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ON THE COVER The cover photo provides a conceptual view of the upward progress of Emerging Leaders, who work together to forge their paths to serve the pharmaceutical industry now and in the future.

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By Jörg Zimmermann


Jörg Zimmermann

COVID-19: A Catalyst for Change and Progress

Who would have thought at the beginning of the pandemic that we would have several highly effective vaccines against the coronavirus and billions of doses administered by the end of 2021? I am still amazed what we as the pharmaceutical industry have achieved.

Novel approaches to vaccination via mRNA technology? Unheard of. Remote inspections, rolling review of submissions by regulatory authorities? Are you kidding? But that's what happened! Imagine the progress humanity has made since the influenza pandemics of 1889–1895 and 1918–1920, and how many lives have been saved.

The world was forced into change and progress with the COVID-19 pandemic: meetings needed to be done online, as were conferences. Digitalization and remote work took a big step forward, with all the advantages and disadvantages: we were able to participate in a webinar in Australia in the morning and another one in the US in the evening, while doing the laundry on the side and taking care of the kids. Coming back into the office, I realized how much had been missing: the small talk over coffee, catching up with colleagues that I had not seen in months, going for a lunchtime run with like-minded friends. The world has changed over the last two years, and we should carry forward the good things that developed.

The challenges are the same for everyone, and by sharing experiences, we can all profit.

CONFERENCES CONTINUE

I recently addressed the Emerging Leaders (ELs) of ISPE at their virtual event in October 2021. It was fascinating to see how ELs from around the world work together in our organization and benefit from networking, both in technical areas as well as in leadership questions and career planning. The challenges are the same for everyone, and by sharing experiences, we can all profit. My talk was on

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"Intercultural Intelligence: Navigating the Global Workplace" and I reported on the things I learned in dealing with different cultures. I am still learning every day and I am grateful for that.

ISPE is moving ahead with hybrid events for 2022. Nothing can replace the in-person experience, but a good portion of our conferences will be available both remotely and in person. We hope that we can reach as many participants as possible in our core strategic areas: manufacturing, supply chain and operational excellence, innovation, and regulatory and compliance.

The 2022 ISPE Aseptic Conference is close to my heart, and it is just around the corner. The program committee has put together up-to-date content on robotics, containment, components, ATMPs and cell and gene therapy, and more. You will hear about recent case studies and executed projects, and as always, the regulatory panel with FDA representatives will be a highlight for discussing your questions in an informal setting. Please join us in person or remotely.

THE YEAR AHEAD

2022 will see two important ISPE projects: first, our strategic plan will be updated and revised to reflect current thinking and pave the way for future growth of our organization. The second project is redefining the structure and relationships between ISPE international and the Chapters and Affiliates. The One ISPE initiative is geared toward better collaboration while respecting the needs of individual local groups. We can only achieve our goal of 25,000 members by the year 2025 if we work together.

As International Board Chair, I want to best serve our organization by listening to the viewpoints of all stakeholders and trying to reconcile different positions. I encourage you to invite me to your local meetings, in person or virtual, and I will do my best to attend as many as possible. Bringing together our different cultures, motivations, and perspectives, we are united at ISPE in our mission: to reliably deliver quality medicines to patients.

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

NEW GUIDANCE DOCUMENT

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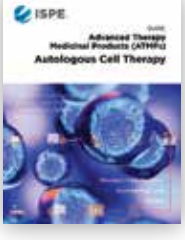

Advanced Therapy Medicinal Products give a new promise and hope to patients with particular rare conditions or diseases. The growing number of autologous products entering the pipeline is evidence of the growth potential of this therapeutic approach.

ATMPs—Autologous Cell Therapy focuses primarily on manufacturing facility development and design for autologous cell therapies for parenteral use while presenting a solid foundation of knowledge for anyone who is entering the ATMP space. This Guide provides an overview of the critical aspects of ATMP facility design, as well as the key relationship between current process/facility attribute alignment and how that changes in the ATMP space.

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By Jennifer Lauria Clark

Jennifer Lauria Clark

Starting a Journey Focused on Your Total Self

ISPE Women in Pharma® (WIP) wants to kick off the new year by focusing on your journey in taking care of your total self. Whether it is your professional or personal mission to better yourself, WIP will provide programming and support this year. We are supporting women and men globally with professional development opportunities and human skills needed to advance careers.

Over the next year, we will help link your physical and mental health to help make you the best version of yourself. There are ways we can be more efficient and can probably eliminate something so you can start doing something else.

It is no secret that tensions are high, people are tired, and many are burned out from the continued aftereffects of a global pandemic. We are also very busy. For instance, today I co-manage my household with my husband; am in graduate school pursuing my MBA; volunteer with WIP, which I love and so continue to volunteer; help with caregiving for my stroke victim father with my sister and momma; have a full-time job I love as VP, Sales and Account Relationship Management at CAI; support my husband in a business we started in 2019; and try to "take care" of my total self.

Realize you are not alone in any journey you are on right now. We are all working hard to navigate how to take care of our jobs, our families, and ourselves. Often, taking care of our total selves falls to the bottom of the to do list.

When I talk about total self, I mean beyond just the basic needs of eating healthy food, drinking water, getting rest, providing shelter for our families, and having access to healthcare. Who is taking care of you? Are you finding time to take care of your physical self to prevent aching joints or diabetes? Are you finding time for mental breaks and releases for your stress and anxiety to prevent depression and hypertension? Are you looking for the joy in the environment around you every day?

There is a woman who I admire in WIP that is as healthy as I would like to be, has an amazing career, and travels the world. I do not compare myself to her. I appreciate the qualities we share and that we chose different paths in life highlighting the talents we possess. Her focus on mental and physical health is strong and her professional career benefits from her choices. She shares her talents willingly with others. Her choices push me to focus my mindset on exercising regularly, making time to travel, and spending time prioritizing work and home.

There is a man I admire at CAI. He has taught me more about leadership and being a better version of myself than I could ever learn on my own. He has pushed me to seek help in all areas of my life. He is my champion. He pushed me to jump in headfirst into pursuing my MBA. I always wanted it, and he gave me the nudge to go after what I wanted. My course work has benefited my organization in many ways and made me a stronger employee, owner, and leader. My mindset shifted to being more strategic and obsessing over less.

People often ask me how I do what I do. My number one response is always, "My husband is my rock." He supports me and all my dreams and takes care of our girls when I am home and away. I also do this for my two girls, Reese and Riley. I want to be their role model.

So how do I really do this? It is simple. Change your mindset. Create a mindset the encompasses a healthy balance between work and play. I do not believe there is ever going to be a perfect balance for either. Some days I am going to give more to work than my kids. And other days, I give more to my family than I do to work. Make sure you work for an organization that allows you the flexibility to succeed in all the areas you desire.

I changed my mindset a few years ago after my dad had a triple massive stroke while working and traveling in our industry. Life is short and I want to be joyful every day that I have on this earth. This requires discipline, cognitive energy, and asking for help. Last year, we hired a housekeeper, a dog sitter, and a nanny to help us. It allows us time to spend more time focusing on our goals and dreams.

To protect my total self, every day I try to work out to relieve stress and generally feel better; meditate to clear my head and ground myself; show up to work ready to slay the day and give what I can today; and slow down in the evenings with family meals, cuddle time with my kids, and a few minutes with my husband before I pass out.

What is one thing you will do today to change your mindset and "take care" of your total self? Take your life into your hands and make it what you want it to be. Good luck, and I look forward to hearing about your journey at our next ISPE event.

Jennifer Lauria Clark is Vice President, Sales and Account Relationship Management, at CAI, and the ISPE Women in Pharma® 2021–2022 Steering Committee Chair. She has been an ISPE member since 2003.

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 By Heather Bennett-Kelley


Heather Bennett-Kelley

Building Connection and Support

The past two years have turned things upside down and forced change in a way that has made many aspects of our lives become unfamiliar. The unforeseen stresses of these changes have pushed many people and companies to their breaking points. Some of these challenges were expected, but came on like a train that we couldn't stop. I've been there, feeling like I don't have the tools to deal with the task or situation at hand, knowing that change is coming because of my own decisions but not realizing I need help until I'm already at rock bottom.

How do we build and support our people and companies to deal with the changing tides? How do we know when to batten down the hatches for an oncoming storm, or when to open up the windows again? How do we know when to ask for help before it is an emergency?

We need to build a strong network in our personal and professional lives (and in our companies), connecting pieces, supporting these pieces, feeding the pieces so they grow, and building resilience to bounce back. ISPE is a unique organization because it assists its members with these. The Emerging Leaders (EL) professional community provides a place to build this network.

CONNECTION

In relation to ISPE, and especially ELs, the word *connection* embodies many different definitions:

- Connecting of ideas, specialties, and innovations to manufacture life-improving therapies.
- Connecting with individuals and companies in the same industry to learn about different ways of doing the same things.
- Connecting with colleagues and mentors to create lasting bonds that help us get through a challenging project or time.
- Connecting the dots with technology, industry partners, and knowledge sharing.
- Connecting strands of DNA, neurons, cells, and biological systems to forge a new way of being.

Continuing the connection building will ensure that we keep innovating, learning, and growing.

This industry and the people and companies in it have to be connected in order to do the work we need to do. To build the future, we need to build these connections and teach our ELs how to build them. Continuing the connection building will ensure that we keep innovating, learning, and growing.

SUPPORT

For connections to stay in place, or to build new ones, a support system needs to be in place. This system acts as a scaffolding or bridge to provide strength and guidance to those starting their careers or to companies pushing off with a new idea. Support can be one person acting as a sounding board, bringing someone lunch when they are buried in a project, participating in mentor circles, or reaching out to the members of a CoP to find the nuances of purified water. Mechanical or automation systems and training or professional development programs are forms of organizational and procedural support. All of these work in tandem, which means we each need to do our part so the whole system works.

Let us reengage in 2022, and use the tools that we learned over the past two years to build new connections and strengthen old ones. Maybe some of these virtual tools have helped us to better understand some aspects of Pharma 4.0™, and how the support systems go far beyond IT concepts. We had to change the way that we do things and how we interact with others; maybe we have stepped out of our old habits enough to know how we can improve on processes, procedures, and business practices. I challenge us to help build the future of our industry, so that our members and patients can rise to their full potential.

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

EMERGING LEADERS:

Nurturing Emerging Talent and the Workforce of the Future

By Scott Fotheringham, PhD

Emerging Leaders has grown from an initiative for interactions among early-career professionals entering ISPE into much more: a training ground, a networking organization, and a new foundation for the future of ISPE and the industry. This article looks at the history of the group, its purpose, current and future initiatives, and a name change that better reflects the path of its members.

