet, this is a great time to network and learn something new. If you are an expert, it is our responsibility to give back to the industry and help those who are interested in our fields to become stronger than us. Please join a CoP and help respond to questions and challenges our members are facing.

If you are interested in volunteering, this is an excellent time to get involved in ISPE. You will become familiar with a group of people who not only will appreciate your technical talents but also will get to know you and network with you. Growing our membership and maintaining strong ties is more important now than it ever has been with the current economic and remote working climate for many of us.

There are also networking events tied to the educational sessions themselves. There will be time to ask questions, meet the speakers, and enjoy a drink (at your home) with fellow colleagues after a great day of training.

By having a blend of entry-level, college-level, and seasoned folks, the conference is more diverse, stronger in its messaging, and can be thoughtfully discussed with the group.

I challenge each attendee to participate in at least one networking event associated with the 2020 ISPE Annual Meeting. Join the Virtual 5K hosted by the ISPE Foundation, a CoP meeting, or one of the Women in Pharma® events.

You never know whose life you are going to influence when you take a few minutes to meet someone new and share something about your career or your life. My husband and I were at an ISPE CaSA networking event almost 10 years ago and one conversation with a fellow member whom we had just met empowered us to say yes to a new job in a new location for my husband. It was scary to think about moving away from our family to a new state alone, but because of a single veteran ISPE member sharing their story with us, we took the leap. We were very grateful for the advice and time this person took to speak with us, and we had no idea we would get a call the next day with this great job opportunity.

What are you most looking forward to hearing about/learning more about at the Annual Meeting?

The keynotes and plenary session are always my favorite parts of the Annual Meeting. I love people and reconnecting with them just before the plenary, and feeling all the energy in the room always sets the stage for a great meeting.

This year will be a little different as we have gone virtual, but if you get online, text a few friends who are watching with you, and listen to the speakers, you will be able to feel some of the same energy we feel in person.

By listening to the plenary session, we get a chance to reflect on a year of discovery, challenges, and successes with our colleagues. We get to hear fresh perspectives from industry experts leading the way for better patient care.

Everyone has a specific reason to attend the 2020 ISPE Annual Meeting & Expo. Please take the time to custom-build your itinerary in the virtual platform. You will be able to set your schedule and note which items you will want to come back to at a later time and listen to after the conference. The flexibility of a virtual conference allows you to access content anytime during the conference and for 12 months after.

While some of our traditional events are not able to happen this year, we are creating new traditions with a virtual platform and anticipate global engagement and access for all members. I look forward to sharing a new experience with you in November.

What else do members need to know about the Annual Meeting?

Over the last three decades in our industry, over 100 companies have consolidated to about 30. Through mergers, acquisitions, leadership changes, and evolution, someone was driving the changes to make a better future for patients.

This year, ISPE is giving you the chance to participate in more educational sessions and networking than ever. We encourage everyone to visit the Exhibit Hall, now renamed the

Find out the latest information on the 2020 ISPE Annual Meeting & Expo:

The program, registration information, and more are at ispe.org/conferences/2020-annual-meeting-expo

Partner Showcase, and see the new ideas and technology from our top-notch exhibitors or just stop in to say hello. I know we are all in much need of one-to-one contact with familiar faces these days, so be sure to add some of these conference events to your itinerary.

As the 2020 ISPE Annual Meeting & Expo Chair, I want to thank each and every one of the people who are attending and helping produce this conference. Moving to virtual while maintaining the integrity of the conference is the best solution for our membership. We welcome your feedback during and after the conference; we are all learning how to navigate our new normal, and your feedback is crucial to make sure we are meeting the needs of our members through content, networking, and access to the latest technologies and information.

As ISPE members, it is a benefit to lead change through our organizational involvement. As members of our industry, it is our responsibility every day to help drive the future of pharma.

About the author

Susan Sandler is the Senior Director, Editorial, for ISPE.

Vital Statistics: 2020 ISPE Annual Meeting & Expo

When: 2—6 November

Where: Virtual conference

Number of education sessions: 41

Number of speakers: Over 160

Number of postconference workshops: 5

Other highlights: Plenary Session, Global Regulatory Town Hall, 2 FOYA Sessions

Education tracks:

- Facilities & Equipment
- Information Systems
- Innovation Forum
- Process Development & Manufacturing
- Quality Systems & Regulatory
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FOYA Category Winners and Honorable Mentions for 2020:

EXAMPLES OF EXCELLENCE

By Marcy Sanford

You can learn more about this year's winners at the FOYA Virtual Education Sessions on Tuesday, 3 November, during the 2020 ISPE Annual Meeting & Expo. Each company will give a 15-minute presentation about the challenges and successes of their project. For more information or to register, visit ispe.org/foya

FOYA 2020
Facility of the Year Awards

Each year, ISPE celebrates innovations and advances in pharmaceutical manufacturing technology with its Facility of the Year Awards (FOYA) program. This year, we added a new category, Social Impact, to recognize companies that developed new standards and practices to prevent drug shortages and increase patients' access to medicine, designed new tools or techniques that reduced the cost of drug products, or accelerated a shift to sustainable facility design that has significantly reduced environmental impact.

The 2020 FOYA winners include well-known names in the pharmaceutical world as well as a relatively new company. All award recipients and honorable mentions share the same dedication to serving patients worldwide.

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In most countries, it is a legal requirement that any new human medication be tested on animals. However, animal facilities are usually housed in the basement and not typically talked about or lauded. With their new in vivo facility in Basel, Switzerland, F. Hoffmann-La Roche has successfully reinvented animal research laboratories. Thanks to a team dedicated to exploring new ways to improve the status quo, Roche was able to discover clever and unorthodox solutions to common issues found at in vivo facilities and created a technological masterpiece that sets a gold standard for future laboratories.

To build a new facility, Roche had to demolish an existing building on their site and extend the pit. Before the new facility, Building (B098), was constructed, animal husbandry was split over various buildings of the Basel site, some of the infrastructure was outdated, and productivity and efficiency were not optimal. Roche found a way to allow natural light into the laboratory without affecting animals' physiological rhythm. Intelligent ventilation and fully automated cage handling outside the barrier zones reduce researchers' exposure to allergens and physical strain. All

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Auditing for GMPs (G07)

5–6 October 2020
Science and Risk-Based Commissioning & Qualification (T40)

12–13 October 2020
GAMP Data Integrity (T50)

13, 15, 20, 22 October 2020
Combination Products (T47)

13–16 October 2020
Aseptic Processing (T63)

19–20 October 2020
GAMP Data Integrity (T50)

20–23 October 2020
Clean in Place Fundamentals (T03)

26–27 October 2020
First Principles (T60)

28–29 October 2020
Basic GAMP® 5 Annex 11/ Part 11 (T45)

29–30 October 2020
Science and Risk-Based Commissioning & Qualification (T40)

9–10 November 2020
Water Generation (T04)

10–11 November 2020
Basic GAMP® 5 Annex 11/ Part 11 (T45)

16–17 November 2020
Water Storage (T23)

18–19 November 2020
GAMP® 5 Process Control Systems (T21)

19–20 November 2020
Biopharmaceutical Overview (T24)

23–24 November 2020
Cross Contamination (Risk-MaPP) (T41)

1–4 December 2020
Clean in Place Fundamentals (T03)

1–2 December 2020
Project Management (T26)

3–4 December 2020
Auditing for GMPs (G07)

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study and animal housing rooms have a modular structure and can be reconfigured from a small study room with anteroom into a large animal housing unit (or any type of room in between); these reconfigurations can be achieved within just two to three weeks, almost silently, and without disturbing adjacent areas. Roche completely redesigned automation and robotics for the building and merged third-party IT products with Roche-specific IT solutions to develop the Roche In Vivo Building IT System—setting new pioneering technological standards.

"The project demanded intensive collaboration and problem-solving skills from everyone involved," said Christof Specht, Roche Project Manager "Our employees have told us that B098 is an in vivo researcher's dream come true, even beyond imagination. Roche is proud to be leading a new era of novel therapeutic modalities."

FACILITY INTEGRATION: PFIZER INC.

New Standard for Physical, Operational, and Intellectual Integration

Thanks to careful planning and astute attention to detail, Pfizer's new Andover Clinical Manufacturing Facility (ACMF), built on their master-planned 70-acre Andover, Massachusetts, campus, looks as if was always meant to be there. Pfizer relocated existing manufacturing capabilities from Chesterfield, Missouri, to the new facility, which allowed them to integrate research and development (R&D) and expand biological products from 14 campaigns to a future maximum capacity of 21.

Pfizer was able to add the 175,000-square-foot clinical manufacturing facility to their Andover site without growing their carbon footprint. They did not have to add any new core utilities, support systems, or amenities to bring the facility online. The five-story building houses five independent manufacturing suites dedicated to the development of new biotherapeutics and vaccines to support trials in disease areas such as oncology, rare diseases, infectious diseases, hemophilia, and rheumatoid arthritis. Each suite operates completely independently of the others, and all five can operate simultaneously.

The ACMF runs both microbial and mammalian processes and deploys both single-use plastic and stainless steel technologies. Each suite can be reconfigured to handle complex steps such as refold reactions and homogenization. Technology innovations include wireless tracking for equipment. Additionally, Pfizer has developed a space where R&D, clinical manufacturing, and commercial manufacturing professionals work together to share their knowledge and expertise.

> "The project demanded intensive collaboration and problem-solving skills."

"A project like this is really months of preparation for the day you will go live—the day you become a productive contributor to human health and wellness, and to Pfizer's mission," said Lauren Gomes, Director, Clinical Manufacturing, Pfizer. "As of June 2020, all suites within the facility are fully operational. The flexibility of the facility and the ensuing relationships with collaborating teams have enabled us to complete technology transfer of complex processes within two months. One of our upcoming projects will be producing a drug substance for pandemic supply of the COVID-19 mRNA vaccine."

FACILITY OF THE FUTURE: SANOFI

Facility Flexibility Reaps Rewards

Sanofi is a pioneer in continuous biologics processing and has several rare-disease enzyme replacement therapies that are produced using large-scale perfusion reactors and novel cell separation technologies. For its digitally enabled integrated continuous biomanufacturing facility in Framingham, Massachusetts, Sanofi used a wide range of cutting-edge manufacturing technologies to develop an efficient, flexible, and sustainable manufacturing platform. One of the most significant aspects of their design is the commercial implementation of integrated continuous biomanufacturing (ICB),

which made it possible for them to adopt a modernized perfusion-based cell culture process where smaller, single-use technologies replace traditional large-scale stainless steel reactors and capture equipment.

Ultimately, the ICB process results in improved product quality and consistency, increased process robustness, the generation of massive process data analytics with 770 million data points sampled each day, and reductions in the facility's processing footprint, raw material usage, and energy consumption. Sanofi developed new and innovative ways to use single-use technologies, many of which had never been commercially implemented. The facility was designed for flexible operations, rapid changeovers, and multiproduct operations. Sanofi created a digitally integrated, paperless ecosystem, and the facility is equipped with large touch-screen displays that help maintenance and operations staff accomplish their daily activities.

"The facility includes many of the traditional concepts of flexible facility design, including single-use technology and flexible 'ballroom' designs, accommodating a wide variety of equipment design and scale. Utilizing digital technologies enhances the flexibility of the facility, enables reconfiguration in response to changes in produce demand, and creates a shop floor experience that is intuitive to the operator. We believe that we have pushed these concepts to new levels with our novel processes, deployment of technology, and digital integration," said Navin Tiwari, Head of Digital Shop Floor and Automation for Sanofi.

OPERATIONAL EXCELLENCE: ELI LILLY AND COMPANY

Improving the Drug Discovery Process

As a global healthcare leader, Eli Lilly and Company strives to discover and bring life-changing medicines to those who need them. In support of this mission, Lilly spent several years examining the traditional, industry-accepted belief that drug development is a drawn-out, time-consuming process characterized by complex challenges and long delays, and set out to determine what facility factors could help improve the pharmaceutical development process. They analyzed many of the basic assumptions of the development process and, as a result, implemented leading-edge improvements throughout their new facility, the Innovation Development Center.

Located at the center of Lilly's Indianapolis, Indiana, campus, the new center brings modeling, analytical, and formulation scientists together with organic chemists and engineers in a collaboration-centric workspace and enables Lilly to effectively accelerate traditional time scales—reducing the development time from years to mere months. One of the most common delays development teams face is the need to reconfigure a laboratory to support a new approach. Sometimes, the progress of the candidate compound is put on hold while the team works to design a new lab, which then has to be constructed before the development process can continue. Lilly's Innovation Center was designed to allow researchers to transform their laboratory to support new or revised processes in a matter of days. As with the laboratories, the work spaces were designed to be flexible and easy to configure based on the users and their needs. There are no assigned work spaces at the Innovation Center; employees can work wherever is best suited for their current activities. Teams are able to organically formulate project groups on a day-to-day basis in areas that match and support what is happening in the lab.

"Since we moved to the Innovation Center, we have seen time and time again how it has allowed colleagues across multiple functions to co-locate and interact directly with each other, ultimately helping to further accelerate development of our new medicines. It truly is a very special place to work,'' said Sarah O'Keeffe, Lilly's Vice President of Small Molecule Design and Development.

PROCESS INNOVATION: JANSSEN PHARMACEUTICALS, BELGIUM CAMPUS

Changing Strategy to Change the Future of Drug Delivery

Until recently, Janssen Pharmaceuticals developed and manufactured all tablet formulations in a multipurpose batch facility. However, as the company formulated a mission that focused on making the patient the center of all decisions, improving quality, reliability, and control, and reducing development and scale-up cycle times, they found that the batch platform did not support their vision. Janssen decided they had to completely change strategy to support their new mission and embarked upon an end-to-end (E2E) strategy that included investing in continuous

manufacturing (CM) as their preferred technology platform for all future oral solid dosage formulations. To support their new E2E strategy and commitment to CM, Janssen designed, installed, and qualified a new CM line, Mirror 1, at their drug product pilot plant in Beerse, Belgium.

Mirror-1 will be used to support all development and clinical manufacturing activities, and an identical CM line, Mirror-2, is under construction at Janssen's commercial site in Latina, Italy. Since Janssen planned from the beginning to build an exact copy of Mirror-1 at a different location, they had to consider the requirements and limitations of both facilities when developing the line. Together, the two identical lines will enable seamless one-to-one tech transfers, without additional scale-up efforts, resulting in overall benefits such as shorter timelines and reduced active pharmaceutical ingredient (API) consumption. Janssen not only developed a new CM line but also set up cross-functional initiatives to make sure the company was ready to start developing new compounds once the Mirror-1 line was complete. Janssen collaborated with academics, partnered with other pharmaceutical companies, and established connections with health authorities worldwide to help them formulate renewed development strategies and best practices and establish new methodologies.

"We strongly believe that our unique strategy will accelerate the development of new medicines, with a significant increased level of process understanding and controls, providing more robust processes and delivering better and safer products," said Luca Russo, Global Head, Clinical Supply Chain, Janssen.

PROJECT EXECUTION: BRISTOL MYERS SQUIBB

Billion Dollar Commitment to Biologics

The biopharmaceutical industry is thriving in Ireland, and Bristol Myers Squibb's Cruiserath Biologics is at its forefront. In 2014, BMS closed their Dublin-based API site and announced a $1 billion commitment to building a new, world-class biologics manufacturing facility in its place. The investment helped BMS increase their biologics manufacturing capacity and played a central role in the company's global manufacturing network. At the time, the project was the largest single investment by BMS outside of the United States and the second largest life sciences sector investment in the history of the Irish state.

The result of this $1 billion investment is a new biopharmaceutical campus where immuno-oncology medicines are manufactured for patients worldwide. The large-scale site (with six 15,000-liter bioreactors) will produce multiple biologic medicines annually on a rapid-turnover, campaign basis for high efficiency and throughput. It is designed for future expansion into a concurrent-campaign multiproduct facility. Innovative concepts were applied to the facility design to facilitate higher throughput and rapid product changeover while minimizing equipment redundancies and maintenance shutdowns. The manufacturing execution system design integrates with the production automation system and collectively utilizes flexible and lean recipes. This allows for easy and quick configuration of the system for the next product to be produced.

"The Cruiserath campus represents the largest ever capital investment for the company and is the first Bristol Myers Squibb biologics manufacturing facility in Europe. We set out with a vision to build a world-class biopharma campus and state-of-the-art facility; to receive this highly coveted award and industry recognition indeed signifies we are well on our way in this endeavor," said Noel Heaney, General Manager, Cruiserath Biologics, and Executive Director, EU Biologics.

SOCIAL IMPACT: GSK–GLAXOSMITHKLINE

Accelerated Delivery to Meet Critical Need

GSK has a broad portfolio of innovative and established medicines. When they partnered with ViiV Healthcare to develop a newly acquired investigational HIV product, fostemsavir, one of the first things they needed to do was develop a new facility to handle production of the first-in-class HIV treatment. Because the drug is typically used by patients with previous viral failures who have limited or no treatment options remaining, time was of the essence. GSK met the challenge, and in just 15 months, the project team constructed and commissioned a greenfield NPI facility for high containment in Parma, Italy.

Meeting the accelerated schedule required a highly integrated program including concurrent design, construction, and commissioning. For the first time in the Italian industry, an integrated project delivery approach was used. Designers, contractors, and suppliers from diverse backgrounds and experiences worked together to capitalize on the talents and insights of everyone on the team. The GSK team reduced the overall design time by overlapping the design, procurement, and construction phases, thus changing the inherently iterative nature of the design process. Interactive and decision-making workshops were held to evaluate different layout, facility, and process manufacturing options. The team also used three-dimensional building information modeling from the early stages of design, developed a strategy to develop user requirement specifications so that equipment could be ordered at the end of concept design, and divided the building into three separate construction zones, each operating simultaneously.

"In December 2019, we filed for FDA approval for fostemsavir, after our fastest-ever project build," said Mike Mungall, Vice President, Global Capital Projects, GSK. "The project team, the Parma site, and everyone who had a part in making this happen is proud to be involved in developing a new treatment that could help people living with HIV who are not able to suppress their virus with other medicines and who could be left with few or no treatments available."

NEW

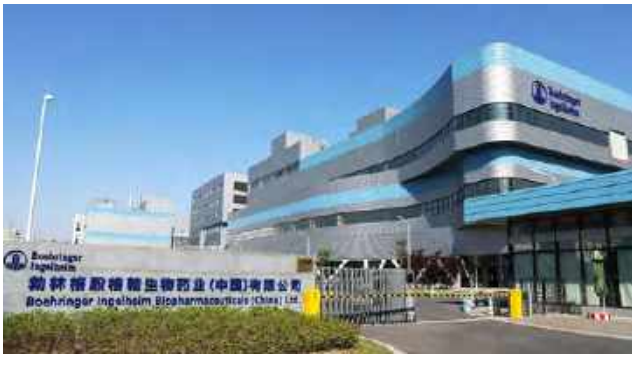
SOCIAL IMPACT: UNITED THERAPEUTICS

A Company Built from Love

In 1994, Dr. Martine Rothblatt learned that her seven-year-old daughter had pulmonary arterial hypertension, a life-threatening orphan disease, with no viable medicine on the market. Because orphan diseases affect a small percentage of the population, cures are not typically a research priority—so Rothblatt took matters into her own hands and made it her life's mission to find a lifesaving treatment. She and her team at United Therapeutics were successful, and several years later, they expanded their focus to include the development and commercialization of unique products to address more unmet medical needs, including those of children with chronic and rare life-threatening conditions. One of those products is Unituxin (dinutuximab), which has proven effective in treating and reversing high-risk neuroblastoma, a rare form of cancer that typically forms on immature nerve cells in children under the age of 5 years and affects approximately 800 children a year. The company's manufacturing and research capability was limited due to their existing biologics manufacturing capacity. To treat more pediatric patients, conduct research on other life-threatening illnesses, and bring hope to more families, United Therapeutics knew they had to expand their operation, and so they decided to build a new facility, the Dinutuximab-Dedicated Oncology Medical and Analytical Laboratory (DDOMAL) in Silver Spring, Maryland.

Space was the first obstacle, so the company partnered with local government to pass legislation that exempted the floor area housing mechanical, engineering, and plumbing equipment required to support the drug manufacturing process from the total gross-square-feet calculation. This legislation not only made the project feasible but also will promote the future development of the life sciences industry in Montgomery County, Maryland. Additionally, United Therapeutics stayed connected to the local community during construction. Throughout the project, the team went above and beyond to create a positive experience for those around them by installing covered walkways; organizing social events for the local community to discuss the project; installing a project signboard to inform neighbors of what they should expect to see, hear, and smell; and providing noise-cancelling headphones to residents of a nearby nonprofit organization.

"DDOMAL was born of a mission to improve the lives of patients," said Patrick Poisson, Executive Vice President, Technical Operations, United Therapeutics. "Against all odds, the DDOMAL team showed an unparalleled commitment to getting Unituxin into production and to market, building strong local relationships, and executing the project to an outstanding level. It is an exceptional example of how a valiant team effort across the board can lead to an innovative and well-functioning pharma manufacturing facility that respects all stakeholders and quickly produces medicine that saves children's lives."



HONORABLE MENTION: BOEHRINGER INGELHEIM BIOPHARMACEUTICALS CHINA LTD.

Boehringer Ingelheim's commitment to bringing lifesaving medication to China to meet increasing needs included not just building a new facility but also working with local government to change regulations. In 2013, Boehringer Ingelheim began supporting efforts by the China National Medical Products Administration to revise relevant regulations. After years of hard work and diplomacy, China's Standing Committee of the National People's Congress approved in 2019 a significant revision of the Drug Administration Law pertaining to the Marketing Authorization Holder (MAH) system. The new system makes it easier for drug developers to bring new drugs to market, while increasing their responsibility to ensure the safety of those drugs. In addition to its efforts to reform Chinese regulations, Boehringer Ingelheim built in Shanghai a modern facility that incorporates environmentally friendly systems and can be expanded to meet patient, business, and market needs.

The OASIS GMP facility, which is located directly in the heart of Zhangjiang Hi-Tech Park, is set up in a modular approach: module 1 covers first bioreactors, including an auto-isolator fill-and-finish line, and module 2 has an expansion option. The entire production is based on single-use equipment to be put together following a toolbox concept, which allows for various combinations and can cope with the requirements of different processes. The bioreactors and vessels are connected through a flexible tube system, instead of pipes, offering options for putting together equipment independent of hardware installations. Additionally, the site is the only biopharmaceutical site of a multinational company on the Chinese market to offer contract manufacturing that meets global standards.

"We were very proud to become the first company starting commercial biopharmaceutical manufacturing under the MAH model in China," said Jiali Luo, General Manager and Site Head of Boehringer Ingelheim Biopharmaceuticals China. "The trial project was smoothly conducted and has now proven successful. The newly established model can be of great benefit for the Chinese healthcare system and can provide Chinese patients broader access to more innovative medicines."

HONORABLE MENTION: JANSSEN PHARMACEUTICAL COMPANIES OF JOHNSON & JOHNSON AND LEGEND BIOTECH, USA INC.

Advancing a Next-Generation Cell Therapy for Blood Cancer

With the current treatment options on the market, the five-year survival rate for patients with multiple myeloma is approximately 50%. Although treatment may result in remission, most patients will relapse and there is currently no cure for the blood cancer. However, an innovative chimeric antigen receptor T-cell (CAR-T) therapy targeting B-cell maturation antigen, currently in global clinical development by Janssen Pharmaceutical Companies and Legend Biotech USA, is offering hope to patients with multiple myeloma.

CAR-T therapy uses the patient's own immune system to identify and attack tumor cells. After collecting the patient's white blood cells, the T-cells are genetically engineered to produce chimeric antigen receptors on their surface, which enables the T-cells to recognize tumor cells. The reengineered CAR-T cells are expanded and formulated in a cleanroom environment before being returned to the patient for infusion. The CAR-T cells attack the cancer and stimulate the immune system to recognize the cancer cells if they return.

Speed of implementation was the driver for the project to establish a CAR-T clinical manufacturing facility in Raritan, New Jersey, as Janssen and Legend Biotech wanted to provide this innovative therapy to patients as soon as possible with no compromise to the companies' standards for quality. Two project design teams, one to design the cleanroom PODs and the other to design the stick-built modular facility, worked closely together to ensure both elements came together seamlessly. They used hybrid construction and a unique combination of on- and off-site modular construction to help them meet their timeline and were able to achieve mechanical completion in just nine months. At the conclusion of the project, a "hope bell" was installed within the open meeting space. Each week, employees ring it for each dose of CAR-T therapy being provided to a patient.

"Initially, the sound of the bell was rare. As a result of tireless efforts to develop personalized treatments for more patients, this bell ringing has become a weekly ritualized event where it is rung numerous times, and each time with deep, personal meaning for everyone involved," said Eric Niebling, Vice President, Advanced Therapies, for Jannsen. "The sound of the hope bell is a celebration for every patient and for every employee who has worked passionately to develop each treatment."

To learn more about these innovation projects, visit ispe.org/foya

About the author

Marcy Sanford is an Editorial Assistant for Guidance Documents at ISPE.

ISPE BRIEFS

Introducing the ISPE Eurasian Economic Union Affiliate

In March 2020, the ISPE Eurasian Economic Union (EAEU) Affiliate was officially established. This event was a significant step along the journey to integrate members from EAEU nations into the international pharmaceutical community, as well as another sign of progress in the development of a harmonized scientific, technological, and regulatory framework among countries and regions in the field of pharmaceutical manufacturing.

In 2005, representatives of the Russian pharmaceutical engineering industry showed interest in bringing an ISPE Affiliate to the Eurasian region and started working toward this goal. At that time, a group of ISPE members from the pharmaceutical industry met in Moscow and decided to pursue development of an affiliate.

However, it was not until 2017 that these efforts were connected to the increasing number of ISPE active members in the EAEU countries, including Russia, Belarus, Armenia, Kazakhstan, and Kyrgyzstan. In 2018, a new team of members started work with ISPE to create a Eurasian Affiliate. This was a logical step because the current intensive technological development of the region's industry depends on having a single, competent platform for global exchanges about current science and industrial leadership.

The new Affiliate has planned activities to achieve these key goals:

- Creating an influential industry platform in the EAEU for testing and promoting new ideas and implementing innovative ideas in pharmaceutical production
- Involving a wide range of industry stakeholders, including pharmaceutical production specialists, employees of architectural, engineering, and construction firms, and representatives from government agencies, universities, pharma and medical device manufacturers, and equipment suppliers

The ISPE EAEU Affiliate Board (left to right): Oxana Pryanichnikova, EAEU Affiliate Vice Chair and Development Director, Urb.ax; Polina Bobyleva, EAEU Affiliate Secretary and Deputy Head of the International Division Russian State Institute of Drugs & Good Practices; Svetlana Minchenkova, EAEU Affiliate Treasurer and Accountant ,FSI "SID & GP"; and Vladimir Orlov, EAEU Affiliate Chair and Division Lead, Department of International Cooperation and Foreign Affairs Russian State Institute of Drugs & Good Practices.

- Organizing events to be held in the EAEU and neighboring countries to support the development of the pharmaceutical industry in accordance with global industry trends
- Creating and updating Russian-language resources for technical literature that has practical applications for pharmaceutical production at all stages of the life cycle of a medicinal product

In April 2019, ISPE global leaders approved the strategic plan for the proposed new Affiliate. A roadmap that included legal, marketing, and communication activities with a horizon of two years was used to direct progress toward affiliate status, and a team of volunteer industry professionals and contractors was formed to organize tasks within the EAEU.

The new Affiliate has created a website and a Facebook page, formed a public relations strategy, and interacted with other professional communities to strengthen relationships. The group is also working on developing a Eurasian ISPE conference. The Affiliate is participating in dialogue and partnership with ISPE members worldwide through regular global teleconferences with the leaders of other Affiliates. Finally, the Affiliate has started to develop key initiatives including ISPE Young Professionals, Women in Pharma®, and Pharma 4.0™.

—EAEU Affiliate Board

Share Your SIG, CoP, Chapter or Affiliate News!

We'd like to feature your Chapter, Affiliate, CoP, SIG, or other ISPE group in upcoming ISPE Briefs. Share highlights from training programs, conferences, social events, or other activities in an article of 250 to 400 words. We welcome photos (at least 300 dpi or >1 MB). Email submissions to Susan Sandler, Senior Director, Editorial, at ssandler@ispe.org

MEET THE ISPE STAFF

DAWN ARBETELLO

Welcome to a new *Pharmaceutical Engineering*® feature: Meet the ISPE Staff. In each issue, we introduce a member of the ISPE staff who provide ISPE members with key information and services. In this issue, we introduce Dawn Arbetello, Brand and Creative Services Manager in ISPE's Marketing Communications group.

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

I'm a passionate creative professional with nearly 30 years of experience in print and digital design and marketing. As the Creative Services Manager at ISPE, I wear many hats. As a Brand Manager, I make sure that all creative assets, both print and digital, adhere to the overall look and feel of the ISPE brand. In addition, I am part of a team that consults with all ISPE business units about marketing strategy and creative assets in support of our international membership.

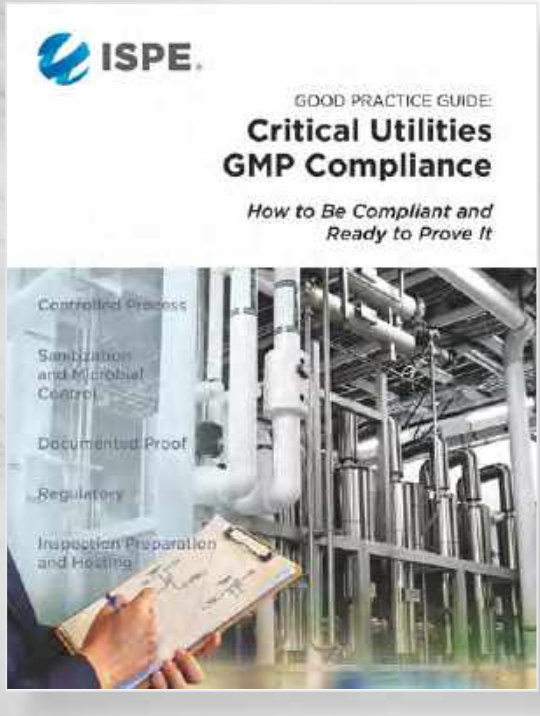
As Creative Director, I also oversee the work of my colleague, Jeffrey Link, in the creation of all marketing and conference assets, including direct mail promotions like postcards and brochures, internal and external digital advertising such as web ads and email banners, conference venue branding such as the ISPE booth and signage at the Annual Meeting, and FOYA with the annual Spotlight on Excellence booklet. Jeffrey, a seasoned design and layout professional who has been a contractor with ISPE for nearly a year, is an invaluable part of the MarCom team.

What do you love about your job?

I love working with the small but talented staff who are passionate about making a difference in people's lives.

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

When I'm not at work, I love traveling with my husband and attending concerts, especially to see my favorite band, the Avett Brothers.



New ISPE Good Practice Guide on Critical Utilities

By Marcy Sanford

ISPE has published a new *Good Practice Guide: Critical Utilities GMP Compliance—How to Be Compliant and Ready to Prove It.* Written and reviewed by a team of experts from around the world, the guide is the first of its kind in the industry. Team co-leads Nik Krpan and Rod Freeman talked with *Pharmaceutical Engineering*® about the importance of critical utilities and the benefits of the new guide.

What are critical utilities? Why are they important?

Nik Krpan: Critical utilities are utilities that have the identified potential to impact product quality or performance in a significant way.

For example, water systems in a plant are much like the circulatory system in your body and the heart—if your heart stops beating, you stop functioning very quickly. In a pharmaceutical manufacturing plant, water is used extensively in the plant for cleaning and formulation of product, and if you can't clean your equipment, you can't formulate product. Problems in the critical utilities can lead to immediate downstream problems in product quality related to microbial control.

Rod Freeman: One common misconception people have about critical utilities is that they think a critical utility is just a utility, when, in fact, it's both a raw material and a cleaning agent used in almost all pharmaceutical processes—it affects every product at the plant.

That is one of the reasons why regulators have such a keen interest in critical utilities, because they affect the patient's health on a broad scale. If those utilities aren't correct and working well, it compromises a lot.

What is the purpose of the guide?

RF: The team felt it needed to be published because ISPE has a lot of material on the technical side of things but nothing to really coach younger companies or associates in the industry on how to interact with inspectors and how to readily have the data needed available for them.

I've been in multiple FDA inspections. I've seen some go well, I've seen some go bad. And when I look at industry literature, there

> "I wish I'd had this guide previously in my career."

really isn't anything out there about how to host an inspection. Learning how to host an inspection is all taught on the job; there's nothing for a younger company or associate to read and learn the best way to handle an inspection and how to best meet the needs of the inspectors.

NK: The idea for the guide came from people who had worked for small manufacturers where they struggle to achieve compliance because they aren't always deploying their resources on the actions that are going to achieve the most compliant results.

The guide covers the steps that are necessary to achieve a continuous state of GMP compliance through correct operating practices, as well as the correct documentation practices and the correct practices to demonstrate compliance. The overall intended result is to provide a more efficient audit so that the auditor can get through their job as efficiently as possible, making better use of limited regulatory resources and improving patient safety.