After Caroline Rocks, a Process Engineer, joined ISPE's Ireland Affiliate, she began attending conferences beyond her home base. She found that when she showed an interest or volunteered in one area, she was soon invited to get involved in another. Rocks laughed when she recalled that one of her first roles was simply holding a sign to direct conference goers to the right bus. Three years later, she was on the ISPE International Board of Directors.

Caroline Rocks

"Newcomers to the industry might have an image that ISPE is a closed-door society and you have to be at a later stage of your career to join," Rocks said. "But from the start, people were welcoming and doors were open to me."

As a Process Engineer, the scope of what she did and her interactions were limited to engineering. All of a sudden, by volunteering with ISPE, Rocks was interfacing with many different industry organizations. She found herself, early in her career, working with people from the C-suite of another pharmaceutical company, the owner of a consultancy, and even a person who had invented manufacturing equipment. "I didn't get that in my 9-to-5," she said. "I got that from my involvement with ISPE."

Rocks wanted to join an Emerging Leaders (EL) group (then known as Young Professionals or YPs) and, in 2014, was invited to help establish one in Ireland by Robert Landertinger, the YP Europe Regional Leader at the time.

"I was in a meeting and realized there was somebody from Eli Lilly there, somebody from Pfizer—all these different companies—and they wanted to hear what we were doing and to support Young Professionals in Ireland."

After her participation with the local Emerging Leaders committee, Rocks broadened her involvement to the global stage, becoming Chair of the International Young Professionals Committee from 2017–2018, succeeding Brody Stara, the first YP chair who had an ex officio role on the ISPE International Board of Directors. Following that, she was elected to the ISPE Board and served from 2018–2020. She is currently Senior Program Manager at AbbVie, Inc.

THE EMERGING LEADERS MANDATE

Emerging Leaders is a program with local committees in many ISPE Chapters and Affiliates. The first ISPE event was held at the 2007 Annual Meeting by an EL committee that had been formed by the Boston Area Chapter. In 2010, "Young Professional" became an official ISPE member type and the community was recognized and given increasing focus across the global Chapters and Affiliates, changing its name to Emerging Leaders in 2021.

John Clarke

Since 2010, the community has actively grown and developed, with over 25 EL committees established across North America, Europe, APAC, and South America. In 2018, at the ISPE Europe Annual Meeting in Rome, ELs were introduced as education track co-chairs for the first time, enhancing their participation in meetings. Each EL committee consists of between 2–20 active volunteers, and there are more than 1,800 members in ISPE International Professional Community (see Figure 1).

"By focusing on networking and building a community, the ELs have established themselves at the forefront of Special Interest

Groups, Communities of Practice, and conference planning," said John Clarke, Chair, International EL Committee, 2020–2021, and a Process Lead with Pfizer. "This experience and development is instrumental in the career progression of our members and it is key to the continuation and growth the community has seen."

EL offers members early career training and networking opportunities, runs Hackathons (see sidebar), and is integral to ISPE's efforts to develop the Workforce of the Future.


Jörg Zimmermann

"ISPE provides a platform for professional development and networking for people in all stages of their career in the pharmaceutical industry," said Jörg Zimmermann, 2021–22 Chair, ISPE International Board of Directors and Vice President, Vetter Development Service, External Affairs, at Vetter Pharma-Fertigung GmbH & Co. In particular, he noted that participation in EL can help members develop leadership, interpersonal skills, confidence, technical understanding, and regulatory knowledge. EL participation also assists in setting aspirational goals and illuminating a path to success.

Since 2014, the Chair of the EL committee has been an ex officio (non-voting) member of the ISPE International Board of Directors, providing access and input to the workings of the Society to a representative from first the YPs, now the ELs. The decision to include the EL Chair highlights the Board's commitment to developing the Workforce of the Future.


Joanne R. Barrick

"Emerging Leaders are the future of ISPE and the pharma industry," said Joanne R. Barrick, RPh, Past Chair, ISPE International Board of Directors, and Advisor, Global Validation, Technical Services/Manufacturing Science at Eli Lilly and Company. "Through leadership opportunities in ISPE, networking, conference planning, and guidance document development, we can help prepare them to become tomorrow's pharma industry leaders. The EL community attracts talent to the industry that will help address the anticipated talent gap in the biopharma segment."

CAREER BENEFITS BEGIN DURING STUDENT DAYS

While universities teach technical content, ISPE opportunities like EL help with ongoing professional development. "The process begins with student chapters," Zimmermann said, "in which those new to the industry can connect with experienced professionals and with subject matter experts; they can work on cross-functional projects where they apply what they learn to real-life problems; and they receive mentoring."

This provides a good foundation for students to move to the next level for a head start to their professional career, including site visits and workshops. They have access to a local Chapter or Affiliate and Communities of Practice for answers to an array of questions, to share knowledge, and to network with other pharma industry leaders.

Figure 1: Emerging Leaders is a global initiative.

- 1,800 members worldwide
- 10 groups in the US, 1 in Canada, and 1 in Mexico
- 11 groups in Europe, representing 15 countries
- 6 groups in Asia and the South Pacific


Heather Bennett-Kelley

"When I was a student in ISPE, I was a sponge, soaking up all the information that anybody would give me," said Heather Bennett-Kelley, Chair of the 2021–2022 International EL Committee and Project Manager/Engineer with ACCO Engineered Systems. "My involvement as a student member of ISPE was pivotal to being able to find a job."

Bennett-Kelley knew that to be successful, she needed to connect with people in industry before she graduated, and her efforts paid off. Of the 15 students in her graduating class of chemical engineers, only half found jobs. "We were all applying to companies that were receiving stacks of anonymous resumes, everybody with the same qualifications. I was able to find something because of an ISPE connection who called me and recommended that I apply for a position at their company."

Bennett-Kelley also conducted informational interviews, including a plant tour where she met workers on the floor to learn what they did. "Having that ISPE connection made this less intimidating than it would have been. Then, the person who was hiring asked one of their colleagues if they knew anyone who could fill a position and my contact mentioned me. The hiring person remembered me from an ISPE student event and contacted me."

She learned how the different aspects of a pharmaceutical plant function, what equipment is used and how, and how a company interacts with the FDA, contractors, and end users. "Getting involved in Emerging Leaders really helped because experienced professionals showed me how everybody was linked together. Not only that, they showed me the soft skills I would need if I wanted to be a future leader, then coached me on how to build them."

NETWORKING AT CONFERENCES AND LOCAL EVENTS

A large part of Bennett-Kelley's experience interacting with industry experts to fulfill her career aspirations came from attending EL events. Networking dinners at conferences allow ELs, ISPE Board members, and staff to mingle and share ideas. Local EL events—one after-work event was held by her San Francisco Bay Area Chapter at a local brewing company—provide opportunities for knowledge and experience sharing in low-stress environments. She finds it allows someone fresh in their career to approach a senior director, even a C-suite executive from a large company,

who has already signaled that they are open to sharing their knowledge and experience.

"At a certain point in your career, there's a shift from what you know to who you know," Zimmermann said. He has seen how connecting with other ELs and receiving mentoring from seasoned industry professionals has helped ELs to advance careers, both in what people know and the positions they are able to get. "International networking across different companies with different focus areas will help them get a better understanding of the industry."

Involvement can also lead to satisfying volunteer opportunities, like organizing conferences, developing webinars, and writing articles for *Pharmaceutical Engineering®*.

Rocks credits what she learned from ISPE and YP/EL networking events as a big driver for her shift two years ago out of engineering and into project management. "I learned more quickly about how the industry is organized," she said. "I learned about regulatory affairs, clinical trials, and validation and, as a result, saw that I wanted a job role that interfaced with all of those functions. You don't know what you don't know, and ISPE opened my eyes to the kind of opportunity I wanted to move into."

The same has been true for Clarke, who first became involved with the YPs in 2014, when he and Rocks were part of the team that helped the Ireland Affiliate establish a new YP committee.

"I had recently begun working with Pfizer in Grange Castle, Dublin, and it was a fantastic way to learn more about the industry and meet peers who were in a similar career situation," Clarke said. "I progressed through roles in engineering, validation, and operations. All the while, my progression within ISPE evolved alongside. Membership in ISPE supported my career progression through attending technical conferences on cutting-edge topics and building leadership skills through holding roles of increasing responsibility on the committee."

BENEFITS TO ISPE


Thomas Hartman

"Students don't graduate out of university programs that specifically teach manufacturing of monoclonal antibodies, or how to submit a biological license application to the FDA," said Thomas Hartman, ISPE President and CEO. "Instead, they learn these things within their company and from the practical knowledge that ISPE offers, including through engagement with ISPE professionals. This is highlighted within the ISPE Mission Statement" (ispe.org/about).

Hartman knows that networking and information sharing work both ways, with senior industry professionals also gaining insights from the unique perspectives ELs bring to the organization. One example is their different view of the pharmaceutical industry from that of more seasoned professionals who consider it to be one entity consisting of three modalities: traditional small molecules, biologics, and ATMPs and C&GT.

"For most young individuals coming out of colleges and universities, the only modalities that they're truly introduced to are the biotechnology centric," Hartman said. "Emerging Leaders also bring a culture to the Pharma 4.0™ initiative (ispe.org/initiatives/pharma-4.0) that is embedded in digitization. They're not afraid of transitioning from a paper-based system to a fully digitized batch record—in fact, they prefer it. Emerging Leaders bring the opportunities to realize acceleration of drug development through licensure employing Pharma 4.0™ concepts."

Bennett-Kelley agreed. "Emerging Leaders are coming in with fresh energy and want to learn in a way that's different from someone who's been at a company for 30 years and may be used to doing things a certain way. Emerging Leaders want to find new ways to do the same thing. They don't just think outside the box, they live outside the box. They try to break the mold, not because they can but because they don't know any better."

Hartman credited ELs, who use digital platforms to chat with their colleagues, engage with ISPE, or secure a guidance document, with pushing ISPE to adapt its communication platforms, which is necessary for it to remain relevant long term.

"We have to be able to engage with that demographic and embrace the ways they communicate, learn, and acquire information," he said. "Most importantly, ISPE needs to be able to adjust our platforms to allow consistency with the way this demographic thinks."

ISPE's broad digitization strategy, much of which has been implemented, is to ensure this demographic and, indeed, all those who have moved to more digital-friendly platforms, can interact with the Society digitally—as often as not via their phones—to do everything from search for a guidance document, peruse the website, and research technical topics, to get information about other members.