RF: During an inspection, there is one inspector and they may not have expertise in your area, your plant, or product. Because of that, they don't always know what they're asking for, so it is important that as the host, you are able to work through it with them and get them the information they need quickly.

I've worked at some plants that shipped up to 400 products at any given time. When you have that many batch records, that many design history files, that many engineering drawings, a big part of your effort in preparation for an inspection is making sure your documentation is ready and easily accessible so when an inspector makes a request, you can get it to them within 20 minutes or an hour. If it's a day or two later, it doesn't present a good impression.

Who do you think will benefit from the guide?

RF: One of the biggest challenges that critical utility professionals have with regulatory agencies is presenting the data in a way that the regulators can understand and easily absorb quickly. I think that this guide will help with that communication between critical utility professionals and regulators.

NK: I also think this guide will be a big benefit to smaller manufacturing facilities where they don't have as much bench depth in their compliance departments. This guide will really help them identify the critical areas they should be focusing on to achieve compliance for their critical utilities.

RF: I wish I'd had this guide previously in my career. It would have helped me in numerous situations to better understand the needs of inspectors and auditors and meet them more quickly.

I hope this guide helps people who don't have as much time working in quality or as much exposure to it better understand the purpose of the inspection: the FDA is there to help protect the public health and safety.

And this guide is intended to help bridge a gap between engineering and the quality area so that you don't have that tug of war between quality and operations and so they work together to meet the needs of the agencies, which will ultimately benefit the patients.

About the author

Marcy Sanford is an Editorial Assistant for Guidance Documents at ISPE.

QUALITY AND REGULATORY SOLUTIONS

for PAT in Continuous Manufacturing

By Gabriella M. Dahlgren, PhD, Kevin A. Macias, RPh, PhD, Antonio Moreira, PhD, Duncan R. Thompson, Christoph Herwig, PhD, and Robert Dream, PhD

Process analytical technology (PAT) is perceived as the main enabler for a robust control strategy with continuous manufacturing (CM) because PAT can aid in implementing CM throughout the entire life cycle. This article discusses quality and regulatory hurdles in the life cycle of a PAT application—including model life-cycle management—in combination with CM for small and large molecules, with the goal of proposing strategies to resolve each challenge.

Continuous manufacturing represents the next generation of pharmaceutical manufacturing processes for both large and small molecules. It is recognized by regulatory authorities as a key emerging technology. The US FDA has approved various small molecule products and recently issued draft guidance for industry on CM [1, 2]. In this article, we do not focus on the capabilities of specific PAT technologies, which have been reviewed in other recent publications [3–6]. Instead, we address how companies can add flexibility and maximize the value of PAT for CM. As we discuss general issues, we focus on how they apply to all or most PAT tools and we use some common PAT tools as aids to describe example scenarios.

Important regulatory guidance on PAT includes ICH Q8 (R2) [7] and the FDA's "Guidance for Industry" from 2004 [8]. The FDA PAT guidance considers PAT to be,

> *A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term* analytical *in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner."*

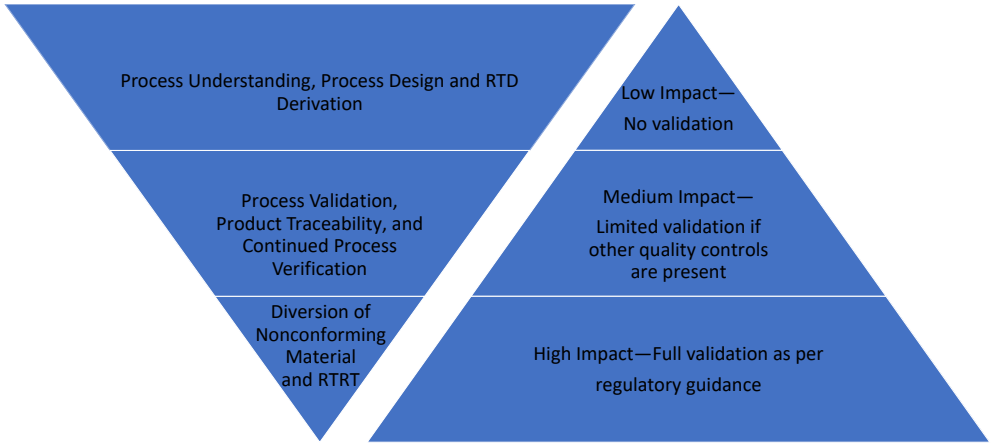
For CM, analytics must move closer to the process. PAT can therefore add significant value in design, analysis, and control of the CM process. Because PAT does not involve pooling or holding of the process, decisions can be made in real time. For example, when designing equipment or modeling unit operation behavior, PAT measurements used to determine residence time distribution (RTD) are critical. During process development, PAT may be used to confirm satisfactory process operation, verify models, inform on divert to waste (DTW) situations, or perform feedback control. The control strategy for a continuous process may also benefit from the use of PAT. Furthermore, PAT can be used for final critical quality attribute (CQA) determination directly or as input to a more complex model that includes process parameters and material attributes.

When developing and implementing a commercial CM line, PAT is recommended, even more strongly than it is for batch manufacturing, for all three phases (design, analysis, and control). However, the extent of PAT use is company- and product-dependent, reflecting the perceived return on investment.

On the continuum from simplest to most complex applications, the optimum level of PAT deployment in various stages of the CM life cycle, from design to routine operation, is a company decision that may be based on perceived risks associated with regulatory and quality considerations. The validation of PAT applications must evolve during their life cycle to ensure they remain fit for purpose. Lack of clarity on regulatory expectations at different points in the life cycle can derail PAT early in the process.

Figure 1 shows how the number of PAT applications tends to decline as we move from process understanding to real-time release testing (RTRT) (left triangle), whereas validation requirements (right triangle) increase as we move from low-impact to high-impact applications. Because successful implementation of PAT can add benefits to a CM process, we suggest in this article ways to increase the utilization of PAT within all stages of the left triangle.

Figure 1: Conceptual representation of the number of pharmaceutical industry–deployed PAT applications in use contrasted with the resources required to develop, validate, support, and maintain the methods and enable defined fit-for-purpose testing.



PAT IN DEVELOPMENT

During early process development, having the tools in place for rapid analysis and visualization helps turn PAT data into immediately actionable knowledge. At this stage, companies often seek to enhance understanding to effectively implement a CM platform, and it might be easy to install a preliminary PAT system for this purpose. Notably, these early data could form the basis of differentiation between good and bad product that determines quality decisions. For this reason, a close-to-GMP-ready system to manage the PAT may be needed earlier in the development process than would be required for a batch process; also, a plan on how to leverage the preliminary system may be required if a permanent system is needed for commercial use. However, in most scenarios, companies do not need to install a commercial release–ready GMP system for initial process development.

Data capture with a PAT system should meet process-specific criteria that are based on the targeted CQAs according to quality by design (QbD) principles. A potential strategy would be to start by using PAT tools, such as semiquantitative or fingerprint methods, to detect relative changes [9]. These are easier methods to qualify or validate, which would then allow organizations to use PAT data for quality decisions and help companies leverage the data for future, more advanced controls or decisions. This approach could also streamline the requirements around robustness and system suitability, which may require significant resources in early development. It would be beneficial if a company established a process for qualified versus validated methods similar to what has been done for traditional testing.

To clarify the relationship between RTD and PAT, the FDA published the initial PAT framework [8], which supports the move from static batch processing to more-dynamic approaches that mitigate the risk of producing poor-quality product. ICH implemented a trio of quality guidance: Q8(R2), Q9, and Q10 [7, 10, 11]. Continuous systems with automation and process control frequently result in high-quality (low-variability) products, whereas traditional batch processing can be less understood, resulting in less-predictable product quality [12].

Using high-frequency PAT sensors can ensure adequate sensing to determine the approximate RTD shape. Aided by a simple peak detection algorithm, analysts can easily detect the most significant spikes. It is logical to assume that detecting the downstream response is easier than detecting the pulse disturbance itself. If a plug flow process were expected, the perturbation would be largely unchanged as it traveled along the system, meaning pulse into the system would result in a pulse response, although this would be difficult to detect without a very rapid measurement. RTD plays an important role in material traceability because it characterizes the spreading of the materials through the system. Thus, a disturbance could be predictively tracked through the entire continuous system, enabling downstream control or even removal of the affected material.

The determination of RTDs is one of the primary areas in which PAT is used in development. RTD aids in the traceability of raw materials in the manufacturing process, which is critical when material is continuously fed into and removed from a process. Once the RTD has been determined for each unit operation, as well as the integrated line, it can be used to facilitate material traceability and help determine sensor placement and measurement frequency to ensure that any unacceptable material variations can be detected, recorded, and addressed.

AUTOMATION AND RTD

Continuous systems with automation and process control result in high-quality, low-variability products. A properly designed continuous system with appropriate sensors to record and display process parameters, such as critical process parameters (CPPs) and

Figure 2: A conceptual integrated small molecule CM process.

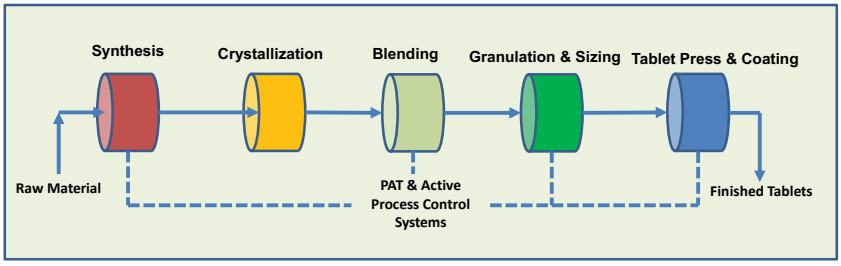
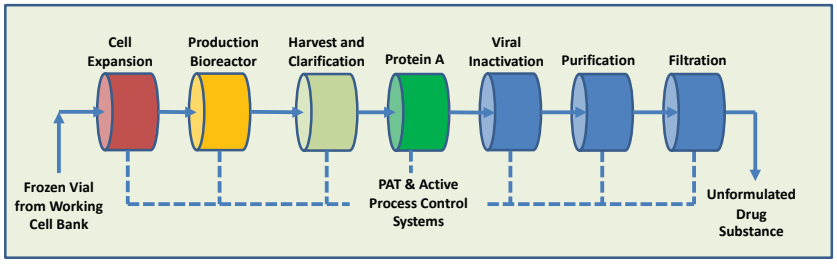


Figure 3: A conceptual integrated large molecule CM process.



non-CPPs, handles small portions of material at any given moment, increasing material monitoring scrutiny. When CM uses product and process knowledge with properly implemented online PAT, it can meet the criteria required to enable RTRT, leading to rapid and reliable batch release of high-quality product (see Figures 2 and 3 for CM processes for small and large molecules, respectively). Despite these vast advantages, CM also has significant challenges, and continued focus by industry and regulators is required to resolve them.

In the chemical processing field, the RTD is used to describe how a material travels inside the unit operations of a continuous process system. RTD is a critical tool in pharmaceutical process understanding, quality assurance, and equipment and sensing design, but it is underutilized due to a lack of acceptance of RTD as an alternative to testing, especially if an automated RTD control system is available as part of the line.

As mentioned, PAT can be a useful tool as part of the control strategy, which is generally developed and initially implemented for production of clinical trial materials. The control strategy is usually refined for use in commercial manufacture as new knowledge is gained. Changes could involve acceptance criteria, analytical methodology (including switching from traditional lab testing to PAT or model-based methods), or the points of control (e.g., introduction of RTRT). Stakeholders across an organization must agree whether the documentation and equipment qualification of any PAT tool done during development activities are sufficient to permit the leveraging of the development data into a final RTRT method that incorporates increased process knowledge and finalized process controls. Additional emphasis on process controls should be considered in cases where products cannot be well characterized or quality attributes might not be readily measurable due to limitations of testing or detectability (e.g., microbial load/sterility, low drug load).

PAT VALIDATION AND LIFE-CYCLE MANAGEMENT

As noted previously, PAT benefits a CM line by helping answer technical and quality-related questions about product and process performance, and by providing the direct answer to product quality requirements. As mentioned, the main hurdles of validation strategy of the PAT and the accompanying methods arise during development. The qualification and validation of PAT applications have significant overlap with traditional analytical equipment qualification and validation and should be conducted in accordance with ICH Q2 (R1) [13], where the capabilities of the equipment must align with the type of test that the technology will address (ID, qualitative, or quantitative measure). When PAT is incorporated into the manufacturing process as inline or online tools, additional issues such as probe fouling and complexity of CM cleaning validation should be addressed. Some examples of how to incorporate these aspects into the line risk analysis are described in detail in ASTM standard E2898-14 [14]. Figure 4 shows the life cycle for method development and validation of analytical methods for PAT applications that is aligned with E2898-14.

E2898-14 includes paths for PAT method validation, including how a risk assessment can document a risk-based approach that identifies what parameters to address based on the use of the PAT

tool and how each parameter should be handled. (This risk-based approach can be found in ASTM E2476 [15].)

Examples of potential areas for confusion around validation requirements in the pharmaceutical industry include:

- How to translate the risk-based approach for a scenario in which PAT is used for DTW and not part of the final product release strategy
- How to validate the PAT measurement if equivalency to a traditional method is not feasible or no traditional methodology is available
- How to leverage development work or data generation when the model is of a lower impact level (Table 1)

Internal education of employees regarding the similarities and differences between PAT and traditional testing is essential to successfully implement and sustain PAT as a tool for ensuring quality. Training programs are needed for all levels of the organization; the scope of education will range from awareness to detailed training in how to install and maintain the PAT, including interfaces with the manufacturing line.

Many common PAT tools require the use of chemometric models to generate the required data. At any stage during the life cycle of the application (e.g., feasibility, development, validation, or routine use for product manufacture), the level of validation of the model, and thereby the validation of the test method, must be aligned with the impact of the application at that time (Figure 1). Table 1 categorizes the impact of the model use into three levels [16] and presents examples and the proposed level of validation/documentation appropriate for the situations.

Table 1 captures the current information from the FDA guidance document [16] and shows that the regulatory expectation on validation and documentation increases as the potential impact of the model on quality increases. The information in Table 1 and the

Figure 4: General flow for the PAT method life cycle.

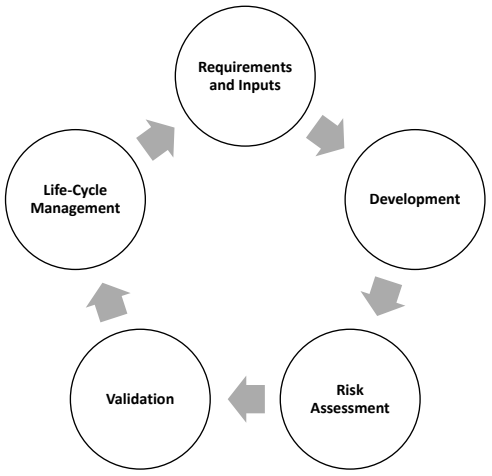
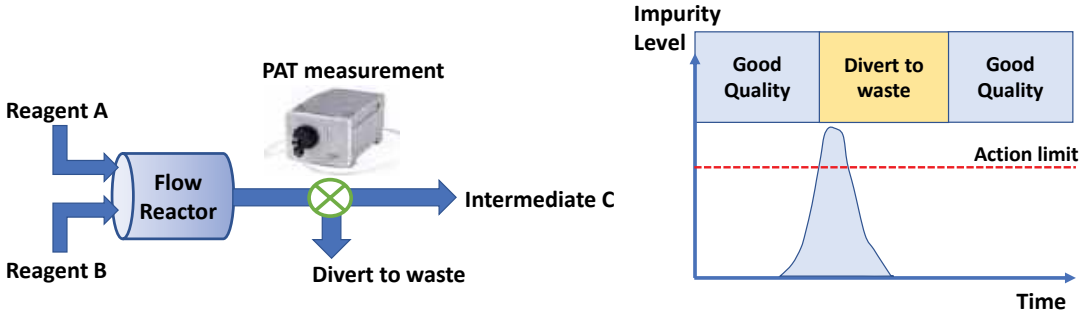


Table 1. Model validation and documentation expectations.