FOSTERING THE WORKFORCE OF THE FUTURE

The benefits that accrue to ELs and ISPE spread even wider, into the pharmaceutical industry as a whole. One current challenge of the pharmaceutical industry is being able to recruit young, capable talent and then train them. Once they've graduated with an engineering degree or a science degree, they need to acquire the knowledge and expertise to function in the highly regulated pharmaceutical industry.

"Involvement in Emerging Leaders provides the technical expertise, project management experience, and soft skills for the next generation of leaders and subject matter experts," Clarke said. "The culture of collaboration and innovation within ISPE Communities of Practice and Special Interest Groups has demonstrated that solutions to industry challenges can be accelerated. Emerging Leaders can be at the forefront of these activities and develop this way of working for the rest of their careers. The potential for this to benefit the industry as a whole is infinite."

Zimmermann believes ELs are essential to the health of the pharmaceutical industry, bringing the latest in scientific knowledge and methods to their companies. The combination of their innovative ways of thinking with existing company and

Hackathons: A Place for Interaction

Hackathons are intensive collaborative events that inspire innovative thinking. They are important to the Emerging Leaders community because they function as an opportunity for members who are early in their careers from different Chapters and Affiliates to work together to solve interesting industry problems.

The Emerging Leaders Hackathon began as a 24-hour event; during the pandemic, this became a virtual event that took place over eight weeks. During the Hackathon, teams of ELs work together to generate innovative solutions to a challenging real-world problem faced by the pharmaceutical industry. The teams scope the problem, create a project plan, and consider the financial implications of their proposed plan. Hackathon concepts developed by each team are then judged by members of the ISPE International Board of Directors and the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF), exposing ISPE EL members to senior leaders from across the industry. The first Hackathon was held in Barcelona in 2017 to coincide with the Europe Annual Conference.

"Our Hackathons were inspired by similar events held in the tech industry," said John Clarke, 2020–2021 Chair, International EL Committee, and a Process Lead at Pfizer. "That first event held in Barcelona in 2017 gathered representatives from across the EU Affiliates and demonstrated the innovation that could be achieved through collaboration on an industry problem." Hackathons have received great support from ISPE, added Zen-Zen Yen, European Emerging Leaders Chair and International EL Co-Chair, and Head of Maintenance Operations at Bayer AG, who worked with Robert Lantinger on organizing the first Hackathon.

After the success of the Barcelona event, Hackathons were organized to coincide with EU Annual meetings in Rome and Dublin and the first North American Hackathon was held at the ISPE Annual Meeting in Las Vegas in 2019. Due to COVID-19, the first fully virtual Hackathon took place in 2020, with more than 50 participants representing 20 Chapters and Affiliates. The idea is so popular that some Affiliates and Chapters, such as the D/A/CH Affiliate, have local Hackathons to keep the momentum going between conferences.

The February 2021 Hackathon was virtual and had 51 Student and Recent Graduates divided into six teams. Fourteen ISPE ELs and industry professionals acted as coaches for the teams as they worked to solve a problem statement provided by Bayer. The challenge was to transform the operations of a CMO to embrace digitalization, including the migration of existing paper documentation to a digital format, with all work to be done virtually under a tight budget.


LeAnna Pearson

"Hackathons allow ELs, students, and industry leaders to collaborate in a safe space that allows for outside-the-box thinking," said LeAnna Pearson, 2018–2020 Chair of the International Young Professionals Committee and Associate Director of Manufacturing Services at PharmEng Technology. "Many of the ideas generated in our Hackathons have been looked at or even introduced by industry."

Caroline Rocks, 2017–2018 Chair of the International Young Professionals Committee and Senior Program Manager at AbbVie, Inc., has seen the positive impact Hackathons have on the industry by getting employees to expand their thinking beyond their day job and their specific roles, showing them the impact they can have in the industry at an earlier stage of their career. "Compared to classic conference offerings—technical lectures or training sessions—in which you attend a presentation, and maybe ask a question at the end of a 40-minute session, Hackathons offer an interactive and immersive experience over the course of a few days."

"Face-to-face Hackathons have always been exciting events for EL members to get involved in, with an opportunity to see a new city and hang out with peers from across the industry," said Clarke. "It can be difficult to replicate the opportunity face-to-face events provide for networking and building relationships."

With that in mind, future EL events, including Hackathons, will either be fully virtual, fully face-to-face, or follow a hybrid model, depending on the aim of the event and the target audience. "Recent Hackathons have demonstrated the dynamic collaboration we can achieve virtually," Clarke said. "Whether face to face, virtual, or a hybrid model. the future of EL events is bright."

—Scott Fotheringham

institutional knowledge creates synergies. He sees vast opportunities for those new to the industry to learn about all areas of pharmaceutical manufacturing, including such things as dosage, quality control, quality assurance, and the regulatory process.

"ISPE has experts in every imaginable topic, from tableting to cleanroom design, from ATMPs to modern analytical testing, from project management to critical utilities," Zimmermann said. "At the same time, recruiting talent to the pharmaceutical industry is key to future growth of our member companies."

Over the past three years, the ISPE Foundation has supported grants as part of the Foundation's broad commitment to building the Workforce of the Future (ispefoundation.org/workforce-future). These grants provide opportunities for students, recent graduates, and ELs to attend conferences, training, and Hackathons. By attending the ISPE Annual Meeting & Expo, students and ELs gain practical knowledge through a comprehensive education program and can network with peers and senior executives throughout the industry. The program curriculum explores the skills needed for the future, including an understanding of the differences between small and large molecules, biotechnology, and cell and gene therapies. Companies recognize that ISPE has a unique program nurturing the Workforce of the Future. In fact, significant donations are being made to the Workforce of the Future initiative.

"We see this as an opportunity for Emerging Leaders to begin their journey to become subject matter experts in these areas," Hartman said.

ISPE has a three-month Diversity Internship Program (ispefoundation.org/diversity-internship-program) offering graduate and undergraduate students the opportunity to spend their summer making a meaningful impact at a top organization in the pharmaceutical industry. A diverse workforce is one that employs people of different cultural backgrounds, genders, disabilities, religions, ages, and varying levels of professional experience. Hartman noted that placement of individuals within operating companies improves the workforce of the future, "not only from a talent and capabilities perspective, but also from a diversity perspective."


Bill Mojica

"This initiative seeks to increase diversity within the pharmaceutical industry and those from underrepresented groups are highly encouraged to apply," said Bill Mojica, ISPE Director of Development & Foundation Operations. The ISPE Foundation, at the request of ISPE International, provided funding for 40 one-year memberships and an all-access pass to the 2021 Annual Meeting in Boston to allow ELs in the Boston area to experience the Annual Meeting firsthand.

FUTURE LEADERS DAYS

The Germany/Austria/Switzerland (D/A/CH), Ireland, and Spain Affiliates co-hosted virtual two-day ISPE Future Leaders Days in October 2021. The conference was international and open for everyone to attend, independent of location and time zone, and offered a three-track program in career development, innovation and technology, and leadership and communication.

> ELs don't just think outside the box, they live outside the box.

Future Leaders Days have been the signature event of the D/A/CH ELs and have been widely attended by ELs and students in the region.


Zen-Zen Yen

"Future Leaders Days are not only bigger than any of our previous events but also much more versatile," said Zen-Zen Yen, European Emerging Leaders Chair and International EL Co-Chair, and Head of Maintenance Operations at Bayer AG. She said that the Future Leaders Days were organized face-to-face annually; with the pandemic, the event became virtual and included teaming with other EL Affiliates' groups.

"There was something for everyone and participants had a hard time choosing which presentation to attend," Yen said. Attending Future Leaders Days allows ELs and students to learn about what is new and challenging, while also challenging themselves with regard to their career development.

"We in the pharmaceutical industry have a common goal—the health of patients," said Yen. "We can only get better if we connect, share experiences and knowledge, learn from each other, and think outside the box. We don't need to find our one solution—we need to find the best solution."

BRINGING ELS TOGETHER VIRTUALLY

Bennett-Kelley has seen that everyone has felt isolated and operating in silos from a technology and expertise standpoint, especially between regions. As EL Chair for 2021–2022, she hopes to help bridge those boundaries.

"Regions are not operating in a vacuum," she said. "The biotech hub in San Francisco is connected philosophically to the East Coast, to Singapore, and to Germany. We're all working together."

She intends to leverage technology to connect Chapters and Affiliates more frequently than just at annual meetings. Given the move to virtual meetings, she will find ways to encourage engagement, even when there's a hybrid in-person/virtual approach. ELs will be exploring building new student chapters, new EL groups, rebuilding EL/student groups that have gone dormant, and linking sister Chapters or Affiliates to facilitate knowledge sharing.

A New Name to Reflect Growth—In Many Ways

Originally known as Young Professionals, many bristled at the implication that they were inexperienced or had graduated recently. Professionals changing industries or roles in the middle of their careers were reluctant to get involved and the committee saw the need to change the name to better reflect its mission.

LeAnna Pearson, 2018–2020 Chair of the International YP Committee and Associate Director of Manufacturing Services at PharmEng Technology, was a graduate student when the initiative that became Young Professionals was launched. "It was exciting to know that ISPE was moving in a direction that was more inclusive of early-career professionals," she said.

In 2018, Young Professionals won the Committee of the Year Award, recognized for its significant contribution to advancing ISPE's mission and goals, use of operational best practices that included partnering with other ISPE groups, and innovation and support of the Society's strategic plan. But, as Pearson's career progressed, she watched Young Professionals develop into a larger group of individuals who were no longer just new graduates, but also those who were not yet senior in their field.

Many found the group's name ambiguous. Did Young Professionals refer to age or to one's seniority in the industry? There was also a disconnect between the working definitions that people used and the ISPE membership tiers. The confusion made it unattractive and YPs lost engagement among some early-career professionals.

The committee conducted a survey among its global membership to gauge how they defined "young professional." The results confirmed the confusion, as most did not consider it to only refer to those in their first five years in the industry and wanted to expand the definition to include newcomers. Pearson proposed to the ISPE International Board of Directors that the name be changed and decoupled from the membership tier. The Board agreed and challenged the committee to come up with a better name, which it did. Henceforth, it would be known as the International Emerging Leaders Committee.

"We thought what they came up with was appropriate because it reflects the accumulated experience that comes with membership in ISPE and the activities and programs that we use to support them," said Thomas Hartman, ISPE President and CEO. "They certainly embraced the Emerging Leaders label far more than they did Young Professionals."