Category	Impact Level		
	Low	Medium	High
Model use	To support product or process development	To help ensure product quality (model predictions are not the sole indicator of product quality)	To predict product quality (model predictions are significant indicators of product quality)
Examples	Formulation, process optimization, and scaling	Design space models, in-process control models; PAT for process control when not part of control strategy	Chemometric models for product assay, surrogate model for dissolution PAT for process control when part of registered control strategy
Validation	Formal validation is unlikely Method development will not include all variability expected in commercial manufacturing	Limited validation may be appropriate	Full model validation is done following relevant guidelines
Documentation	Includes discussion of how the models were developed and used to guide process development	Model assumptions; a tabular or graphical summary of model inputs and outputs; relevant model equations (e.g., for mechanistic models) either in the submission or via a reference; statistical analysis where appropriate; a comparison of model predictions with measured data; and a discussion of how the other elements in the control strategy help mitigate uncertainty in the model, if appropriate	Data and prior knowledge (e.g., for established first principles–driven models), such as model assumptions; appropriateness of the sample size, number, and distribution of samples; data pretreatment; justification for variable selection; model inputs and outputs; model equations; statistical analysis of data showing fit and prediction ability; rationale for setting of model acceptance criteria; model validation (internal and external); and a general discussion of approaches for model verification during the life cycle

Figure 5: Illustration of a medium-impact PAT application applied to flow chemistry. Demonstration of the concept of PAT measurement prior to a DTW valve (left) is not directly linked in scale to the graph (right).



FDA guidance [16] can be leveraged to create appropriate internal requirements depending on the intended use of a model at any phase of the PAT life cycle. It should be noted that based on long-term intent of a model, a company can decide to increase the validation and documentation requirements at an earlier phase of application development to facilitate the end use. In a similar manner, qualification activities may be performed earlier for chemical manufacturing control (CMC) deliverables.

Regulatory guidance documents for near-infrared spectroscopy (NIRS) cover what is in or out of scope. For example, European Medicines Agency (EMA) NIRS guidance [17] states that "NIRS for non-regulatory purposes, such as generating process knowledge, is out of scope of this guideline." FDA guidance on NIRS [18] applies to applications used "during the manufacture and analysis of pharmaceuticals (including raw materials, in-process materials and intermediates, and finished products)." It is generally assumed that this FDA guidance applies to applications that will be included in regulatory submissions aligned with EMA NIRS guidance, although that is not specifically stated. The FDA and EMA NIRS guidance can be applied to similar PAT technologies.

According to current guidance documents, organizations must obtain additional regulatory approval during the life cycle of the PAT application. This is a challenge, and it is compounded by the differences in the requirements of various regulatory bodies. Certain changes to the scope of the NIRS method (EMA guidance) require regulatory notification and acceptance before a model update can be implemented [19]. FDA guidance also requires a prior approval supplement when there are major changes to the application or a change-being-effected in 30 days (CBE-30) filing for a moderate change. If the PAT application were required to manufacture using continuous processing, manufacture would have to cease during this time period unless an alternative control strategy that did not rely on the PAT application were accepted by regulatory authorities.

The following are two potential solutions to mitigate this challenge in EMA guidance and general expectations of approval of model changes:

- The use of performance-based established conditions (ECs) for PAT methods versus parameter-based ECs: This option would require a clear description of model outputs that must be met, such as accuracy, precision, linearity, and so on, instead of just the software version, spectral pretreatment, and equipment model. If performance-based ECs were used, a range of changes to the PAT method would not require a filing because those changes would be verified through the confirmation of the output and tracked within the pharmaceutical quality system (PQS).
- The use of postapproval change management protocol (PACMP): This is a two-step process. First, the organization submits a written protocol that describes the proposed change, its rationale, and risk management, as well as proposed studies and acceptance criteria to assess the impact of the change(s). Regulatory authorities must approve this protocol in advance of the implementation of the proposed change(s). Second, the organization submits the actual results/data based on the protocol approved by the regulatory authorities and according to the agreed categorization (classification). In certain cases (e.g., noncritical or repetitive changes), regulatory approval of the second step may not be required because that step will be managed within the applicant's PQS.

The second approach can result in the downgrade of notification requirements (e.g., 1B to $1A_{IN}$), which could obviate the need to halt CM while awaiting regulatory approval. Overall, this is an area of ongoing conversation between industry and regulators.

The goal of PAT model validation is to have a fit-for-purpose validation and documentation approach for model use. In general, industry stakeholders agree on health authority expectations for low- and high-impact models. The requirements for medium-impact models are less clear.

Consider the following example, in which two reagents (A and B) are reacted together in a single-stage flow process to form an intermediate (C) of a multistage synthetic process (Figure 5). A PAT

measurement is made at the exit of the reactor, which is capable of quantifying an impurity in solution that is difficult to purge and can impact API quality downstream. Intermediate (C) is collected in a batch vessel, sampled for analysis, and tested against a specification, irrespective of the PAT measurement. This offline analysis forms the basis for ensuring control of the impurity. However, using PAT to DTW at the appropriate times can reduce the level of impurity in the intermediate or potentially prevent a batch failure. (With enhanced confidence in the PAT method and RTDs, the extended DTW time shown in Figure 5 may be reduced to match the point where the impurity is below the action limit.)

In this case, the application should be considered medium impact. The level of assurance required for this PAT measurement is less than if the impurity were not controlled by subsequent downstream analysis, and the process can run without the PAT measurement. Fit-for-purpose application validation is required, as this is a business risk and presents no risk to the patient.

Similarly, consider a PAT measurement performed on a mixture or blend for an oral solid dose formulation used to ensure proper composition to determine when to DTW. If the final product has another PAT or traditional test with appropriate sampling frequency, this initial PAT method is considered medium impact, and limited validation and model maintenance requirements are required.

INDIRECT PAT APPROACHES: SOFT SENSORS AND DIGITAL TWINS

The previous sections focused on direct PAT approaches; however, many products are too complex to measure all CQAs in real time. In many cases, a process variable or a CQA is considered hardly measurable because the measurement is not specific enough, the resolution does not suffice, or the variable is intracellular (in the case of biologics). In these situations, indirect measurement and correlation techniques are needed, and soft sensors, which use a combination of other measurements and mathematical calibration algorithms to accurately predict potentially difficult to measure variables, can be used.

There are multiple approaches for the generation of soft sensors [20]. The most desirable soft sensors are fully mechanistic ones, which use first-principle approaches, such as energy, mass, and elemental balances [21]. When complexity must increase to accurately predict the target variable, mechanistic modeling approaches are appended with data-driven correlations (also called hybrid models) [22].

Mechanistic or hybrid kinetic models can be implemented in a real-time environment and thereby mimic the process as a digital twin. Digital twins can be used to estimate the current state of process variables by using observed algorithms, such as Kalman or particle filters. Furthermore, they allow prediction and

Overall, the quality requirements—and, thereby, the quality systems—are not changed by the implementation of continuous manufacturing.

(model-predictive) process control, a key requirement for continuous bioprocessing [23]. Because digital twins derive variables that cannot be easily measured, they can even be used as tools for controlling on variables that are normally not measurable. Hence, together with workflows known as "good modeling practice," digital twins provide means to measure less and allow new opportunities for extended experimental design and enhanced process characterization [24]. Although these techniques are good to predict performance, they have limited use for establishing release criteria.

METHOD AND MODEL UPDATES

PAT methods focused on product life-cycle management (ICH Q12) require routine verification of performance beyond what is required for traditional test methods. Enhanced attention must be given to the validation of the models, as well as the continued verification that the model is operating in its validated space. Therefore, computational model life-cycle management, which includes routines for model diagnosis and drift detection, must be established [25]. This will enable identification of a transition point where models are allowed to self-learn on additional data sets, or where the model needs to be maintained by process experts. More research is required on the following questions: What would be necessary to allow a self-tuning model? What would preclude a self-tuning model and would require a process expert's intervention? How would life-cycle management be performed?

Q12 is proposed as the update mechanism for changes to all models, such as addition of spectra to a model or providing proof of being able to use a model for RTRT. Many strategies for self-learning algorithms have been in place for many years and will be enhanced by machine learning and artificial intelligence strategies in the future. However, the changes to a digital twin and soft sensor must remain traceable in a GxP environment. Moreover, the validated space of the method/model must be declared, and data integrity must be ensured, which can be a challenging task for data-driven approaches and will be a research field in the near future. We need to address questions such as the following: Do sufficient criteria exist to declare the validated space and ensure data integrity? If the validated space changes from a previously approved model but is irrelevant for the operating space, is this a model change? In many cases, mechanistic approaches are encouraged because model parameters have a mechanistic meaning. Their value can be compared to literature values, which allows easier validation, and can therefore be easier to interpret and judge for model validity during unforeseen perturbations.

Another potential solution is to allow for the use of "or equivalent" with PAT methods, similar to what is done with traditional analytical methods, and only the spectra that were part of the original validation would be used for these equivalency assessments. To make this approach possible, updates to current regulatory guidance documents would be required, as described in the PAT validation section. If updates to guidance documents to allow for "or equivalent" can be realized, certain activities, such as the addition of a second software and the addition of a second analyzer of the exact same model with no change in original acceptance criteria, could be captured within the quality system. This would simplify reporting because changes could be submitted as part of the annual report instead of in a regulatory filing.

OTHER POTENTIAL HURDLES

When PAT is used in a CM process, the number of data points or measurements will be significantly higher than with a traditional batch process. This greater amount of data allows for the use of alternative statistical methodologies to show product quality, but it also requires additional discussions and strategies around sampling plans, as discussed in detail by De Los Santos and colleagues [26]. Overall, the quality requirements—and, thereby, the quality systems—are not changed by the implementation of CM. However, timing and responsibilities for activities such as batch review, release strategy, stability strategy, rejection strategy, and contingency plans for PAT may change.

As discussed previously, in CM, some activities may shift to an earlier phase in the manufacturing process development, especially because the process may be developed at scale. Similarly, process validation may also be done sooner because a CM line is more integrated than traditional batch processes (as discussed by the FDA in new draft guidance for CM [2]). The combination of PAT with CM may enable continuous process verification because it allows for immediate feedback of process performance and the use of a QbD approach if used throughout development.

CONTINGENCY PLAN FOR PAT

As described in guidance documents [17, 18], regulators expect that organizations will include a contingency plan as part of the strategy when implementing PAT. A range of potential approaches can be taken with respect to the contingency plan, and each has its own advantages and disadvantages.

Multiple PAT

One option for contingency planning involves creating a line with multiple equivalent PAT tools for a specific measurement. This can be done by ensuring available backup PAT tools to insert into the

line when the "primary" tool goes down, or the organization can have multiple tools built into the line at equivalent points to measure the same parameter.

It is critical that organizations have a predetermined, scientific and risk-based strategy around hierarchy of the multiple values/PAT outputs during routine operation to eliminate confusion. The backup PAT tool can also be offline equipment not intended for direct connection to the line.

Alternative Test Methods

If PAT is unavailable, or does not function as expected (i.e., does not pass suitability tests), alternative or traditional test methods can be employed. It should be noted that this statement only applies to scenarios where the testing method has been appropriately documented through the control strategy and overall product risk. One drawback to this approach is the organization may need to collect a high volume of samples to show process control. Also, the traditional test usually takes longer than the PAT test and can delay product release, especially if RTRT is employed.

Shutdown

If an organization uses PAT but does not use multiple PAT tools or an alternative test method as the contingency plan, it may need to shut down the line if the PAT is unavailable. In this scenario, no product is manufactured until the PAT tool is again available. This will require the organization to maintain higher inventory volumes to minimize the risk for potential out-of-stock events, which can be cost prohibitive. The benefits, although minor, of this approach are that the organization will not require additional PAT tools or analytical equipment as part of its upfront investment and long-term maintenance costs may be lower.

If a company is not willing to invest in backup PAT, they are also less likely to implement PAT from the start due to the high risk of not being able to run the standard planned commercial process or meet the demand plan. This can then lead to drug shortages, as noted previously, which is otherwise a problem that CM can alleviate.

CONCLUSION

Throughout this article, we have shown how PAT can aid in the implementation of CM throughout the life cycle and have highlighted areas of concern for PAT implementation. Based on the product and company strategy, PAT can be used for process development, control, monitoring, and product release. Guidance documents are clear on the requirements and expectations for PAT when used for real-time release or to make final quality decisions. However, there are major hurdles for increased implementation of PAT within CM, for which we have proposed some solutions:

- Validation requirements for medium-impact models.
- Model maintenance and updates: Guidance documents from various health authorities offer differing requirements regarding the expectations for model maintenance. Our recommendation is to continue harmonization discussions as Q13 and Q14 are being drafted to clearly capture what is expected and to align expectations with requirements for traditional test methods. Also, by shifting to a performance-versus-parameter-based description of methods, more changes can be managed through the PQS instead of in regulatory filings. This would decrease the time requirement for implementation of a change and allow for increased use of PAT.
- Processes and system for traceability: The use of PAT requires models, which need to be adjusted throughout the product life cycle. Therefore, it is critical to have tools to trace the need to adapt the models in a GxP environment. Workflows and decision trees must be available as data science solutions.
- Skills, knowledge, and mindset within the organization: It is important to share knowledge and develop the skill set of the entire organization from the introduction of PAT and CM to allow for better understanding and sustainability of these initiatives.
- Business case requirements: Companies need to think holistically about how they develop the business requirements for and benefits of PAT. The first application will always be relatively costly and time consuming; however, once the tool and the skills are in place, companies can realize significant benefits at significantly lower costs. Through the use of PAT, companies may also increase overall knowledge of the process, which supports the holistic approach to the business case.
- Options when unable to measure all CQAs with PAT: Companies should acknowledge these issues and develop appropriate processes for modeling if PAT tools are unavailable.
- Software solutions: Workflows for digital twins are in place; however, a digital twin needs a suitable real-time environment, and standardization is key in this respect; therefore, the industry needs software as a service (SaaS) solutions.

References

1. Su, Q., S. Ganesh, M. Moreno, Y. Bommireddy, M. Gonzalez, G. Reklaitis, and Z. Nagy. "A Perspective on Quality-by-Control (QbC) in Pharmaceutical Continuous Manufacturing." *Computers and Chemical Engineering* 125 (June 2019): 216–231. doi:10.1016/j.compchemeng.2019.03.001
2. US Food and Drug Administration, Center for Drug Evaluation and Research. "Quality Considerations for Continuous Manufacturing: Guidance for Industry—Draft Guidance." February 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-continuous-manufacturing
3. Fonteyne, M., J. Vercruysse, F. De Leersnyder, B. Van Snick, C. Vervaet, J. P. Remon, and T. De Beer. "Process Analytical Technology for Continuous Manufacturing of Solid-Dosage Forms." *TrAC Trends in Analytical Chemistry* 67 (2015): 159–166. doi:10.1016/j.trac.2015.01.011
4. Laske, S., A. Paudel, O. Scheibelhofer, et al. "A Review of PAT Strategies in Secondary Solid Oral Dosage Manufacturing of Small Molecules." *Journal of Pharmaceutical Sciences* 106, no. 3 (2017): 667–712. doi:10.1016/j.xphs.2016.11.011
5. Holzberg, T., V. Watson, S. Brown, A. Andar, X. Ge, Y. Kostov, L. Tolosa, and G. Rao. "Sensors for Biomanufacturing Process Development: Facilitating the Shift from Batch to Continuous Manufacturing." *Current Opinion in Chemical Engineering* 22 (December 2018): 115–127. doi:10.1016/j.coche.2018.09.008
6. Jiang, M., K. Severson, J. Love, H. Madden, P. Swann, L. Zang, and R. Braatz. "Opportunities and Challenges of Real-Time Release Testing in Biopharmaceutical Manufacturing." *Biotechnology and Bioengineering* 114, no. 11 (July 2017): 2445–2456. doi:10.1002/bit.26383

7. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Guideline Q8(R2) on Pharmaceutical Development." European Medicines Agency website. August 2009. https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development
8. US Food and Drug Administration. "Guidance for Industry. PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." September 2004. https://www.fda.gov/media/71012/download
9. Rajamanickam, V. S. P., O. Spadiut, and C. Herwig, "Impurity Monitoring as Novel PAT Tool for Continuous Biopharmaceutical Processes." In *Continuous Bioprocessing—Industry Best Practices by Repligen*, edited by J. Bonham-Carter, 89–101. Waltham, MA: Repligen, 2018. https://www.repligen.com/applications/perfusion
10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Guideline Q9 on Quality Risk Management." European Medicines Agency website. November 2005. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf
11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Q10 Pharmaceutical Quality System." European Medicines Agency website. June 2008. https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system
12. Plumb, K. "Continuous Processing in the Pharmaceutical Industry: Changing the Mind Set." *Chemical Engineering Research and Design* 83, no. 6 (June 2005): 730–738. doi:10.1205/cherd.04359
13. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline. Validation of Analytical Procedures: Text and Methodology Q2(R1)." European Medicines Agency website. October 1994. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-2-r1-validation-analytical-procedures-text-methodology-step-5_en.pdf
14. ASTM International. ASTM Standard E2898-14: *Standard Guide for Risk-Based Validation of Analytical Methods for PAT Applications*. West Conshohocken, PA: ASTM International, 2014.
15. ASTM International. ASTM Standard E2476-16: *Standard Guide for Risk Assessment and Risk Control as It Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture.* West Conshohocken, PA: ASTM International, 2016.
16. US Food and Drug Administration. "Guidance for Industry. Q8, Q9, and Q10: Questions and Answers (R4). ICH Revision 1." November 2011. https://www.fda.gov/downloads/Drugs/Guidances/UCM210822.pdf
17. European Medicines Agency, Committee for Human Medicinal Products. "Guideline on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations." June 2014. https://www.ema.europa.eu/en/use-near-infrared-spectroscopy-nirs-pharmaceutical-industry-data-requirements-new-submissions
18. US Food and Drug Administration, Center for Drug Evaluation and Research. "Development and Submission of Near Infrared Analytical Procedures: Guidance for Industry—Draft Guidance." March 2015. https://www.fda.gov/media/91343/download
19. European Medicines Agency, Committee for Human Medicinal Products. "Addendum to EMA/CHMP/CVMP/QWP/17760/2009 Rev 2: Defining the Scope of an NIRS Procedure." https://www.ema.europa.eu/en/documents/scientific-guideline/addendum-ema/chmp/cvmp/qwp/17760/2009-rev-2-defining-scope-nirs-procedure_en.pdf
20. Luttmann, R., D. G. Bracewell, G. Cornelissen, et al. "Soft Sensors In Bioprocessing: A Status Report and Recommendations." *Biotechnology Journal* 7, no. 8 (2012): 1040–1048. doi:10.1002/biot.201100506
21. Herwig, C., I. Marison, and U. Von Stockar. "On-line Stoichiometry and Identification of Metabolic State Under Dynamic Process Conditions." *Biotechnology and Bioengineering* 75, no. 3 (2001): 345–354. doi:10.1002/bit.10058
22. Solle, D., B. Hitzmann, C. Herwig, et al. "Between the Poles of Data-Driven and Mechanistic Modeling for Process Operation." *Chemie Ingenieur Technik* 89, no. 5 (April 2017): 542–561. doi:10.1002/cite.201600175
23. Kroll, P., A. Hofer, S. Ulonska, J. Kager, and C. Herwig. "Model-Based Methods in the Biopharmaceutical Process Lifecycle." *Pharmaceutical Research* 34, no. 12 (December 2017): 2596–2613. doi:10.1007/s11095-017-2308-y
24. Golabgir, A., T. Hoch, M. Zhariy, and C. Herwig. "Observability Analysis of Biochemical Process Models as a Valuable Tool for the Development of Mechanistic Soft Sensors." *Biotechnology Progress* 31, no. 6 (2015): 1703–1715. doi:10.1002/btpr.2176
25. Chiang, L., B. Jiang, X. Zhu, D. Huang, and R. D. Braatz. "Diagnosis of Multiple and Unknown Faults Using the Causal Map and Multivariate Statistics." *Journal of Process Control* 28 (2015): 27–39. doi:10.1016/j.jprocont.2015.02.004
26. De Los Santos, P.A., J. Hofer, E. Jayjock, T. T. Kramer, K. R. Lief, and M. Otava. "Sampling Considerations in Continuous Manufacturing." *Pharmaceutical Engineering* 39, no. 3 (May–June 2019): 55–63.

About the authors

Gabriella M. Dahlgren, PhD, has a doctorate in chemistry from the University of Michigan. She has been part of the Janssen Product Quality organization since 2015, focusing on implementation of new technologies such as PAT, real-time release, and continuous manufacturing. She is currently Co-lead of the ISPE Product Quality Lifecycle Implementation (PQLI)® subteam on continuous manufacturing. Prior to joining Janssen, Gabriella's experiences included more than 10 years as an Analytical Chemist in various functions focused on the creation of processes for method development end to end, development and validation of test methods, evaluation of new technology to speed up release testing, and implementation of hydrophilic coatings on new medical devices. She has also served as the cross-functional subject matter expert for vendor changes and resolution of production issues as they relate to testing and chemical characterization. Gabriella has been an ISPE member since 2017.

Kevin A. Macias, RPh, PhD, obtained a BS in pharmacy from St. Louis College of Pharmacy and a PhD in industrial and physical pharmacy from Purdue University. Kevin is currently a Principal Scientist in Drug Product Development within Global Product Development & Supply at Bristol Myers Squibb. In his role, Kevin merges analytics, spectroscopy, pharmaceutical materials science, and drug product processing fundamentals to develop real-time analytical techniques that enable efficient drug product development and manufacture. In addition to spectroscopic applications for process control, his research interests include powder flow characterization, roller compaction, and novel small molecule drug delivery systems.

Antonio Moreira, PhD, is Vice Provost for Academic Affairs and Professor of Chemical, Biochemical, and Environmental Engineering at University of Maryland, Baltimore County (UMBC). He was previously Chair of the Chemical and Biochemical Engineering Department, Associate Dean of Engineering, and Associate Provost for Academic Affairs. Prior to his appointment to UMBC, Antonio spent nearly 10 years in the private sector, with senior management positions both in the food industry with International Flavors and Fragrances, Inc., and in the pharmaceutical/biotechnology area with Schering-Plough Corporation (now Merck & Co.). He has significant experience with R&D, scale-up, and introduction to commercialization of biotechnology products, such as alpha interferon, granulocyte-macrophage colony-stimulating factor (GM-CSF), and monoclonal antibodies. Antonio holds a BS in chemical engineering from the University of Porto, Portugal, and has an MS and PhD in chemical and biochemical engineering from the University of Pennsylvania. He has been an ISPE member since 1992.

Duncan R. Thompson has 25 years of experience in analytical chemistry and PAT, leading a team at GSK that developed and implemented many PAT applications in both batch and continuous processes covering API and DP. He has expertise in PAT supporting process development and the validation and registration of applications for control strategies. He represented GSK on a European Federation of Pharmaceutical Industries and Associations team for regulatory advocacy with EMA. More recently, he joined CatSci as Analytical Team Leader, where he is expanding analytical capabilities, including PAT, to deliver innovative process research and development.

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

Robert Dream, PhD, is an accomplished industry leader with broad experience in the biopharmaceutical industry from early process development to commercial manufacturing. He has been working in depth in the biopharmaceutical industry for 30 years and has been involved in all aspects of manufacturing, regulatory, process validation, financial planning, development of drug substance and drug products, and program and project management globally. Robert has assisted companies to expand their operations and businesses worldwide, contributing to planning, audits, gap analyses, and BLA/NDA preparations and submittals. His work has been published in numerous industry textbooks and technical journals, and he has participated in numerous seminars and technical conferences. A registered professional engineer, Robert has been a member of ISPE since 1990.

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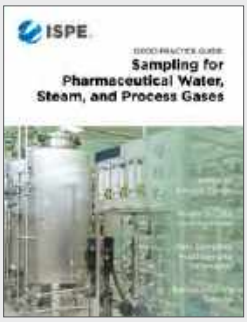

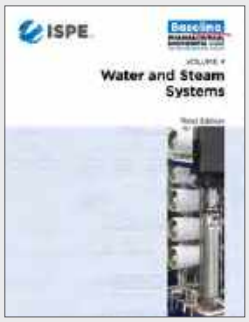

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USING CFD MULTIPHASE MODELING

to Predict Bioreactor Performance

By Elijio Prado and Albert Dyrness

Computational fluid dynamics (CFD) can reduce or eliminate the need to perform bioreactor scale-up studies because full-scale manufacturing bioreactors can be simulated to predict performance. This article discusses the use of CFD for that purpose, to predict the performance of a manufacturing-scale bioreactor under various operating conditions.

Parametric studies on process conditions provide valuable insight for early-stage bioreactor design and process development. The advantage of CFD is that it enables rapid and cost-effective simulation of various conditions and provides detailed visual data that can complement or exceed experimental methods. Furthermore, individual parameters within CFD simulations can be varied with precision to facilitate design optimization with results interpreted at a level that is often masked by natural variation in physical testing.

The goal of this article is to provide a method for simulating and analyzing impeller mixing and gas sparging in a bioreactor using multiphase CFD modeling. In particular, the oxygen transfer rate, k_La, is the primary performance parameter of interest, and to ensure the validity of the solutions, a mesh-independent CFD model is benchmarked against an experimentally determined k_La. Operating parameters (i.e., impeller speed, gas sparge rate) for the mesh-independent and benchmarked CFD models are then changed, and a comparison is made between the CFD model prediction and experimental data. One bioreactor CFD model is created and solved to simulate three different operating conditions. The model can then be used for further parametric studies for the purpose of design optimization, specifically for changing operating conditions such as sparge gas flow rate and impeller speed. These simulations were performed with ANSYS CFX version 2019R3. The method presented here is not limited to oxygen transfer and may also be used for other species (e.g., CO_2 stripping) undergoing liquid and gas mass transfer.

METHODOLOGY

Our modeling approach incorporated the homogeneous multiple size group (MUSIG) model to account for multiple sizes of bubbles, bubble breakup, and bubble coalescence. This model assigns the same velocity to the different bubble size groups in the bioreactor. This essentially means that small bubbles will have the same velocity as large bubbles even though, in reality, different sizes of bubbles have different terminal rise velocities. For air bubbles in a water-type liquid environment, the MUSIG model is appropriate for bubble sizes in the approximately 1 mm to 17 mm range.

Using the formulas from Talaia [1] and liquid and gas densities of 993.5 kg/m^3 and 1.65 kg/m^3, respectively, the terminal rise velocity for air bubbles ranging from 1 mm to 17 mm is 0.15 m/s (1 mm) to 0.61 m/s (17 mm). The terminal velocity of the largest bubble can be approximately four times that of the smallest bubble. In practice, for these gas-sparged vessel mixing setups, most bubbles cluster within a tighter size range than the size range in which the MUSIG model applies. In addition, other studies have compared the inhomogeneous and homogeneous MUSIG models for vessel mixing with the homogeneous model, providing good results against experimental data [2].

We made four sets of simulations, with each set containing three different operating conditions, for a total of 12 simulations. Different setups were used to determine which options predict better results. The different setups used are summarized as follows:

- Setup 1: Compressible fluid for gas phase, second-order Rhie-Chow option for pressure-velocity coupling
- Setup 2: Incompressible fluid for gas phase, second-order Rhie-Chow option for pressure-velocity coupling
- Setup 3: Incompressible fluid for gas phase, fourth-order Rhie-Chow option for pressure-velocity coupling
- Setup 4: Incompressible fluid for gas phase, fourth-order Rhie-Chow option for pressure-velocity coupling, virtual mass, and enhanced turbulence using the Sato-enhanced eddy viscosity model

This article illustrates which setup provides better agreement with experimental data.

Oxygen Mass Transfer Rate

There are several theories for calculating the oxygen mass transfer coefficient, k_L. Sarkar and coauthors [3] used the following equation:

$$k_L = \frac{2}{\pi}\sqrt{D_O}\left(\frac{\varepsilon_L \rho_L}{\mu_L}\right)^{1/4} \qquad \text{Equation 1}$$

where D_O is the oxygen diffusivity in water, m^2/s; ε_L is the liquid turbulent eddy dissipation, m^2/s^3; μ_L is the liquid viscosity, Pa·s; and ρ_L is the liquid density, kg/m^3.

Others have used different mass transfer formulas, as shown in Equations 2, 3, and 4:

$$k_L = \frac{2}{\sqrt{\pi}}\sqrt{D_O}\left(\frac{\varepsilon_L \rho_L}{\mu_L}\right)^{1/4} \qquad \text{Equation 2 [2]}$$

$$k_L = 0.4\sqrt{D_O}\left(\frac{\varepsilon_L \rho_L}{\mu_L}\right)^{1/4} \qquad \text{Equation 3 [2]}$$

$$k_L = 0.5\sqrt{D_O}\left(\frac{\varepsilon_L \rho_L}{\mu_L}\right)^{1/4} \qquad \text{Equation 4 [4]}$$

Petitti and colleagues [5] state that the constant in front of $\sqrt{D_O}\left(\frac{\varepsilon_L \rho_L}{\mu_L}\right)^{1/4}$ is sometimes replaced with one that is tuned with experiments; this was the approach taken in our study. In Table 3 of Ranganathan and Sivaraman [2], it is the eddy cell theory, with a constant of 0.4, that provided the best k_L estimate against experimental data. We initially used this same 0.4 constant in our study to solve the models; then, the constant was adjusted so CFD $k_L a$ (see equation 5) matched experimental data for the benchmarking case (for each of the four different setups). The $k_L a$ constant for the other two simulations was then updated to that of the benchmarked $k_L a$ constant, and the percent difference between CFD and experimental $k_L a$ was determined.

The volume-averaged mass transfer coefficient is the product of k_L and the interfacial area, a, as shown in equation 5:

$$k_L a = k_L \frac{6\alpha_g}{d_{32}} \qquad \text{Equation 5 [3]}$$

where α_g is the gas volume fraction and d_{32} is the Sauter diameter, m.

Modeling Approach

The technique we used to model the rotating impellers is a frozen rotor method. The frozen rotor method keeps the impeller static and changes the frame of reference to capture the rotating impeller physics. This technique requires that the fluid volume within the vessel be divided in the following way:

1. A fluid volume that is assigned a rotation speed and encompasses the impeller (typically, a cylindrical volume). For multiple impellers, a single rotating volume can encompass all the impellers or several rotating volumes can be used, one for each impeller (see Figure 1).
2. A static volume for the vessel, which encompasses the vessel wall, free surface, air sparger, part of the impeller shaft, and baffles.

Assumptions

The following assumptions were made in our study:

1. The liquid was assumed to be water and exhibit water-like properties at 37°C (98.6°F), actual bioreactor temperature.
2. The air was assumed to be injected at a temperature of 26.7°C (80°F) and was modeled as an ideal gas (varying density) for one set of simulations and as an incompressible gas (constant density) for the other set of simulations.
3. As is common practice with these types of simulations, small components such as bolts and side ports were not modeled because these components were assumed to only affect the flow locally and have an insignificant influence on the overall flow structure. In addition, modeling of small components requires the mesh density to increase, thereby needlessly increasing the solver time.
4. The free surface was modeled as a horizontal degassing surface; thus, surface effects due to gravity were ignored. This assumption is reasonable when the vessel contains baffles because they eliminate any large rotating vortex structure that may develop at the center of the vessel due to the impeller(s). The degassing surface acts as a free-slip condition for liquid and allows gas to escape the surface.

Selected Conditions

We used the following conditions for this study:

1. The following properties were used:
   - A liquid density of 993.5 kg/m^3
   - A liquid viscosity of 0.0007 Pa·s
   - A liquid surface tension of 0.07 N/m
   - An air-to-water oxygen diffusion coefficient of 3.0×10^{-5} cm^2/s
2. A total of 10 bubble size groups were used for the population balance model based on an equal diameter distribution (i.e., bubbles increase in diameter by an equal amount).
3. Isothermal conditions were used because bioreactor temperature is actively controlled and temperature gradients should be minimal due to mixing.
4. To model turbulence, the two-equation k-ε model was used because it provides reasonable results for vessel mixing [6] with baffles.
5. All physical walls contained a no-slip condition for the liquid phase. A sensitivity study was performed for the gas-phase slip condition, and no significant difference in results was found; for the gas phase, a no-slip condition was also used.
6. The bubble breakup model was based on Luo and Svendsen [7], and the coalescence model was based on Prince and Blanch [8].
7. The Ishii-Zuber drag model [9] was used. This model accounts for bubble distortion and dense particle effects. The drag limits from small spherical bubbles and large spherical cap bubbles were also taken into account.

8. Turbulent dispersion forces were modeled and based on the Favre averaged drag model [10]. Turbulent dispersion allows bubbles to disperse from regions of high concentration to regions of low concentration due to turbulent fluctuations. A turbulent dispersion coefficient of 1.0 was used for the dispersion force because it is appropriate for dispersed fluids that are of low density relative to the continuous phase, as was the case in our study.
9. The high-resolution scheme was used for turbulence and advection. This scheme tries to use second-order numerics as much as possible. A sensitivity study was performed using first order for turbulence, and there was a significant difference in $k_L a$.

Bubble Diameter Exiting the Sparger

The initial bubble size out of the sparger was taken as uniform (a typical CFD approach for an air-sparged bioreactor) with a size that was calculated from equation 6 [3].

$$d_B = \left(\frac{6\sigma d_H}{g(\rho_L - \rho_G)}\right)^{1/3} \qquad \text{Equation 6}$$

where σ is the water surface tension, N/m; d_H is the sparger hole size, m; ρ_G is the liquid density, kg/m³; and ρ_G is the air density, kg/m³.

Because the bubble diameter is related to the one-third power of the sparger orifice diameter, the sparge orifice diameter would have to reduce by a factor of 8 to cut the exit bubble size by half. For our study, a sparger-exit air bubble diameter of 9.8 mm was calculated, and 10 different bubble size groups were used. The smallest bubble diameter modeled was 1.60 mm (group 1) and the largest was 16.40 mm (group 10). The bubble size between adjacent bubble groups increased in size by an equal amount of 1.64 mm (e.g., the bubble diameter in group 2 was 3.2 mm).