The name change has allowed the EL Committee to develop and grow as the needs of the members and industry change.

—Scott Fotheringham

"The increase in digital working in the last two years has definitely enhanced the connection and collaboration across the regions," said Clarke. "While great success has been experienced opening up online events to ELs across APAC and South America, there is more to be done to support Affiliates and Chapters across the regions, establish EL committees, and increase ISPE membership and engagement. This is something that will be a goal for the International EL Committee over the coming years."

The pandemic has had some unexpected benefits. More events have been virtual and global—including the most recent Hackathon—and this is a trend that will continue. And it has raised the profile of those who work in the industry.

"The pandemic has meant that now, when folks know you are part of the pharmaceutical industry, they want to engage with you," Hartman said. "This is an opportunity for ISPE to really focus energy on Emerging Leaders. We're seeing more younger people in high school become interested in the pharmaceutical industry and that is something that ISPE and the industry need to take advantage of."

Bennett-Kelley would like to use this momentum to encourage companies to embrace their younger employees. Some companies have programs set up to foster the growth of their young people, including new generations coming out of school that often have different priorities than people who have been in the industry.

"We need to tap into that and breathe that life into our companies and the industry," she said. "It's not just about recruiting new talent. It's about recruiting new ideas and the new ways of doing things that come with them. We need to keep stepping outside the box and harnessing that energy."

About the author

Scott Fotheringham, PhD, is a freelance medical and science writer with interests that span fields as diverse as pharmaceuticals, biotechnology, molecular genetics, and medical cannabis. Most recently, he was Senior Medical Writer at Canopy Growth Corporation. Scott has been a contributor to *Pharmaceutical Engineering* since 2015.

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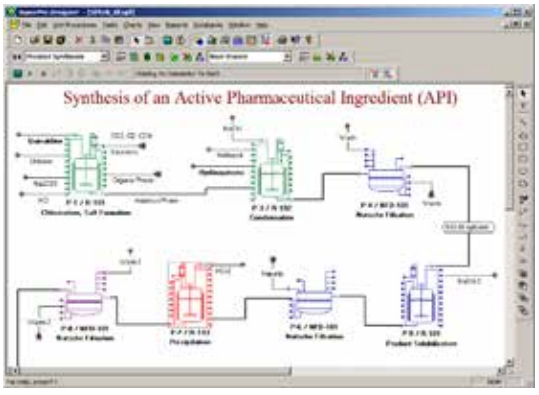

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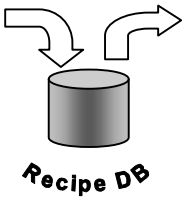

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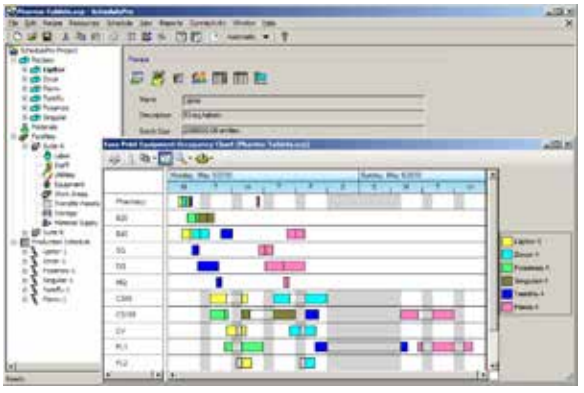

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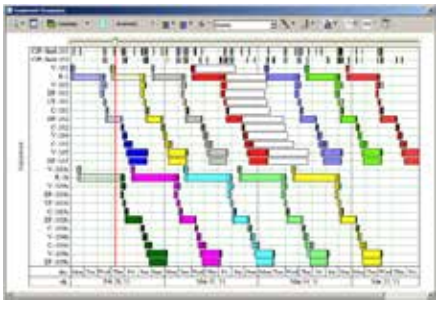

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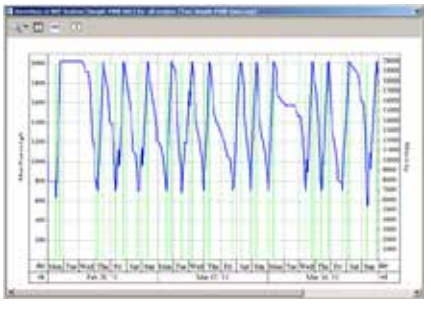

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TOWARD A SINGLE GLOBAL CONTROL STRATEGY:

Industry Study

By Jill Beierle, MS, Nina S. Cauchon, PhD, Timothy W. Graul, Ylva Hedberg, Marianne Braathen Holm, John V. Lepore, PhD, Ryan MacKenzie, Kavita Mistry, PhD, Xinhua Qian, KeAndra Robinson, Gregory Rullo, Kin T. Tang, PhD, and Timothy Watson, PhD

During the past decade, industry has experienced a proliferation of regulatory divergence regarding the interpretation and implementation of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (and control strategies) across geographic regions. This article shares data that highlight instances where well-established ICH regulatory members diverge from ICH quality guidance in their evaluation of the same scientific data in chemistry, manufacturing, and controls (CMC) regulatory documents submitted by industry. The data illustrate instances when regulatory divergence led to modifications to control strategies that in turn led to multiple regional and local control strategy variants globally. A common understanding of the degree of divergence and impact is an important step toward improved global harmonization of control strategies and will ultimately benefit regulators, industry, and patients globally.

Scientific and risk-based approaches in pharmaceutical development were first explicitly described in ICH Q8 and further elaborated in ICH Q9, Q10, and Q11 [1–4]. Conceptually, quality by design improved confidence in the quality of pharmaceutical products, enhanced scientific understanding, and demonstrated the robustness of the manufacturing process. It also encouraged continuous process improvement for manufacturing. A primary incentive for industry to follow quality by design guidance is to establish a common foundation for continual improvement through global regulatory concordance for new applications.

Lately, rather than truly harmonized regulatory expectations, localized interpretations of ICH guidelines have resulted in different regulatory requirements and/or control strategies, which poses significant challenges to marketing a single product in global markets. As a result, the increased complexity of manufacturing supply chains and the regulatory burden associated with maintaining compliance with these diverse regulatory expectations have created difficulties: There are additional burdens and challenges in carrying out continuous improvement initiatives and innovation in product development is hindered. And these supply no substantive improvement in product quality, safety, or efficacy. Divergence has become a disincentive to improvements and has even caused temporary drug shortages in some markets.

GUIDANCE AND DIVERGENCES

ICH technical guidelines are used by the pharmaceutical industry to develop manufacturing control strategies. A growing number of regulatory authorities apply these guidelines to assess marketing applications to ensure pharmaceutical product quality (safety and efficacy). Applicants are consistently finding divergence in the interpretation of ICH guidelines by regulators from different countries. This suggests that determining an acceptable control strategy can be subjective [5]. The metrics presented in this article—collected from core control strategy contents in marketing applications and corresponding review outcomes by health authorities—provide specific instances of divergence. This article

Table 1: Drug substance and drug product core documents for benchmarking study. (Source: ICH M4Q(R1): Guideline for Good Clinical Practice [ich.org])

Drug Substance	Drug Product
3.2.S.2.2 Description of Manufacturing Process and Process Controls	3.2.P.3.2 Batch Formula
3.2.S.2.3 Control of Materials	3.2.P.3.3 Description of Manufacturing Process and Process Controls
3.2.S.2.4 Controls of Critical Steps and Intermediates	3.2.P.3.4 Controls of Critical Steps and Intermediates
3.2.S.4.1 Specification	3.2.P.5.1 Specification(s)
3.2.S.7 Stability	3.2.P.8 Stability

presents metrics and examples of divergence from 112 marketing applications, covering both new synthetic and biological entities, from 11 companies from a benchmarking study conducted by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)–Control Strategy Global Harmonization (CSGH) Working Group. The study's objective was to evaluate the industry's experience of divergence, build awareness of commonalities, and elucidate the implications for stakeholders (including regulators, industry, and patients). A global harmonization of control strategies should begin with a common understanding of the degree of divergence and its impact.

Data Set Criteria

Manufacturing control strategy in a submission is depicted by core common technical documents (CTDs) in Module 3 per ICH Q11. Therefore, the benchmarking survey was based on defining a set of "core documents" in a submission as a manufacturing control strategy. The core documents defining a manufacturing control strategy are described in Table 1: these include control strategy elements of material attributes, process design, in-process controls, and drug substance and drug product specifications. Study participants agreed that the control strategy described in the core documents was based on enhanced scientific understanding and in alignment with the science and risk-based approach described in ICH Q8–Q11.

Participants also agreed that, ideally, a single, complete set of core documents submitted globally is used for the survey. Companies that expect potential rejection of any core documents generally create country-specific core documents based on either previous application experience or prevailing knowledge of a country's requirements (either explicit, published control strategy expectations, or interpretational differences). Even when core documents are submitted, a health authority may impose a revision to control strategy during application review. As a result, country-specific variation from a control strategy can be attributed to three sources:

1. A company's interpretation of country-specific regulation deems that the control strategy would not be accepted.
2. A company's experience with previous submissions that resulted in creating country-specific variant control strategy.
3. Request by a country-specific regulatory authority to alter the control strategy to gain acceptance.

A global harmonization of control strategies should begin with a common understanding of the degree of divergence and its impact.

Benchmarking Data Set

After establishing a common foundation for core documents, the IQ CSGH Working Group focused on five drug substance and five drug product CTDs in Module 3, all critical in defining a control strategy, as listed in Table 1.

For every country where a product was submitted, study participants entered:

- Blinded company name and drug identifier
- Year of submission
- Country, market, or region (can refer to as an entity for regulatory acceptance; e.g., the EU represents several countries)
- Molecule type (biologic or synthetic)
- Manufacturing process parameter terminology used (proven acceptable range, design space, or a combination)
- Acceptance status for each of the core documents. For example:
  - Enter "yes" if a core document was accepted without change.
  - Enter "no" if a core document was altered prior to submission because of known regional requirements or if, during review, a change to control strategy was required to gain acceptance.
  - If "no" is entered, then a description of deviation from the core document was provided and counted as the control strategy not accepted by health authority.

Figure 1: Entry form examples for control strategy benchmarking survey.