Air Mass Flow Rate and Density at Sparger

A total mass flow rate was specified at the sparger holes. The volumetric airflow rates provided in Table 2, later in this article, were referenced to a temperature of 0°C (32°F) and pressure of 1 atmosphere, representing normal flow conditions (European standard). The appropriate mass flow rate was determined by multiplying the volumetric flow rate by the air density at 0°C and 1 atmosphere of pressure, which is taken to be 1.295 kg/m³. The following is an example of this calculation:

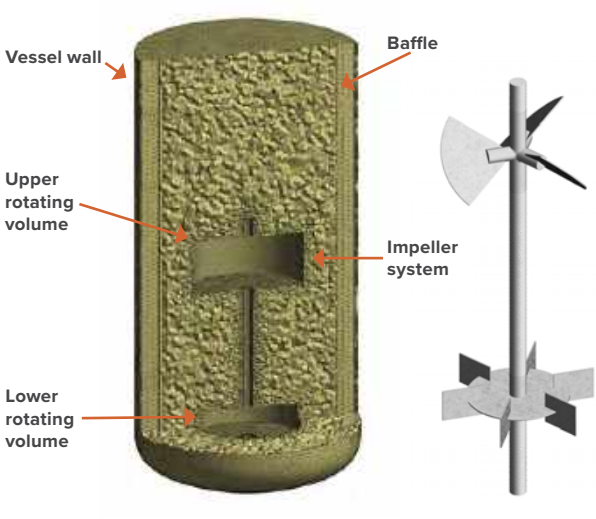
Mass flow rate = 200 L/min × (m³/1,000 L) × 1.295 kg/m³ = 0.259 kg/min

The density at normal conditions was only used to determine the mass flow rate out of the sparger; however, this did not represent the actual density of the air coming out of the sparger. The air density coming out of the sparger was based on an assumed temperature of 26.7°C (80°F) and accounted for vessel pressure along with hydrostatic head. The ideal gas law was used to calculate density, which for air is shown in equation 7:

$$\rho_G = \frac{P}{287\,T} \qquad \text{Equation 7}$$

where P is the absolute pressure, Pa, and T is the air temperature, K.

Figure 1: Fluid volume mesh (left) and impeller surface mesh (right).



For this study, a sparger-exit air density of 1.662 kg/m³ was calculated. This density was used to compute the initial mass of the bubbles exiting the sparger. For the compressible gas model, ANSYS automatically calculates the changing density within the vessel due to pressure variations.

Mesh Independence Solution

An unstructured mesh using tetrahedral elements was used with mesh inflation. The final mesh parameters were set by performing a mesh independence study on the volumes surrounding the impellers, and literature available in the public domain was used to set the vessel mesh. Figure 1 illustrates the mesh used for final simulations.

The mesh included inflation layers at solid surfaces and was adjusted to provide an area average y+ value of approximately 30. Three inflation layers were used, with a default growth rate of 1.2 (i.e., successive inflation layers are 20% thicker). The y+ values were monitored individually for the top impeller, bottom impeller, and vessel. The mesh independence study performed by Sarkar and colleagues [3] was leveraged for the nonrotating vessel mesh. This reference achieved mesh independence with 1.24 million elements for a CFD model that contained three impellers. Within our study, the static vessel volume alone was meshed with approximately this number of elements (1.2 million elements), so it was assumed that mesh independence was achieved for the vessel volume; this approach is considered conservative. If one wished to speed up the solver progress, it might be possible to coarsen the nonrotating vessel mesh and

Table 1: Mesh study for simulation 3 (incompressible).

Parameter	Run 1	Run 2	Run 3
Vessel elements	1,168,768	1,168,768	1,168,768
Top impeller elements	305,292	547,739	915,661
Bottom impeller elements	236,710	413,539	714,283
Total elements	1,710,770	2,130,046	2,798,712
Gas holdup (%)	0.52	0.52	0.51
k_La (hr^{-1})*	7.7	8.0	8.1
Torque (N/m)	79.6	80.5	82.3
Sauter diameter (mm)	3.6	3.6	3.6

*k_La shown is based on using a 0.4 constant.

still get accurate results. Although we did not perform a mesh independence study on the static vessel volume, a mesh sensitivity study was performed on the rotating impeller volumes using setup 2 (incompressible gas model with second-order pressure-velocity coupling) for simulation 3 (see Table 2, later in the article, for operating parameters). Table 1 shows the results of this study.

Three mesh sensitivity runs were performed, which included increasing the mesh density of the individual impellers by approximately 70% when going from run 1 to run 2 and again when going from run 2 to run 3. From the various outputs (e.g., k_La, torque) shown in Table 1, it seemed that mesh independence was achieved with the mesh of run 2, although the torque seemed to move up with each run. In reality, the torque, as well as many other parameters, fluctuated in a tight range, and there was no significant difference in torque when the fluctuations were considered.

The k_La values for the individual (impeller and vessel) volumes and for the overall volumes were tracked throughout the solver run. The overall k_La shifted higher from run 1 to run 2, but it remained approximately the same from run 2 to run 3. The k_La displayed evidence of monotonic convergence, where the difference in k_La between runs 2 and 3 was negligible and much smaller than the difference between runs 1 and 2. It is unlikely that further mesh refinement would change the k_La value; thus, it was assumed that mesh independence had been reached.

The k_La for the top impeller shifted an insignificant amount when going from run 1 to run 2 and remained the same when going from run 2 to run 3. For the bottom impeller, the k_La jumped slightly when going from run 1 to run 2, and again when going from run 2 to run 3; however, the k_La from run 3 trended back down to approximately the same level as run 2.

For conservatism in subsequent simulations:

- The bottom impeller mesh from run 3 was used (although the coarser mesh from run 2 could also have been used); and
- The top impeller mesh from run 2 was used—except in simulation 3, which used the top impeller mesh from run 3. Note that this likely did not impact the results because the k_La was practically unchanged between run/mesh 2 and run/mesh 3.

This translated to a total of 2,430,790 mesh elements being used for the subsequent runs of simulations 1 and 2 and a total of 2,798,712 mesh elements for subsequent runs of simulation 3.

RESULTS

Figures 2 and 3 show the air volume fraction and oxygen transfer rate distributions, respectively, for all final simulations. The differences between the noncompressible and compressible second-order pressure-velocity coupling runs are not as significant as the differences between the fourth-order and second-order pressure-velocity coupling runs. This is not surprising because fourth-order numerics will capture more detail. The air volume fraction figures (Figure 2) show evidence that flooding occurred for simulation 1, which was operating at 25 RPM and 200 NLPM (see Table 2) because the impellers were not properly dispersing the gas phase; regions in blue contained little to no gas.

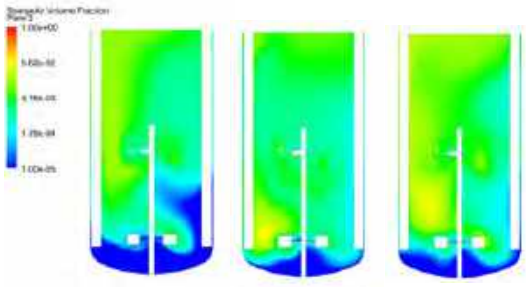
Convergence

We tracked residuals, various outputs (e.g., forces, Sauter diameter, k_La), and imbalances during the solver run for insight into convergence. Residual root mean square (RMS) levels typically fell below 5E-3 for all equation classes (e.g., momentum, mass, bubble-size fraction), although not all equation classes fell below RMS values 1E-4. Other researchers encountered similar high residual levels for these types of simulations [2, 3, 6]. We also used double precision and found no noticeable improvement for lowering residual values.

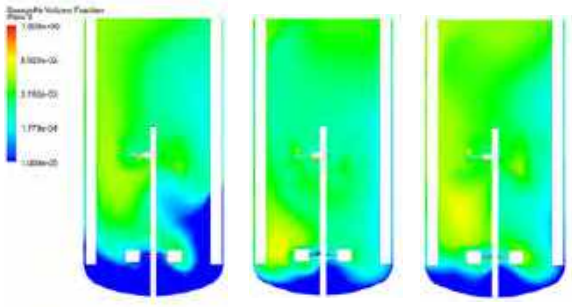
We tracked all imbalances, and most equation classes bounced around an imbalance of zero. Typical CFD guidance suggests that all imbalances are less than 1% before a solution can be considered converged; however, for these simulations, this was not possible

Figure 2: Air volume fraction for simulations 1 (left), 2 (middle), and 3 (right) in four setups.

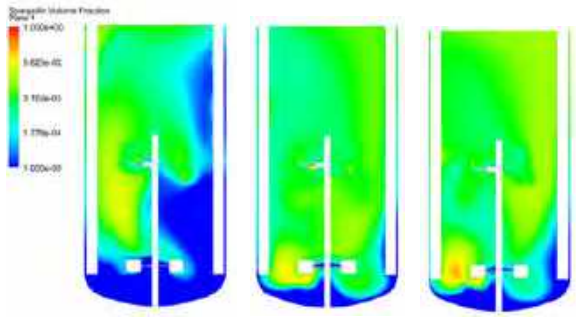
Setup 1: Compressible second-order pressure-velocity.



Setup 2: Incompressible second-order pressure-velocity.



Setup 3: Incompressible fourth-order pressure-velocity.



Setup 4: Incompressible fourth-order pressure-velocity, virtual mass, enhanced turbulence.

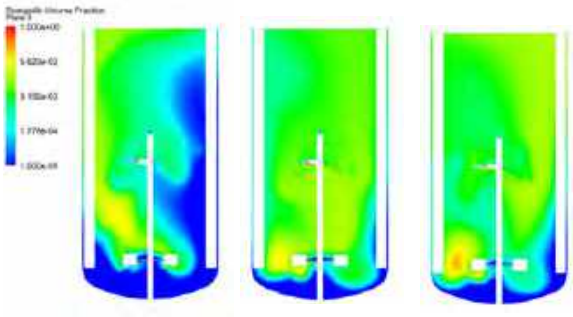
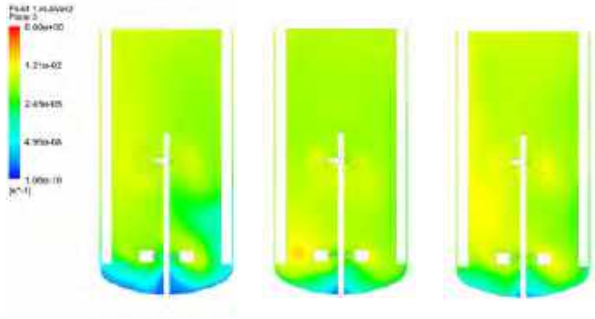
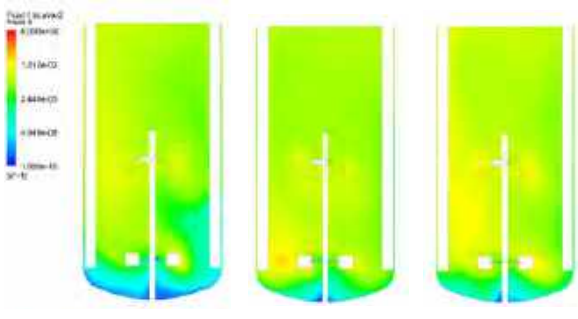


Figure 3: Oxygen transfer rate, $k_L a$ (sec^{-1}) for simulations 1 (left), 2 (middle), and 3 (right) in four setups.

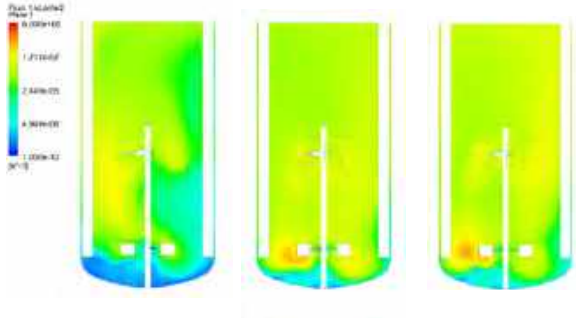
Setup 1: Compressible second-order pressure-velocity.



Setup 2: Incompressible second-order pressure-velocity.



Setup 3: Incompressible fourth-order pressure-velocity.



Setup 4: Incompressible fourth-order pressure-velocity, virtual mass, enhanced turbulence.

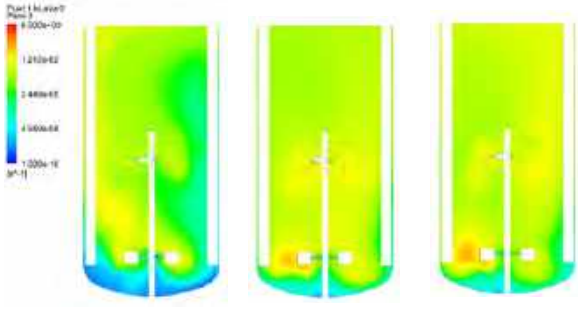


Table 2: CFD versus experimental data for two bioreactors.

Simulation No.	Impeller Speed (RPM)	Sparge Air Rate (NLPM)	Experimental k_La (hr^{-1})	CFD k_La (hr^{-1})	% Difference
Setup 1: Compressible second-order pressure-velocity					
1**	25	200	4.25	4.10	3.4
2**	38	200	10.33	7.06	31.6
3*	38	400	12.43	12.43	0.0
Setup 2: Incompressible second-order pressure-velocity					
1**	25	200	4.25	4.22	0.6
2**	38	200	10.33	7.14	30.8
3*	38	400	12.43	12.43	0.0
Setup 3: Incompressible fourth-order pressure-velocity					
1**	25	200	4.25	4.14	2.4
2**	38	200	10.33	8.96	13.2
3*	38	400	12.43	12.43	0.0
Setup 4: Incompressible fourth-order pressure-velocity, virtual mass, enhanced turbulence					
1**	25	200	4.25	4.06	4.5
2**	38	200	10.33	9.47	8.3
3*	38	400	12.43	12.43	0.0
New bioreactor using setup 4					
1*	41	250	5.76	5.76	0.0
2**	28	158	2.27	2.18	4.0
3**	28	250	4.35	3.68	15.4
4**	28	333	5.90	4.97	15.9

*Benchmarked case
**Predicted case

because it was typical for some equation classes to bounce around at ±5%.

In all the simulations, the steadiness of various output parameters (e.g., forces, k_La, gas holdup) was tracked for a prediction on convergence. A time-step size no larger than 0.01 seconds was used for all final simulations, although one must initially use a much smaller time step (such as 1E-5 sec) to avoid crashing the linear solver. This time step is then steadily increased up to 0.01 seconds as the solution progresses. The time step acts as a relaxation factor for steady-state ANSYS CFX simulations, and one may have to experiment with it for each unique model.

DISCUSSION

Because only k_La experimental results were available, this was the only parameter that was compared between CFD simulations and experimental data. Simulation 3 was used as the benchmarking case to adjust the k_La constant so its k_La matched experimental data. Benchmarking required for the k_La constant to be updated

from 0.4 to 0.53 for setup 1, from 0.4 to 0.58 for setup 2, from 0.4 to 0.53 for setup 3, and from 0.4 to 0.50 for setup 4.

After discovering setup 4 (i.e., incompressible, fourth-order pressure-velocity coupling, virtual mass, enhanced turbulence) provided for the most accurate results, we applied this setup to a completely different bioreactor, which had a different working volume, dual-pitched blade impellers, and a different gas sparger design. A mesh independence study for this bioreactor was not performed. Instead, this bioreactor was meshed with a total of 2,548,980 elements using a similar mesh-sizing approach as the previous bioreactor model. The bottom impeller volume was meshed with 563,407 elements, the top impeller volume was meshed with 591,214 elements, and the vessel was meshed with 1,394,359 elements. The predicted results were similar in that k_La was predicted accurately (within 16%), this time using a k_La constant of 0.4 from the benchmarked case. Table 2 shows the CFD versus experimental data for both bioreactors.

As can be seen in Table 2, CFD correctly predicted the k_La trend with setup 4, with the best agreement against experimental data (within 16%). Further, CFD visually illustrated the local k_La and gas fractions, providing valuable insight into potential design and process improvements.

CONCLUSION

The difference between the compressible and incompressible second-order models was minor, with the incompressible model providing slightly better results with experimental data. This result is counterintuitive because the air bubbles change density as they travel toward the free surface. The incompressible fourth-order pressure-velocity coupling models offered a better comparison against experimental data, with the virtual mass and enhanced turbulence (Sato) model predicting results within 16% of experimental data, tested on two different bioreactors; however, CFD underpredicted k_La.