Company	Project Identifier Code	Year of submission	Country	Molecule (Synthetic or Biologic)	Dosage Form (Sterile or non-Sterile)	Describe Substance and Product manufacturing process (Design Space, PAR, combination)
Company 1	Company1_Drug 1	2014-2017	USA	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	EU	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	Canada	Synthetic	non-Sterile	PAR
Company 1	Company1_Drug 1	2014-2017	Japan	Synthetic	non-Sterile	PAR

Core Accepted S.2.2	Core Accepted S.2.3	Core Accepted S.2.4	Core Accepted S.4.1	Core Accepted S.7	Core Accepted P.3.2	Core Accepted P.3.3	Core Accepted P.3.4	Core Accepted P.5.1	Core Accepted P.8
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Yes = Team members identified the Core was accepted without modifications during submission review

Table 2: Core document acceptance rate and acceptance probability.

	Submissions	Core Document Acceptance Rate [a]										Average Acceptance
		S.2.2	S.2.3	S.2.4	S.4.1	S.7	P.3.2	P.3.3	P.3.4	P.5.1	P.8	
US	30	63%	67%	63%	50%	57%	87%	47%	53%	23%	57%	57%
Japan	17	35%	41%	53%	47%	76%	76%	47%	71%	18%	65%	53%
EU	35	34%	34%	31%	29%	71%	71%	49%	54%	17%	57%	45%
Canada	30	67%	63%	80%	50%	80%	80%	43%	63%	40%	70%	64%
Overall acceptance	112	51%	52%	56%	43%	71%	79%	46%	59%	25%	62%	54%
Probability of acceptance by all four countries [b]		5.0%	5.9%	8.3%	3.4%	24.6%	37.6%	4.7%	12.8%	0.3%	14.8%	8.7%

a. Acceptance rate/acceptance is calculated in percentage by dividing total number of "yes" answers for core document(s) with the total number of submissions from one or multiple countries/regions.
b. Probability of acceptance by all four countries is calculated as a product of multiplication of individual core document acceptance rates of all four countries.

The entry form is illustrated in Figure 1.

The data set included information from 112 marketing application submissions from 11 companies to established ICH countries/regions: US, EU, Canada, and Japan. The data set represented 64 synthetics applications and 48 biologics applications, with 104 submitted after 2014 and 63 after 2018.

RESULTS AND DISCUSSION

The results focus on control strategy divergence caused by different expectations of ICH guidelines between the industry and health authorities. The method used to generate metrics does not delineate details of divergence from health authorities because these details do not alter the trend and study conclusion. Using the agreed-upon criteria for core document acceptance, the average core document acceptance rate across the US, EU, Canada, and Japan is 54% for synthetic and biologic products, as shown in Table 2. Country average acceptance rates range from 45% to 64%, with the EU having the lowest and Canada and the US the highest, at approximately 60%. When translating overall acceptance rate (54%) to the probability of core documents being accepted by all

Table 3: Core document acceptance rate and acceptance probability for synthetic products.

Country	Submissions	Core Document Acceptance Rate [a]										Average Acceptance
		S.2.2	S.2.3	S.2.4	S.4.1	S.7	P.3.2	P.3.3	P.3.4	P.5.1	P.8	
US	17	88%	88%	88%	65%	82%	88%	71%	71%	29%	76%	75%
Japan	12	50%	42%	50%	58%	92%	67%	50%	75%	17%	83%	58%
EU	19	42%	16%	26%	26%	84%	63%	37%	58%	21%	63%	44%
Canada	16	81%	56%	94%	69%	94%	75%	31%	50%	50%	75%	68%
Overall acceptance	64	66%	50%	64%	53%	88%	73%	47%	63%	30%	73%	61%
Probability of acceptance by all four countries [b]		15.0%	3.3%	10.8%	6.8%	59.6%	27.9%	4.1%	15.4%	0.5%	29.8%	13.0%

a. Acceptance rate/acceptance is calculated in percentage by dividing total number of "yes" answers for core document(s) with the total number of submissions from one or multiple countries/regions.
b. Probability of acceptance by all four countries is calculated as a product of multiplication of core document acceptance rates of all four countries.

four countries, a probability of 8.7% (Table 2) is found, which indicates a > 91% likelihood that at least one of the four countries will not accept a consistent control strategy/core documents.

To determine areas of significant divergence, the overall probability of 8.7% (Table 2) was compared with the individual core document acceptance probability for the four countries; where the probability of individual core document acceptance was lower than 8.7%, the control strategy is deemed an area of significant divergence. Using this criterion, significant areas of divergence were identified in 60% of core documents, including S.2.2, S.2.3, S.2.4, S.4.1, P.3.3, and P.5.1, as highlighted in red in Table 2, with each at a > 91% likelihood of not being accepted by at least one of the four countries. The data demonstrate that local jurisdictional considerations hamper the desired outcome of a globally harmonized control strategy. Because the EU has the lowest average acceptance rate, it also has the most impact to the calculated probability of individual core document acceptance.

Although the number of Japan submissions used in this study is lower than the other three countries/regions, it is important to include the study results reflecting Japan's reliance on Module 1 and a separate application form, which create a single country variant of control strategies. Removing the Japan data and recalculating a revised threshold for the remaining three countries did not change the areas of divergence, nor the finding that the EU was the most divergent. Hence, including Japan in calculating the probability of acceptance for an individual core document does not change the trend of the identified significant areas of divergence, and this trend is consistent when considering the metrics separately for synthetic and biologic products.

Although the data set is slightly weighted toward synthetic products, adequate data are collected for both molecule types, which ensures the metric analyses reflect the trends objectively. The acceptance rate and probability in the US, EU, Canada, and Japan separated by molecule type, synthetic product, or biologic product are shown in Tables 3 and 4, respectively. Overall, the observed amount of divergence in control strategy is more for biologic products than for synthetic products.

The number of synthetic product submissions included in the data set, 64, allows for a review of country-specific acceptance rates and areas of significant divergence as presented in Table 3. Core document average acceptance rate ranged from 44% to 75% indicating significant divergence, with the EU having the lowest acceptance rate. Both the US and Canada had an average acceptance rate of ~ 70%, which tracks the combined trend. The overall acceptance rate is 61% for synthetic products, which is 7% higher than the combined trend of 54% (Table 2). The high severity of divergence of control strategy is reflected by a low probability of 13.0% for the core documents being accepted by all four countries (Table 3), translating to an 87% likelihood of at least one country not accepting the core document. Using the overall probability of 13.0% (Table 3) as a threshold to compare with individual core document acceptance rate for the four countries, the significant areas of divergence included S.2.3, S.2.4, S.4.1, P.3.3, and P.5.1 as highlighted in red in Table 3. Additional sections that were close to the threshold included S.2.2 and P.3.4.

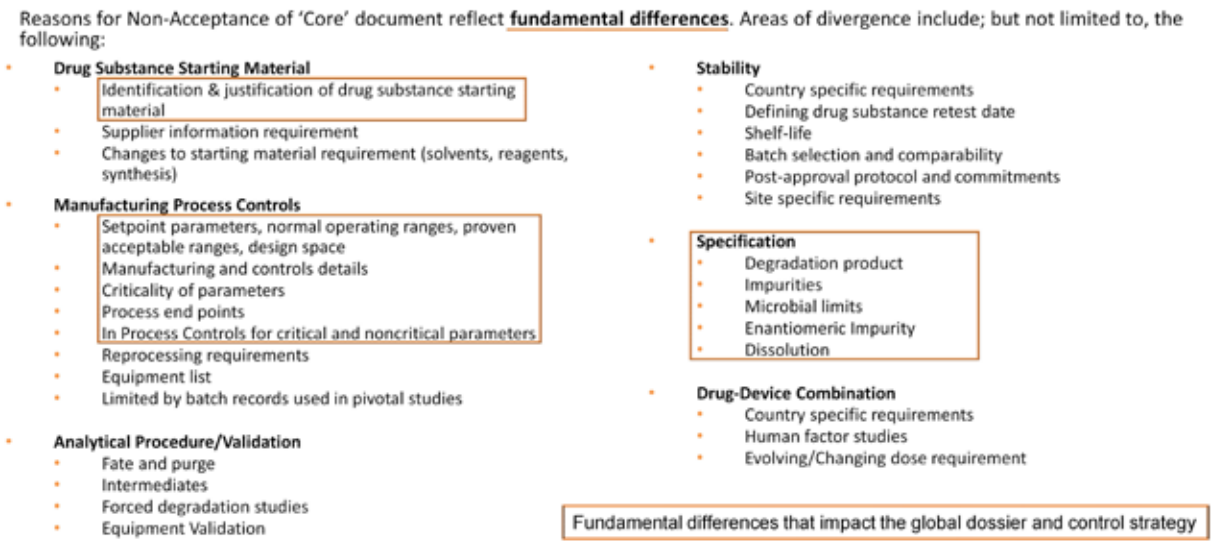
Although the biologic product submissions (48) included in the data set are less than the number of synthetic product submissions, it is sufficient to identify specific areas of significant divergence on control strategy for biological products, as presented in Table 4. For biological products, the individual country core document acceptance rate range is 33% to 59%. The range is lower than for synthetic products, but it indicates significant divergence among the four countries. The overall acceptance rate for biologic products is 15% lower than synthetic products (61%; Table 3). The US had the most divergence observed and Canada had the least, with average core document acceptance rates of 33% and 59%,

Table 4: Core document acceptance rate and acceptance probability for biologic products.

Country	Submissions	Core Document Acceptance Rate [a]										Average Acceptance
		S.2.2	S.2.3	S.2.4	S.4.1	S.7	P.3.2	P.3.3	P.3.4	P.5.1	P.8	
US	13	31%	38%	31%	31%	23%	85%	15%	31%	15%	31%	33%
Japan	5	0%	40%	60%	20%	40%	100%	40%	60%	20%	20%	40%
EU	16	25%	56%	38%	31%	56%	81%	63%	50%	13%	50%	46%
Canada	14	50%	71%	64%	29%	64%	86%	57%	79%	29%	64%	59%
Overall acceptance	48	31%	54%	46%	29%	48%	85%	46%	54%	19%	46%	46%
Probability of acceptance by all four countries [b]		0.0%	6.0%	4.5%	0.6%	3.3%	59.2%	2.2%	7.3%	0.1%	2.0%	3.6%

a. Acceptance rate/acceptance is calculated in percentage by dividing total number of yes answers for core document(s) with the total number of submissions from one or multiple countries/regions.
b. Probability of acceptance by all four countries is calculated as a product of multiplication of core document acceptance rates of all four countries.