Although experimental data were used for benchmarking, applying this method (i.e., setup 4) does not require experimental data if the purpose is to determine what operating conditions (i.e., impeller speed and sparge rate) will maximize mass transfer for a fixed-system geometry. One can just use a k_La constant of 0.4 (or any other reasonable value) to gauge the relative difference in performance between operating conditions. The method described here shows that good CFD results are achieved even for a flooding scenario and with high residual values, as long as the various variables of interest have shown a plateau.

The results of this study demonstrate that CFD can be valuable for predicting bioreactor mass transfer performance and for optimization purposes, provided the model is setup appropriately.

References

1. Talaia, M. A. R. "Terminal Velocity of a Bubble Rise in a Liquid Column." *World Academy of Science, Engineering and Technology International Journal of Physical and Mathematical Sciences* 1, no. 4 (2007): 220–224.
2. Ranganathan, P., and S. Sivaraman. "Investigations on Hydrodynamics and Mass Transfer in Gas–Liquid Stirred Reactor Using Computational Fluid Dynamics." *Chemical Engineering Science* 66, no. 14 (2011): 3108–3124. doi:10.1016/j.ces.2011.03.007
3. Sarkar, J., L. K. Shekhawat, V. Loomba, and A. S. Rathore. "CFD of Mixing of Multi-Phase Flow in a Bioreactor Using Population Balance Model." *Biotechnology Progress* 32, no. 3 (2016): 613–628. doi:10.1002/btpr.2242
4. Taniguchi, S., S. Kawaguchi, and A. Kikuchi. "Fluid Flow and Gas-Liquid Mass Transfer in Gas-Injected Vessel." Presented at the Second International Conference on CFD in the Materials and Process Industries. CSIRO, Melbourne Australia. 6–8 December 1999.
5. Petitti, M., M. Vanni, D. L. Marchisio, A. Buffo, and F. Podenzani. "Simulation of Coalescence, Break-up and Mass Transfer in a Gas–Liquid Stirred Tank with CQMOM." *Chemical Engineering Journal* 228 (2013): 1182–1194. doi:10.1016/j.cej.2013.05.047
6. Aubin, J., D. F. Fletcher, and C. Xuereb. "Modeling Turbulent Flow in Stirred Tanks with CFD: The Influence of the Modeling Approach, Turbulence Model and Numerical Scheme." *Experimental Thermal and Fluid Science* 2, no. 5 (2004): 431–445. doi:10.1016/j.expthermflusci.2003.04.001
7. Luo, S. M., and H. Svendsen. "Theoretical Model for Drop and Bubble Breakup in Turbulent Dispersions." *AIChE Journal* 42, no. 5 (1996): 1225–1233. doi:10.1002/aic.690420505
8. Prince, M., and H. Blanch. "Bubble Coalescence and Break-Up in Air-Sparged Bubble Columns." *AIChE Journal* 36, no. 10 (1990): 1485–1499. doi:10.1002/aic.690361004
9. Ishii, M., and N. Zuber. "Drag Coefficient and Relative Velocity in Bubbly, Droplet or Particulate Flows." *AIChE Journal* 25, no. 5 (1979): 843–855. doi:10.1002/aic.690250513
10. Burns, A. D. B., T. Frank, I. Hamill, and J. M. Shi. "The Favre Averaged Drag Model for Turbulent Dispersion in Eulerian Multi-Phase Flows." Presented at the 5th International Conference on Multiphase Flow, ICMF-2004, Yokohama, Japan.

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About the authors

Elijio Prado is a Senior Mechanical Engineer for ADVENT Engineering, a Trinity Consultants Company, which is an engineering and compliance solution provider to the life sciences industry. He received his BS in mechanical engineering from California Polytechnic State University and his MS in mechanical and aeronautical engineering from the University of California, Davis. Elijio has 18 years of experience working in the biopharmaceutical and energy industry and is a registered professional mechanical engineer in the states of California and Washington. His background spans biopharmaceutical projects that include validation, commissioning, bioreactor studies, and quality assurance. His mechanical engineering projects include mechanical equipment sizing, analysis, design and testing. Elijio was first introduced to the world of CFD approximately 15 years ago and has used CFD to study various physical processes, including heat transfer, fluid flow, and mass transfer.

Albert Dyrness is the Managing Director of ADVENT Engineering, a Trinity Consultants Company. Albert has more than 20 years of experience in process engineering and consulting. He is a member of the American Society of Mechanical Engineers Bioprocess Equipment (ASME BPE) Standards Committee and the Chairperson for the ASME BPE System Design Subcommittee. Albert received an MS in mechanical engineering from Massachusetts Institute of Technology and holds professional engineering licenses in the state of California for chemical engineering and mechanical engineering. He has been an ISPE member since 1997.

SELF-CALIBRATING THERMOMETERS

for Use in Medical Autoclaves

By Fritz Röder and Dietmar Saecker

A temperature sensor in a medical autoclave is typically calibrated once a year. If the sensor proves to be inaccurate, all batches produced since the last calibration must be evaluated. Endress+Hauser has developed a self-calibrating sensor that automatically verifies its accuracy during each sterilization batch. This article describes a case study at the Merck Healthcare KGaA sterile facility in Darmstadt, Germany, using the new sensor in a steam sterilizer and corresponding risk and benefit considerations for possible routine use of this type of sensor in pharmaceutical applications.

Pharmaceuticals intended for injection into the human body or for implantation must be sterile. It is common knowledge that sterility is always a probabilistic attribute, not absolute. Sterility of a product means the theoretical probability of a nonsterile unit (PNSU) must be less than 10^{-6}. To guarantee this level of sterility assurance, the materials may undergo different types of sterilization processes. According to EMA [1] and US Pharmacopeia [2] guidelines, steam sterilization is the preferred method when the material to be sterilized is capable of withstanding these high temperatures.

Typical sterilization processes employ temperatures around 121°C. The steam sterilization process is conducted as follows: Air is removed from the autoclave during consecutive prevacuum stages. A supply of saturated steam is then introduced into the process chamber under pressure to heat the products to approximately 123°C for more than 15 minutes (to always be above the desired 121°C). If temperatures in the sterilization process are not verified to be accurately measured, it cannot be determined whether the autoclave functions as it should. For that reason, calibration of temperature sensors is essential.

Mechanical impact on the temperature sensor can significantly affect its measuring accuracy. For example, the thermometer could be mechanically damaged when goods are pushed onto the carriage if the products slip during loading or unloading and remain suspended on the slightly protruding temperature sensor. Regular, automatic calibration for each batch (i.e., each time goods are loaded/unloaded) would eliminate the risk of this error remaining undetected for a long period.

SELF-CALIBRATING SENSOR FUNCTIONALITY

The sensor in this study (specifically, an iTHERM TrustSens TM371) employs a self-calibration method that uses the Curie temperature (T_c) of a reference material as the built-in temperature reference. The reference material in the sensor is not subject to change due to its properties and because this fixpoint cell is protected inside the sensor itself. Because the T_c of the reference material is a constant, it is used as the calibration reference.

Figure 1: Diagram of the self-calibrating sensor showing the optimal cooling rate for calibration.

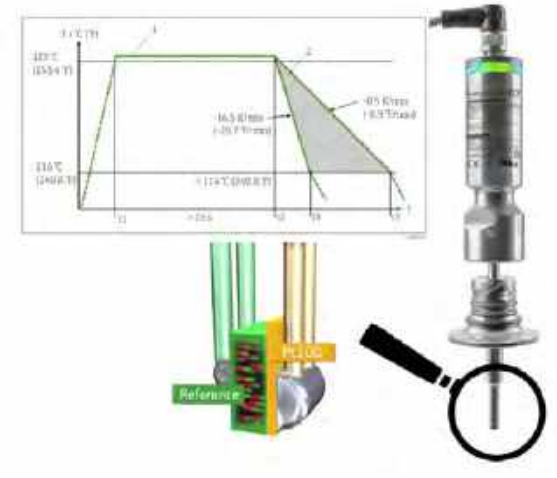
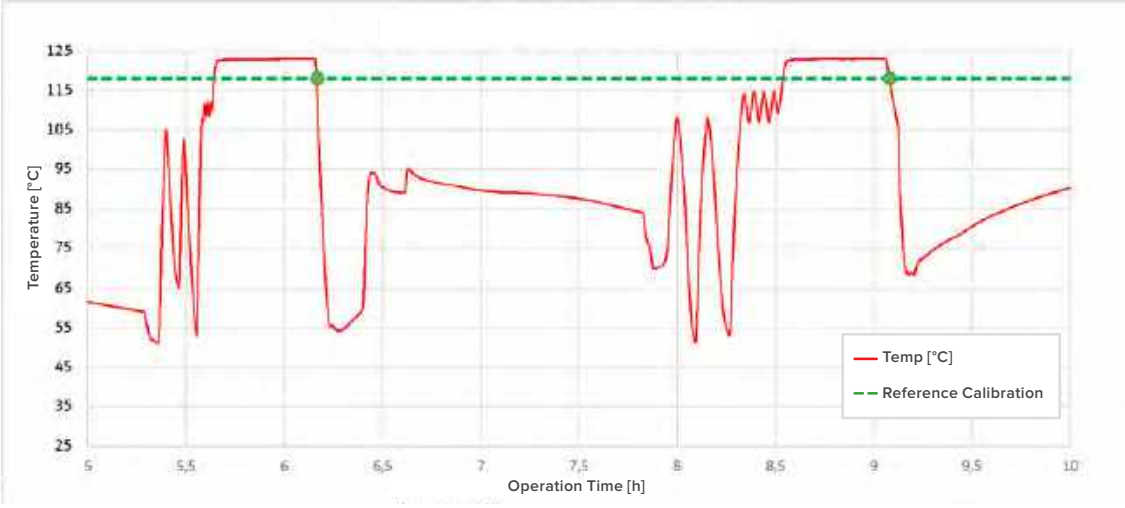


Figure 2: A typical temperature profile for two consecutive batches, including calibration.



Once the reference material reaches the T_c, the material undergoes a phase change associated with a change in its electrical properties (capacity). The self-calibrating sensor's electronics unit detects this change in properties automatically and compares the temperature measured by a Pt100 sensor—a resistance temperature detector with a resistance (R) of 100 ohms at 0°C—with the known T_c (Figure 1).

Self-calibration is performed automatically when the process temperature (T_p) drops below the nominal T_c of the device. A flashing green LED indicates that the self-calibration process is in progress. Once complete, the thermometer's electronics unit saves the calibration results.

This in-line self-calibration makes it possible to continuously and repeatedly monitor changes to the properties of the Pt100 sensor and the electronics unit. Because the in-line calibration is performed under real ambient or process conditions (e.g., heating of the electronics unit), the result is more closely aligned with actual function than a sensor calibration performed under laboratory conditions.

Self-calibration is verified directly in the thermometer's terminal sensor head, which can be accessed from outside of the autoclave. The sensor's measuring signals (T_p, number of calibrations completed, and the calibration deviation factor) can be transferred directly to the process control system or to a suitable data manager capable of handling data in accordance with data integrity requirements.

A calibration certificate can be automatically created for the self-calibration. The automatically generated calibration certificate can be assigned to every sterilization batch, providing not only documentary proof that the temperature sensor is functioning correctly at that particular time but also evidence of the sterility of the batch, given sufficient exposure time. Self-calibration is only completed if the temperature at the sensor also reaches the required sterilization temperature.

CASE STUDY METHODS AND FINDINGS

The study was conducted using the self-calibrating sensor in a steam sterilizer for a period of about four weeks. During this time, about 80 successful calibrations were performed, which means there were nearly two batches and two calibrations performed each day.

To facilitate the most efficient calibration procedure possible, a slow temperature change in the process is required. As shown in Figure 1, the optimum cooling rate for sensor calibration lies between –0.5 K/min and –16.5 K/min. In the case of the steam sterilizer, the calibration point of the self-calibrating sensor was 118°C, which is very close to the T_p of 123°C (see Figure 2); therefore, the automatic calibration was performed in the working range of the desired sterilization process parameters. The temperature elevated through the calibration point of 118°C before the sterilization period and passed it again during the cooling phase after sterilization. The cooling phase was chosen to perform calibration because the temperature change is slower during cooling.

Typically in a steam sterilizer, four to six temperature sensors are installed in different locations and for different purposes. For the study, the self-calibrating sensor was installed at the coldest point in the autoclave, next to an existing sensor to establish a second temperature reference (see Figure 3). During qualification of a sterilizer, temperature mapping is usually carried out to determine the worst positioning of the sensor. In the case study, this position was on the chamber floor near the door.

Figure 3: Position of the temperature sensor inside the sterilizer. Reprinted with permission from Merck Healthcare KGaA Darmstadt. T indicates the thermometer; C is carriage.

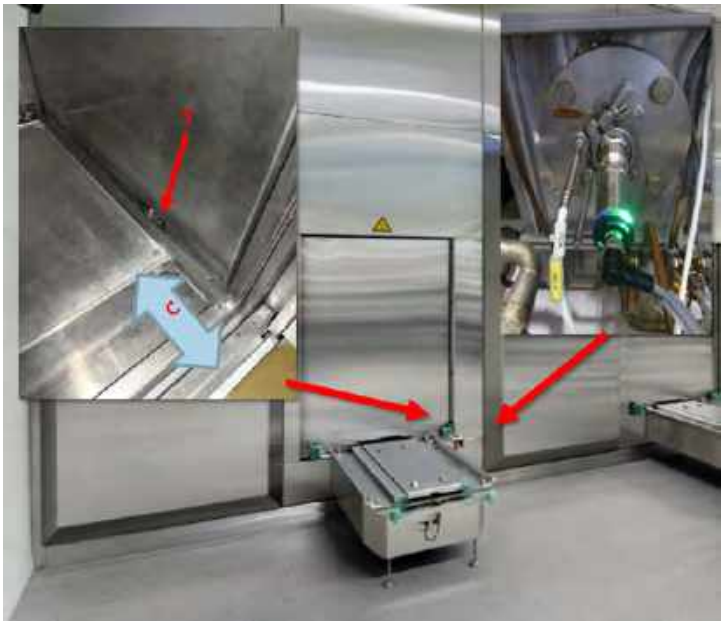
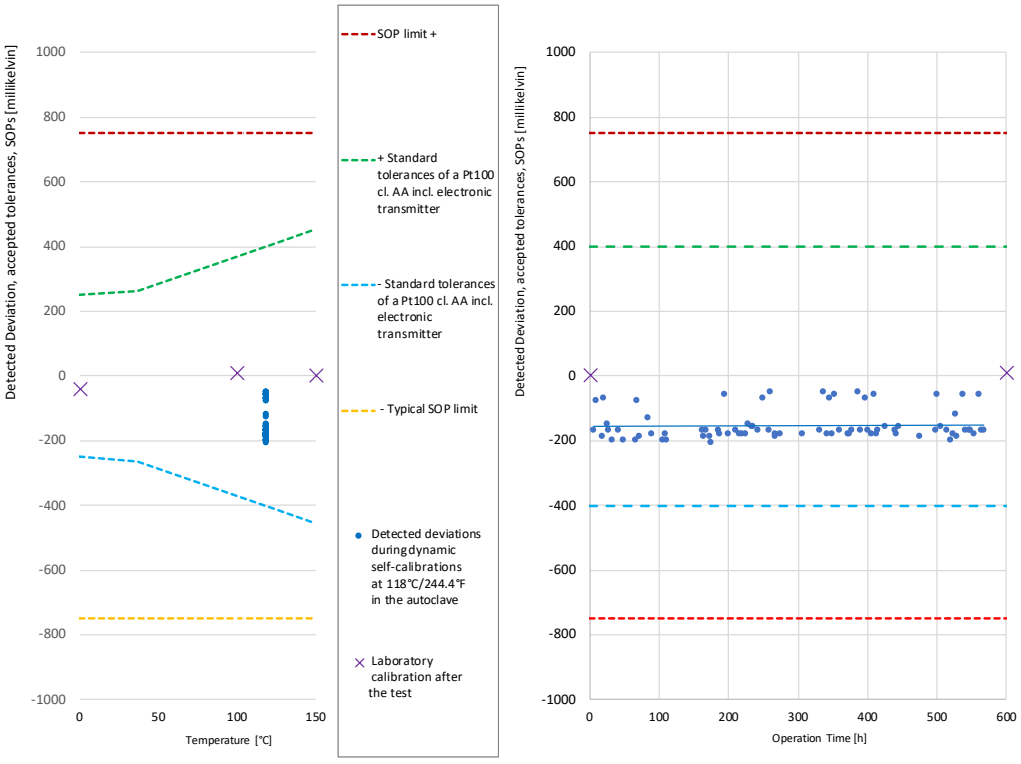


Figure 4: Calibration results of self-calibration vs. temperature and time related to standard operating procedures (SOPs) and conventional standards.