Figure 2: Common areas of divergence of core documents.



respectively. Control strategy divergence is more than that of synthetic products and is reflected by a threefold decrease to a very low probability of 3.6% for core documents being accepted by all four countries (Table 4); this means there is a > 96% likelihood that at least one of the four countries would not accept core documents. Using the threshold of the overall probability of 3.6% (Table 4) in comparing with individual core document acceptance probability for the four countries, the significant areas of divergence with lower individual acceptance probability included S.2.2, S.4.1, S.7, P.3.3, P.5.1, and P.8 (highlighted in red in Table 4). To the extreme, Japan did not accept S.2.2 core documents in any submission, translating to a 100% certainty that the S.2.2 document would require at least one additional regional version. Similarly, low acceptance rates by multiple countries reflected a close to 100% probability that S.4.1 and P.5.1 would not be accepted by at least one country.

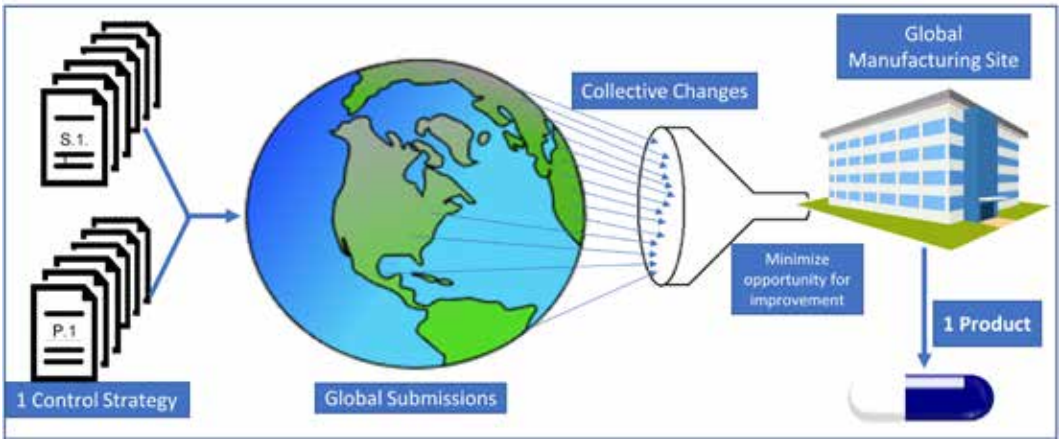
Upon review and discussion of the data, all IQ Working Group members agreed on the common areas of divergence across both modalities for drug substance and drug product, which are illustrated in Figure 2.

The key areas of significant divergence on control strategy based on metrics align well with the areas that have the most common areas of divergence. For both synthetic and biologic

Table 5: Key areas of divergence on control strategy.

Key Area of Divergence	Significant Divergence on Control Strategy
Specification	Justification of impurity acceptance criteria. Justification of required test types, including tests considered yet omitted, in specification.
Description of manufacturing process and process controls	Utilization of ICH terminology and the level of details required in describing process parameter ranges. Justification of criticality of process parameters and/or in-process controls.
Control of materials	Identification and justification of drug substance starting materials.

Figure 3: Industry develops a single global control strategy.



products, key areas of control strategy divergence are related to specification(s), description of manufacturing processes and process controls, and control of materials. For each key area of control strategy divergence, the associated top significant divergence is summarized in Table 5 and its impact is discussed later.

The data shows wide variation in acceptance rates and overall low acceptance rate of documents that industry believes meet ICH control strategy requirements based on their acceptability in at least one ICH region. This is concerning in light of the well-established nature of these regulators within ICH. When considering new ICH regulators and observers, it is reasonable to assume the overall acceptance rate may drop significantly. Industry has an important harmonization strategy to develop and use a single set of control strategy documents, but regional and local preferences drive a plethora of additional commitments.

Pharmaceutical products are typically globally manufactured and released for all marketed countries, not a single or group of countries. As a result (and as illustrated in Figure 3), industry must collate all requested modifications and requirements to create a single set of requirements for "one-product manufacturing." Industry must then accommodate regulatory requests by amending CMC controls or segregating materials for supply in a specific market.

Thus, differing accepted test methods and specifications become barriers to innovation and continual improvement for all global products and patients.

CONTROL STRATEGY DIVERGENCE AND PATIENT IMPACT

The lack of harmonization of control strategies delays access of new medicines to global patients. Applicants must stagger global submission plans for new medicines to allow time to answer questions from global quality regulators. Although applicants submit a single core control strategy to supply the global markets, the same science, justification, and data sets are often interpreted differently by health authorities. This difference in interpretation of control strategy suitability results in the high degree of variability in the volume of questions from global quality reviewers on the same set of documents. Frequently, an applicant will not only experience a large variation in the number of questions, but will also encounter multiple rounds of questions from a given regulator on a particular topic. Additionally, some health authorities have limited windows for an applicant to respond to questions.

As a result, subject matter experts with specific knowledge of the process, testing, and specifications must prioritize preparation of responses over other R&D efforts and spend many hours to provide additional justification for the control strategy that was

submitted and/or implement control strategy changes. The time spent on these efforts limits the ability of a company to submit global applications and inhibits further development and expansion of supply that would allow global patients to have access to potentially life-saving medicines. Among the companies that participated in the control strategy survey, many observed a drastic difference in the number of questions received on the same data between agencies (for example, 19 from one agency and 184 from another). The difference in questions is all too common and reflects notable differences assessing suitability of the control strategy.

Country-specific control strategy requirements can also potentially lead to a drug shortage if material made and released for one region is unsuitable for a different jurisdiction. Pharmaceutical products are typically manufactured for global release, not for a single or group of countries. Local constraints on control strategy, such as tightened manufacturing ranges and/or specifications based on a limited number of manufactured batches, are especially costly. Alternatively, a comprehensive science- and risk-based approach is strongly favored. Although additional control strategy requirements by any given country can be accommodated, the combined requirements of over 100 countries can add significant manufacturing and supply barriers.

The lack of a single control strategy for all countries will lead to needless supply chain complexity and can have profound impact on supply of critical medicines to patients. Although companies may manufacture to the most stringent control (parameter range or specification limit) in the case of failure to meet the tighter controls, country-specific release may be applied. However, country-specific release is inherently a complex process because it is intended to be used by exception and could delay the release of product for distribution. For products with supply constraints due to manufacturing capacity, complex manufacturing process, or unforeseen supply chain disruptions, this can lead to potential stock-outs.

Sponsor X reported a case in which it was requested that an impurity specification limit, based on available batch data, be tightened, even though the process had been demonstrated to tolerate a higher limit consistent with safety considerations. In this situation, a tighter impurity limit for the intermediate would have led to a delay in availability of the new medicine in this country because the product for the launch was made with intermediate that did not meet the tightened specification. The company's rationale for keeping the originally proposed specification was accepted, but often sponsors are forced to accept a lower limit.

ICH CONSIDERATIONS

Expansion of new ICH members and observers is expected to result in continued escalation of divergence and increased obstacles to realizing globally harmonized control strategies. New ICH members have the challenges of adopting ICH guidelines while building internal capability to use them properly, which creates at least temporary divergence as the health authority transitions to the ICH-enabled future state.

At the time of marketing applications, when there is limited experience and data, constraints imposed by global regulators on licensed control strategies are inconsistent with ICH and limit innovative changes after approval. One example of such limitations is how companies describe their product manufacturing controls in the marketing authorization application. Using process control terminologies—such as proven acceptable range (PAR), normal operating range (NOR), or design space (DSp)—resulted in varying interpretations of ICH guidance and led companies to abandon strict adherence to terminology to instead focus on basic scientific principles and a robust, well-controlled process. When scientific principles are applied, some health authorities insist on applying these categories in assessing applications within their jurisdiction [6, 7].

Divergent interpretation and implementation of ICH guidelines among regulators is therefore a growing problem for industry. Applicants are typically left with unnecessarily constrained control strategies, which can limit shelf life, reduce process capability, and restrict changes that could otherwise be implemented through a pharmaceutical quality system. Applicants are frequently left with no option but to accept a country-specific control strategy requirement rather than risk product nonapproval or delays to approval. Examples related to selection and justifications of drug substance starting materials clearly demonstrate the negative impact of such divergence.

As an example, Sponsor A proposed two crystalline products as starting materials that were justified by ICH Q11. Regions/Markets A, B, and Q did not query the sponsor's starting material strategy; Market E was not satisfied with the proposal and requested more of the synthetic steps to be put under GMP control, stating that the proposed regulatory starting materials do not meet ICH criteria, given short synthetic routes from each starting material to the drug substance. The sponsor acquiesced to Market E, defining submissions with starting materials consistent with Market E's preferences, creating a divergence of the control strategy that was approved in other markets. Additional drug substance process performance qualification (PPQ) requirements and other control strategy adjustments can lead to delayed approvals and delayed availability of new medicines for patients.

Similar divergence was observed in a presubmission advisory meeting. Sponsor B proposed starting materials of a synthetic drug substance consistent with ICH Q11 and sought agencies' advice. Agency X agreed with the proposed starting materials. Agency Y did not agree with the proposal and required additional steps from the syntheses of the starting materials to be under GMP control. Agency Y's view was that there was no way to track changes to the starting material processes in the absence of GMP control, which is inconsistent with the intent of ICH Q11. Control strategy changes were made and additional PPQ on drug substance was conducted to satisfy Agency Y. A separate marketing application with revised starting materials was submitted for Market Y, though acceptance of the original starting materials would have provided for earlier submission and approval.

Although not directly part of the survey, recent regulatory response to submissions for COVID-19 vaccines presents an interesting and positive example. Companies initially sought Emergency Use Authorization (EUA) rather than normal submission processes, and supplies were being provided from a clinical manufacturing process. The ability to gain broad approval with a single control strategy has allowed rapid distribution of the vaccines throughout the world. Had the EUA approval process been slowed by protracted control strategy queries, it is possible that access to vaccine would be limited, even now. Increasing efforts toward convergence, a collaborative review, e.g., Orbis, will improve harmonization and lessen divergence. Historically, industry CMC organizations have not held up submissions due to numerous changes to the control strategy caused by divergent interpretations of ICH guidance, but rather as more innovative technology is used to manufacture pharmaceutical products, it will become more challenging for industry to be able to accommodate local needs without resulting in delays.

CONTINUAL IMPROVEMENT AND IMPACT ON POSTAPPROVAL CHANGES

After a product has been approved by the regulatory agencies, it is standard to make improvements in the pharmaceutical manufacturing process to increase production scale, or to implement technological advancements such as real-time testing, or to modify control strategies.

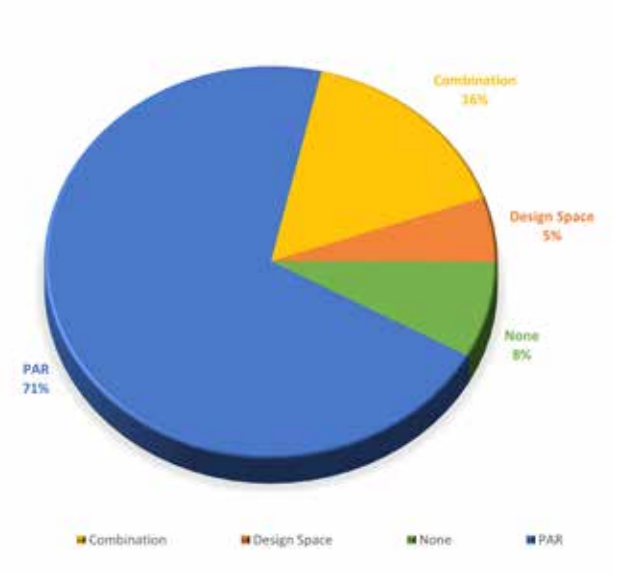
Continual monitoring efforts are in line with ICH Q8, Q9, and Q10 guidance: ICH's Questions & Answers for ICH Q8, Q9 and Q10 states:

> Continual monitoring (e.g., via Continuous Process Verification) can further demonstrate the actual level of assurance of process consistency and provide the basis for continual improvement of the product. Quality Risk Management methodologies of ICH Q9 can be applied throughout the product life cycle to maintain a state of process control [8].

A holistic approach to quality improvements as described in the ICH guidance is the desired state for a robust quality improvement. The FDA and EMA further describe the principles of continuous process verification and how companies may take advantage of new advancements when applying enhanced process understanding coupled with risk management tools and a pharmaceutical quality system. Application of continual improvement in the current regulatory environment is a challenge, made more so when a product has customized controls for multiple markets [9, 10].

In the collected data set, companies were asked to describe their drug substance and drug product manufacturing process (Figure 4). The data illustrated that the term of design space is not used as frequently as PAR, despite most companies routinely undertaking some degree of enhanced development and studying interactions between process variables and product quality in developing the control strategy.

Figure 4: Drug substance/drug product manufacturing process control strategy.



Companies indicated that expectations for justification and change management for control strategy features such as PAR and design space differ across regions and may not be aligned with expectations in ICH guidance [11]. In addition, guidance for postapproval changes globally may categorize all changes to design space as major prior approval changes, regardless of the risk to quality. This discourages the use of design space and does not align with the concepts of quality risk management in ICH Q8–11 or with ICH Q12 [12].

Furthermore, some companies expressed concern that ICH Q12, which will provide guidance on how consideration of risk is used to inform which process parameters should be established conditions and how consideration of risk should inform the notification category for changes, may further confuse the use of the term "design space."

Industry would like the focus to be on the science where production data is reviewed within the quality system for process capability and stability to drive continuous quality improvements. Unfortunately, the aggregated effects of imposed, divergent control strategy requirements by health authorities hamper continual improvement.

New medicines are typically manufactured at a single facility for global use, especially early in the product's life cycle. Drug product batches are manufactured to a single quality standard and are designed to supply the global market. Master batch records, analytical test methods, and specifications must reflect the combined global control strategy requirements. Although control strategy requirements imposed by a single country may appear to have small impact, the combined effect of country-specific requirements is immense. For instance, Module 3 may contain nearly 40 documents and because of known or imposed control

Table 6: Comparison of acceptance rates.

Country	Submissions	Core Document Acceptance Rate										Average Acceptance
		S.2.2	S.2.3	S.2.4	S.4.1	S.7	P.3.2	P.3.3	P.3.4	P.5.1	P.8	
Combined	112	51%	52%	56%	43%	71%	79%	46%	59%	25%	62%	54%
Synthetic	64	66%	50%	64%	53%	88%	73%	47%	63%	30%	73%	61%
Biologic	48	31%	54%	46%	29%	48%	85%	46%	54%	19%	46%	46%

strategy requirements, the global set of documents will result in hundreds of documents to manage at the conclusion of a single life cycle review. In the collected examples, one member company cited four documents that had expanded into 24 documents approved globally due to country-specific control strategy requirements. Therefore, under current circumstances, quality improvement implementations are difficult because multiple market-specific Module 3 documents must be revised to support a given change and to meet the requirements of each market.

Although some country-specific requirements are expected, the industry strives to maximize alignment of control strategies such that the low-risk improvements can take place most efficiently and industry and regulator dialogue can be reserved for the essential elements of the control strategy. However, industry must adapt when markets have differing requirements, including postapproval requirements to support the change. These requirements may include generating additional data such as stability data prior to submission, which results in significant delays. Once global approval has been achieved, industry then implements changes to mitigate the supply chain burden and maintain supply continuity. As markets approve the change, staff members carefully track and update internal document management systems to accurately record hundreds of approvals [8]. Manufacturers have found there are few degrees of freedom to operate due to the combination of specialized requirements and although the recent implementation of ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management is intended to streamline postapproval changes that require regulatory submissions, the lack of agreement on control strategy presents an obstacle that must be overcome to implement ICH Q12. As a result, optimization and improvement may continue to be limited to the few degrees of freedom to ensure manufacturers stay within the combined regulator-imposed control strategy requirements rather than adopting a holistic approach to quality improvements as described in the ICH guidance.

FUTURE PERSPECTIVES

An overall < 9% probability for all four established ICH markets to accept a single control strategy, based on a study of 112 submissions, indicates the need for industry and regulators to work together to develop a common understanding of control strategies. This is a global problem that should be solved together; regional approaches will not address the issue. Although regulator receptivity for a global control strategy is low for both synthetic and biologic molecules, the acceptance rate of control strategy for biologics is significantly lower, as shown in Table 6.

Conventional synthetic small molecules typically require a finite amount of defined CMC content in regulatory submissions, but even here there seems to be little agreement among regulators of sufficiency criteria. Even more information is expected for large molecules such as monoclonal antibodies. Experience to date with control strategy dialogue among sponsors and agencies has been complex, but not unfamiliar to both parties.

It is not unreasonable to anticipate ever-increasing information expectations for new modalities including oligonucleotides, live modalities, oncolytic viruses, hybrid modalities such as antibody-drug conjugates, and nanobodies [14]. Given current circumstances, advanced modalities will likely present unique and unknown challenges as well as potential for greater differences within the industry and among regulators. Harmonization of new modality control strategy questions must be addressed in a more streamlined, rapid manner because the variability of health agency questions and the industry responses to these entities have added years to launching harmonization efforts.

Collaboration among industry and regulators to achieve a globally acceptable control strategy is possible and has been proven even more urgent during the current COVID-19 public health emergency. Collaboration extended beyond the ICH regions provides first steps to provide safe and effective quality life-saving medicine to patients globally [15]. (For example, see the April 2020 statement from the International Coalition of Medicines Regulatory Authorities [ICMRA].) This trend toward better and more productive dialogues between regulators with mutual recognition and workload sharing is very promising, because it is essential for regulators to move toward a common scientific understanding of the core CMC information for a global product. In addition, parallel review opportunities such as Project Orbis and the ACCESS consortium can be used to drive international regulatory harmonization efforts for quality information [16–18].

One possible solution to transform not only the regulatory submissions process itself, but to also streamline parallel health

authority reviews is to develop a cloud-based data exchange platform for one global quality dossier [19, 20]. Such a platform would improve the transparency of sponsor–regulator interactions for the CMC content across different health authorities as well as allow visibility to data packages and queries, thus encouraging commonality of technical detail while reducing redundant requests for information. Automation of CMC content and data with the use of structured content and data management would also improve submission authoring efforts and enable real-time updates and data tracking [21].

CONCLUSION

The efforts toward global regulatory harmonization of product control strategies and CMC content are more essential now than ever before to accelerate the delivery of innovative therapeutics to millions of patients around the globe. As health authorities have pursued use of work-sharing or mutual reliance to accelerate new medicines to patients and reduce workloads, the value of a global dossier available to all global regulators has been made apparent. Despite these potential benefits to global patients, industry, and regulators, this benchmarking study revealed that country-specific requirements can emerge.

Ultimately, the IQ Working Group's goal is to provide data and understanding for rapid improvement toward global harmonization of control strategies driving collaborative reduction in divergence and increase in harmonization, with the support of industry and regulators. This would enable accelerated drug development including novel modalities, advance innovative technologies, and ensure product supply and continual improvement through efficient lifecycle management [14]. The metrics reported here are the first steps toward dialogue and solutions. The gain will be when we do a deeper dive on specific issues that are common across and engage in dialogue with health authorities. The Working Group's recommendation is to have discussions with multiple health agencies in the near future, together, in a forum with real working solutions. The group is open to other ideas from other member companies.

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MEASURING PHARMA'S ADOPTION OF INDUSTRY 4.0

By Toni Manzano and Agustí Canals, PhD

With the rise of new technologies and predictive analytics capable of handling the huge amounts of data within and across existing information systems, Industry 4.0 has been thriving in many sectors, such as industrial automation, financial technology, retail, and semiconductors. But the health sector in general [1], and the pharmaceutical industry in particular [2], has been considered a conservative area, in which innovation has not been adopted as quickly as in other sectors. This article explores how the pharmaceutical industry's adoption of innovation is measured and how the regulated nature of the industry may influence its pace of innovation.

Given the significant advances digital technologies have brought to the automotive, agricultural, and retail industries [3], the pharmaceutical industry should start adopting these technologies to stay competitive in an evolving market. Potential causes of delays in pharmaceutical innovation include recent mergers between large corporations [4] and the influence of pharmaceutical CEOs on their companies' research and development (R&D) priorities [5]. There is a lot of evidence that shows the slow adoption of innovation in the pharmaceutical industry, but how much delay exists in the pharmaceutical industry when compared with other sectors? Could this delay be quantified? Are the regulatory bodies as slow to innovate as pharmaceutical firms? This article seeks to answer these questions.

Pharmaceutical regulations have expanded globally since the early 1960s, leading some observers to suggest that resources dedicated to meeting regulatory requirements and exhaustive quality control are diverted from R&D and innovation [6, 7]. A prominent explanation lies in the regulatory requirements of the pharmaceutical industry [8, 9]. Regulators are involved in the process of new technologies, working with the industry on these and approving them through often accelerated processes.