Upon completion of the study, all data were collected and analyzed. In addition, the probe was calibrated in an accredited calibration lab before and after the study.

All 80 performed calibrations were successful, and the sensor accuracy was within specified limits (see Figure 4). The 80 calibration results were more accurate than a class AA Pt100 sensor [3], considering that a state-of-the-art digital temperature transmitter adds another uncertainty of ±0.1 K.

Neither the laboratory calibrations before and after the test nor the trendline of the automatic calibrations showed any significant signs of wear or drift. Overall, the study was considered as successful and the sensor was found suitable for sterilization processes.

INCREASED PRODUCT SAFETY

Our study showed that 80 automatic calibrations can be generated in 600 operation hours. If the critical temperature sensor is working as expected, that would lead to more than 1,100 calibrations per year, not including the manual standard calibration completed periodically (e.g., once a year) according standard operating procedures (SOPs).

Calibration automatically performed with every batch ensures that a damaged thermometer is promptly detected. If the sensor verifies its accuracy and the calibration counter has increased, this indicates that the sterilization was successful. However, if the thermometer gives incorrect results, a warning message is generated by the self-calibrating sensor to immediately indicate a problem, informing the user that the actual product batch might not be fully sterilized and must not be used in further production until a second sterilization cycle has taken place (assuming a second cycle is possible).

In contrast, if normal calibration intervals used in conventional systems (e.g., once a year) are used, a thermometer identified as faulty after a manual calibration cannot be linked to a single batch. Instead, all batches that have been sterilized since the last calibration event have to be incorporated into the deviation investigation. This results in complex root-cause analyzes and, at worst, product recalls, causing considerable expense and damage to the brand.

TRADITIONAL VS. AUTOMATED PROCEDURES

Notably, traditional calibration conducts testing at three points, whereas the automated procedure employs one-point calibration. These approaches are discussed in the following sections.

Automatic Detection of Sensor Drifts

At T >0°C, the characteristic relationship between the raw signal (resistance) and the temperature of every Pt100 sensor follows the Callendar–van Dusen equation [3]:

$$R(T) = R(0)\,[1 + A \times T + B \times T^2]$$

where T is measured in °C.

As the name of the Pt100 sensor suggests, the average value $R(0)$ for the sensor is 100 ohm at 0°C; additionally, each self-calibrating thermometer is calibrated during the production process to individually determine the exact values for A, B, and $R(0)$. This delivery state is recorded electronically.

As long the Pt100 sensor is not broken (wire-cut or short-circuited), it follows this equation. But for a "bad" (already drifted) sensor, the value of at least one parameter—$R(0)$, A, or B—has changed. In every case, this will change not only a single temperature but also the complete characteristic curve.

The principle of the one-point automatic calibration is as follows: If a significant deviation between the Pt100 temperature and a reference temperature (which was not 0°C) is detected, the thermometer cannot be accurate at any other temperature, which is also not 0°C. To avoid the risks of undetected drifts, the self-calibrated thermometer will alert operators about the malfunction.

Conversely, the following principle also applies: If the thermometer does not show any significant change in the calibration deviation at the reference point, it is extremely unlikely that the parameters of the equation have changed since the previous calibration. With unchanged values for $R(0)$, A, and B, the thermometer is not only accurate at the calibration point but also measures all other temperatures as accurately as it did previously.

One-Point Self-Calibration Measurement Uncertainty

An analysis conducted by Technische Universität Ilmenau (TU Ilmenau) verifies how a deviation at 118°C affects the entire measuring range [4, 5]. Calibration uncertainty at T_c of ±0.35 K was certified by the German technical inspection association TÜV [6]. Additionally, TÜV examined the calibration process as part of a study. In particular, they analyzed more than 24,000 calibrations [7], and none of the results analyzed presented a deviation of more than 0.2 K.

Manual Calibration Measurement Uncertainty

To definitively assess the in-process self-calibration procedure, it is advisable to take a closer look at the method commonly used today. To check the accuracy of thermometers for hygienic applications, companies often use dry block calibrators for onsite calibration. Three temperature points are usually used in this process. However, thermometers in this industry usually have quite a short immersion length, as thin pipes or agitators in tanks only offer limited space for installation, and this means that there is often a significant physical distance between the point where a reference thermometer measures the temperature of the calibrator and the position of the sensor to be tested.

To determine the uncertainty of measurement that a calibration of this kind can have, it is advisable to refer to the website of a national accreditation institute, such as Deutsche Akkreditierungsstelle GmbH (DAkkS) in Germany. The directory of accredited bodies also lists numerous companies specialized in performing onsite calibrations.

We suggest the accredited calibration laboratory TEMEKA GmbH (DAkkS D-K-15024-01-00) in Germany as a benchmark. This company does not produce measuring instruments itself but is specialized in performing calibrations onsite at its customers'

Table 1: Comparison of calibration methods.

	Offline Three-Point Manual Calibration	In-Process One-Point Self-Calibration	Dynamic Control of Manual Calibration Interval, Triggered by Self-Calibration Results
Positives	• Well-known and established method. • No change of SOP documents.	• No deinstallation or process interruptions are required. • Sensor failures can be detected with every batch. • After detection of thermometer drift, the number of batches produced with a "bad" sensor = 1 (i.e., the product that was in the autoclave).	• Manual calibration interval can be extended, but an additional calibration will be performed immediately if sensor shows a significant tendency to drift toward a SOP limit or if detected deviation changes suddenly. • Sensor failures can be detected with every batch. • After detection of thermometer drift, the number of batches produced with a "bad" sensor = 1 (i.e., the product that was in the autoclave). • GMP rules do not prescribe specific calibration intervals (e.g., 12 months), although length of intervals must be justified.
Negatives	• No chance to identify sensor drift between two manual calibrations. • Frequent deinstallation with process interruption is required. • After drift detection, the number of batches produced before is unknown.	• Method is new and must be explained to the inspectors. • SOP documents must be changed.	• Self-calibration method is new and must be explained to the inspectors.
Operating expense	• No effect.	• High cost-saving effect.	• Medium cost-saving effect.

premises. According to the accreditation certificate, the company uses dry block calibrators to check resistance thermometers [8]. These specialists reach ±0.75 K as the accredited best measurement capability in the sterilization temperature range. For the industry user, this raises the following questions:

- Can a calibration in the dry block calibrator, which is performed by the user, be more accurate than calibration completed by specialists?
- Was this calibration uncertainty value already included into the SOP limit for the acceptable deviation of a thermometer?
- Would an in-process one-point calibration provide more accuracy than an offline three-point calibration?

A direct comparison reveals the following: Given its far lower uncertainty of measurement, an in-process single-point calibration (±0.35 K) provides a more reliable statement of conformity than a manual check performed at three points using a dry block calibrator (±0.75 K), particularly for the critical temperature range around the sterilization temperature; this conclusion is especially true if we consider whether calibration is performed manually once a year or automatically for every cleaning process. Table 1 outlines the advantages, disadvantages, and operating expenses identified when comparing in-process one-point calibration and offline three-point calibration as well as a third method in which the manual calibration interval is triggered by self-calibration results.

ENHANCED FUNCTIONALITY

Self-calibrating thermometers that are connected to a modern process control system or data manager can provide other data in addition to temperature measurement values. Using the HART protocol, it is also possible to collect "calibration counter" and "last recorded calibration deviation" values.

When these values are continuously queried, an alarm can be generated if the calibration deviation exceeds an established limit. The date and time of the calibration can be checked in a connected system (e.g., process control system or data manager) because the deviation is marked at the moment when the calibration counter increases by 1. With this technology, it is possible to generate an online calibration certificate that can be viewed any time on site or in the network.

PROCESS SAFETY AND AUDIT RELIABILITY

SOPs and the Change Management Process

Many companies have established SOPs that stipulate a three-point calibration for thermometers. Such SOPs reflect the current

state-of-the-art method used to obtain the clearest possible temperature curves for calibration. This approach aligns with expectations of auditors and regulatory authorities because there was no alternative until now.

Notably, the biggest risks for a thermometer in a hygienic system arise from the conventional calibration process itself. Opening the devices, removing the insert, connecting and disconnecting electrical contacts, introducing the thermometer into the calibrator, or transporting the thermometer to the laboratory increases the likelihood of mechanical damage, such as from impact. Furthermore, it is often unclear what is the best way to return the measurement to the exact same measuring position in the process after removing the insert for calibration purposes. With the in-process single-point calibration temperature sensor, these risks are reduced because the sensor stays in one position while being self-calibrated.

Data integrity risks related to the self-calibrated sensor were assessed prior to starting the study, and no potential data integrity breaches could be identified [9, 10]. All data are stored directly in the sensor, and after each calibration, a PDF calibration report is automatically generated and can be stored in a protected and compliant manner.

Continuous Process Verification

In recent years, the life-cycle model has been adopted in regulatory landscapes all over the world. The shift from the traditional process validation approach to continuous process verification (CPV) is evident in the US [11], EU [12], and elsewhere. Because the new calibration technology strongly increases process control, it supports the CPV approach. In-process single-point calibration reduces the risk of a deviation going undetected until the next calibration to the absolute minimum level possible with current technology. This is achieved without compromising calibration accuracy.

In addition, any calibration deviation with the new sensor would only affect a single batch (the one inside the sterilizer at the time of deviation), and the equipment can immediately generate an alarm. With the traditional approach, all batches since the last calibration (probably one year ago) would be subject to the investigation. In addition, many of the products processed in the compromised sterilizer could have already been administered to patients.

The ISPE Pharma 4.0™ Special Interest Group (SIG) launched its Pharma 4.0™ operating model, which describes the digital maturity of a company and the traceability of information. With the addition of self-calibration, traceability and trust of sensor-generated information about temperature are enhanced. If other process parameters could also self-calibrate, that would provide benefits for the process analytical technology concept and real-time release testing.

CONCLUSION

The study conducted using the sterilizer at Merck Healthcare building PH50 in Darmstadt, showed successful results concerning the implementation of a self-calibrating thermometer in sterilization processes. The overall process control was increased, which should be a main goal for any pharmaceutical company.

Some considerations regarding cost have been assessed. For a typical application, the return on investment should be reached after approximately 1.5 years, assuming all temperature sensors for one sterilizer are replaced with self-calibrating temperature sensors.

Important topics for future discussion include overall risk and the comparison of the batch-wise one -point calibration to the traditional approach. Opinions from regulatory representatives on the future outlook of this new process would be appreciated.

References

1. European Commission. "EudraLex Volume 3: Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container." 6 March 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-sterilisation-medicinal-product-active-substance-excipient-primary-container_en.pdf
2. United States Pharmacopeia. USP Chapter <71>: Sterility Tests.
3. International Electrotechnical Commission. "International Standard: IEC 60751:2008—Industrial Platinum Resistance Thermometers and Platinum Temperature Sensors." 17 July 2008. https://webstore.iec.ch/publication/3400
4. Schalles, M. "Kalibrierung von Thermometern in situ im Prozess [Calibration of Thermometers In Situ in the Process]." Technische Universität Ilmenau, Lecture at Dresdner Sensor-Symposium, 4–6 December 2017. http://www.ama-science.org/proceedings/details/2718
5. Vrdoljak, P., and M. Schalles. "In situ Einpunktkalibrierung von Thermometern mittels Fixpunkten [In Situ One-Point Calibration of Thermometers Using Fixed Points]." In *Messunsicherheit praxisgerecht bestimmen und Prüfprozesse in der industriellen Praxis [Determine Measurement Uncertainty in a Practical Manner and Test Processes in Industrial Practice].* Düsseldorf, Germany: VDI Verlag GmbH, 2017.
6. TÜV Thüringen. *"Measuring Uncertainty of the In-Situ Calibration."* Certificate 3610-0013-17-B05. 2017.
7. TÜV Thüringen. *"Validation of the In-Situ Calibration Process."* Certificate 3610-0013-17-B1. 2017.
8. Deutsche Akkreditierungsstelle GmbH. *"Anlage zur Akkreditierungsurkunde D-K-15024-01-00 nach DIN EN ISO/IEC 17025:2005 [Annex to the Accreditation Certification of Calibration Body D-K-15024]."* 15 October 2019. https://www.dakks.de/as/ast/d/D-K-15024-01-00.pdf
9. US Food and Drug Administration. "Guidance for Industry. Part 11, Electronic Records; Electronic Signatures—Scope and Application." August 2003. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf
10. International Society for Pharmaceutical Engineering. *GAMP® Good Practice Guide: A Risk-Based Approach to Calibration Management,* 2nd ed. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2010.
11. US Food and Drug Administration. "Guidance for Industry. Process Validation: General Principles and Practices." January 2011. https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf
12. European Commission. "EudraLex Volume 4: Good Manufacturing Practice (GMP) Guidelines. Annex 15: Qualification and Validation." March 2015. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2015-10_annex15.pdf

About the authors

Fritz Röder is a recognized expert in the pharmaceutical industry who is currently employed as Senior QA Manager at Merck Healthcare KGaA, in Darmstadt, Germany. He has experience in pharmaceutical media supply, GMP environments, and the processing of solid, semisolid, and liquid (sterile) dosage forms, and has managed various large projects involving solid, semisolid, and liquid sterile dosage forms. He has also contributed to several audit projects for regulators in the US, Brazil, Germany, Russia, and other nations. Fritz is a member of the European Directorate for the Quality of Medicines & HealthCare Working Group on Water, the ISPE D/A/CH Affiliate Expert Group on Water and Steam, the ISPE Critical Utility CoP Steering Committee, and the Parenteral Drug Association. He has been an ISPE member since 2018.

Dietmar Saecker is Senior Application Expert for Industrial Temperature Measurement at Endress + Hauser Temperature + System Products in Germany. In this role, he consults worldwide with users of temperature measurement in process automation to select and design the best-fitting thermometer to increase accuracy, response time, and safety. Dietmar is also a Lecturer for Measurement Technology at the Kempten University of Applied Science in Kempten, Germany, where he teaches students how to select flow, pressure, and temperature measurement devices for specific applications.

INDEX

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JANUARY/FEBRUARY 2010 VOL. 30 NO. 1
"Microreactor Technology: Innovations in Production Processes"

JULY/AUGUST 2010 VOL. 30 NO. 4
"Virtualization – Compliance and Control"

MARCH/APRIL 2010 VOL. 30 NO. 2
"Design and Optimization of a Large Scale Biopharmaceutical Facility Using Process Simulation and Scheduling Tools"

SEPTEMBER/OCTOBER 2010 VOL. 30 NO. 5
"Lean Maintenance – A Risk-Based Approach"

MAY/JUNE 2010 VOL. 30 NO. 3
"Simple Strategies to Improve Bioprocess Pure Culture Processing"

NOVEMBER/DECEMBER 2010 VOL. 30 NO. 6
"Risk-Based MES Implementation Using Hazard Analysis and Critical Control Points (HACCP)"

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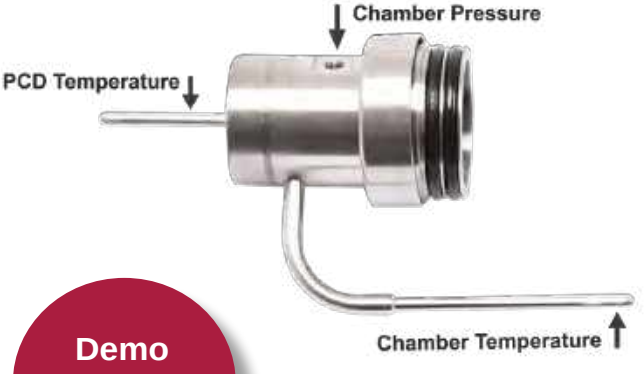

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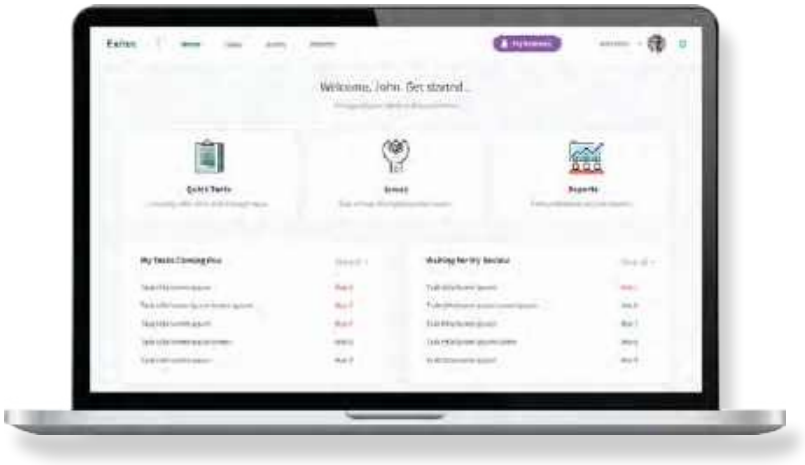

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