Furthermore, health authorities are making efforts to spur innovation in the pharmaceutical industry. For example, in 2017, the US FDA created the Emerging Technology Program [10], with the objective of promoting innovative approaches for pharmaceutical product design and manufacturing. The FDA members who participate in this program discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of novel technologies, with a clear purpose of supporting innovation initiatives. In Europe, the EMA established the Process Analytical Technologies (PAT) Team and in the UK, the MHRA leads this topic though the Innovation Office. The Pharmaceutical and Medical Devices Agency of Japan manages equivalent proposals within the Innovative Manufacturing Technology Working Group.

INDUSTRY 4.0 RESEARCH

In 2017, Liao and colleagues completed a systematic literature review of the past, present, and future of Industry 4.0 [11], identifying 224 papers focused on a direct prevalence of the Fourth Industrial Revolution. In the conclusions of this study, the authors noted there were no relevant references regarding regulatory framework, which would be most associated with pharma contexts. The uniqueness of the research topic makes it difficult to explore academic resources describing how recent technologies, mainly brought by Industry 4.0, have been implemented in the pharmaceutical industry.

Some examples of technologies that have seen early adoption in industries other than the pharmaceutical industry include infrared spectroscopy [12], radio frequency identification (RFID) [13], specific software for continuous quality control [14] and, more recently,

artificial intelligence (AI) [15] and big data [16] applications. There are also differences regarding technology adherence within the pharmaceutical industry itself. There is a prominent divergence in the success seen by manufacturing operations compared with R&D departments, which further bifurcates the data [17]. Finally, some initiatives are establishing a scale for the digitization maturity level [19] or the technology adoption degree assumed by emergent pharmaceutical markets versus consolidated geographical areas [16].

The Influence of Regulators

Regulatory agencies can influence the implementation of innovation, as illustrated by the thalidomide episode and the American pharmaceutical industry. After the incident, an attributable slowdown was confirmed by the American pharmaceutical industry, and there was widespread impact that lasted for more than 10 years after the fatal episode [18]. In Europe, a mimetic reaction ended in a comprehensive benefit for both patients and business due to regulation, ensuring the expected quality of final products, reducing the probability of harm in society, and protecting companies from potential counterfeit products [20]. Other views hold both regulatory agencies (specifically the FDA) and pharmaceutical companies responsible for the lack of innovation. Old facilities, legacy technologies, and outdated production procedures contribute to, and may be the ultimate cause behind, the lack of modernization in drug manufacturing [8]. However, pharmaceutical companies may have to use outdated technology and process due to the cost of revalidation tasks: Overhead costs resulting from quality requirements for the R&D and manufacturing operations can add up to 40% of the total structural cost in companies [21].

However, regulators work to support innovation: Initiatives promoted by public administrations like the Emerging Technology Program [10] created by the US FDA are oriented to facilitate the adoption of new technologies in the regulated manufacturing industry. Previous attempts proposed by worldwide institutions, such as the ICH Q8 guideline [22], describe how to get and apply knowledge through specific technology elements in pharmaceutical development to ensure quality product by means of a scientific approach. Additionally, the initiatives such as the FDA guidance accelerate approvals for medicines required to treat rare and life-threatening maladies [23].

Pharma 4.0™

During the opening plenary session at the 2018 ISPE Continuous Manufacturing Workshop [24], Lawrence Yu, Deputy Director of the Office of Pharmaceutical Quality in the FDA Center for Drug Evaluation and Research, highlighted the potential impact of Industry 4.0, through the use of AI and other 4.0 technologies, on pharmaceutical manufacturing and personalized medicines. Under the concept of Pharma 4.0™, systems and equipment have become increasingly interconnected with the use of digital technologies, which can provide unprecedented opportunities for the pharmaceutical industry. Regulatory agencies are demonstrating flexibility when faced with critical events that require a particularly quick response, such as during the COVID-19 pandemic [25]. This same attitude has been shown regarding innovation adoption. A clear example is the request for support published by the FDA to consider AI as a valid component to be included in medical devices [26].

Determining the pace of adoption for specific technologies in the pharmaceutical sector and other manufacturing industries can provide a clear picture about the overall pace of adopting innovation.

PACE OF ADOPTING INNOVATION

Determining the pace of adoption for specific technologies in the pharmaceutical sector and other manufacturing industries can provide a clear picture about the overall pace of adopting innovation and, specifically, the lack of innovation attempted by pharmaceutical manufacturing. Drugs are products with sensitive impact in society, and they need to be well controlled throughout their entire life cycle. Taking this assumption as a legal imperative, regulators have a crucial role around the entire process. In terms of innovation, regulatory agencies must determine how new technology implementations will impact the quality, safety, or efficacy of the final product and ensure these technologies are under control and can be implemented without risk to the patient [27]. When changes are introduced within already approved procedures, they must be revalidated; this fact is usually considered as a penalty introduced by the regulatory requirements [28]. Nevertheless this assumption is completely wrong. Regulatory bodies are enablers and facilitators of innovation that always ensure patient rights and mainly their health. A clear evidence of the regulatory agencies support of new technologies is based on the incorporation of companies' technology recommendations into their guidelines [22].

COMPARATIVE STUDY

In this comparative study across industries, historic moments will be examined, including when specific technologies were adopted by pharmaceutical companies compared with early adopters in other industries. Looking at similar technologies that have been

adopted by the pharmaceutical industry and comparing their early acceptance with when they were endorsed by other sectors can help illustrate the different pace of technology adoption between both groups and provide a clear picture about the lag experienced by pharmaceutical manufacturers. (Actually, the pharmaceutical industry is still progressing through the automation challenges related to Industry 3.0, although it may bypass further implementation and progress directly to Pharma 4.0™ [28]).

This idea can be extended to other functions within the pharmaceutical industry, specifically the large difference between R&D and manufacturing [17]. The measurement of technology adoption will be the basis to create an index that might be used to establish a quantification for the adoption of innovation in the pharmaceutical industry. In addition, a broad perspective will be drawn, which will include the technologies' date of discovery/invention and when they were officially included by regulatory agencies in the pharmaceutical industry.

For example, the ICH Q8 guideline referenced previously was designed to help companies, reviewers, and inspectors perform their tasks more efficiently. The foundation of this guidance establishes the demonstration of deep knowledge of pharmaceutical and manufacturing sciences as the main driver to create a basis for flexible regulatory models. An explicit reference to near-infrared (NIR) is designated in this document as valid technology for real-time release when it is properly described in terms of process understanding within the submission. The guidance describes how the implementation of NIR for unit dose uniformity control would be integrated into the process when the expected uniformity is achieved, without waiting for a fixed time as is usually required in classic recipes. But NIR is not the only spectroscopical technology used to perform homogeneity tests; other implementations include Raman or mass spectroscopy. When more than one technique is available for a specific innovation, those techniques are also considered for inclusion in the documentation.

The selected technologies have been identified as relevant and innovative applications that were deployed in drug manufacturing at some stage of the product life cycle. To be included in this study, the technologies had to be referenced by regulatory bodies. Records associated with official regulations in the pharmaceutical industry supporting or describing guidelines for the proposed technologies have been included in the analysis to identify potential links among official constraints and speed of technological adoption effects.

TECHNOLOGIES AS TRANSFORMATION ENABLERS

The collected records correspond to technologies that are considered transformation enablers within manufacturing processes because the industries experienced improvement after or during implementation of these technologies. Examples of enhancements in the pharmaceutical industry provided by innovation are associated with a reduction of variations brought on by the inevitable manual operations and uncontrolled properties of raw materials. Applying this reasoning, the following technologies were considered in the research.

Spectroscopy

Spectroscopy allows real-time testing during manufacturing. It is usually mentioned in pharmaceutical guidelines motivating systems for nonintrusive measurements and is broadly referenced for PAT applications [30]. NIR, Raman, and mass spectroscopy are the spectroscopy techniques discussed here. Regulatory agencies extensively recommended NIR as a way to implement process control to acquire online knowledge of product attributes without physical contact. Spectroscopy techniques have been used and standardized in pharmaceutical manufacturing as an analytical method for quality control and process verification [31].

Chromatography

Chromatography is a multivariate technique used for substance identification in production environments and for purification in biotechnology processes. It is used to separate components in mixtures, presenting different methods depending on the characteristics of the components contained in the sample. Using chromatography for purification is an implementation widely applied in pharma-biotechnology operations, and it is well established in the pharmaceutical and other industries [32]. For this reason, chromatography will be included as a relevant method in manufacturing. High-performance liquid chromatography (HPLC) and mass chromatography are the representative techniques of this technology.

Lyophilization

Lyophilization is a physical process in which water is eliminated by sublimation in products and the manufactured item is then subjected to vacuum conditions. Lyophilization is extensively used in the food industry and mainly applied in drug manufacturing for batch process freeze-drying and continuous process spray-drying [32]. It's worth noting that 46% of FDA-approved protein, peptide, vaccine, oligonucleotide, and cell-based products are produced using this technique [33].

Radio Frequency Identification

RFID is a widespread technology used in logistics and manufacturing to track and ensure traceability of materials and products, and it requires sophisticated mechanisms that have been globally adopted. RFID enables total traceability along the product supply chain. Product traceability is required in drug manufacturing and one of its most known applications is to avoid counterfeits [13].

Artificial Intelligence

Although is a computing term that, strictly speaking, is not a technology, the introduction of this discipline in the industry boosted technological breakthroughs driven by the Industry 4.0 wave [15], impacting the pharmaceutical industry as well [34].

3D Printing

3D printing is a technology born in the 1980s that creates three-dimensional objects by adding layers of material to fill sequential

Table 1: Innovation dates extracted from literature.

Innovation	Discovery or Invention	Nonpharma Industry	Pharmaceutical Industry	Regulatory
NIR Spectroscopy	1800 [37]	1938 [38]	1977 [39]	2004 [22]
Mass Spectrometry	1917 [43]	1920 [43]	1990 [44]	2003 [45]
Raman Spectroscopy	1928 [46]	1987 [47]	2002 [47]	2004 [22]
High-Performance Liquid Chromatography (HPLC)	1941 [48]	1966 [48]	1972 [48]	1994 [49]
Gas Chromatography	1952 [54]	1962 [54]	1985 [54]	1994 [49]
Lyophilization	1890 [40]	1935 [41]	1950 [33]	1993 [42]
Radio Frequency Identification (RFID)	1948 [50]	1973 [51]	2005 [52]	2007 [53]
Artificial Intelligence (AI)	1956 [55]	1988 [56]	2012 [57]	2017 [58]
3D Printing	1984 [35]	1986 [35]	2009 [59]	2015 [60]
Big Data	1985 [36]	2002 [61]	2011 [62]	2019 [27]

and consecutive sections of the object. More than 30,000 patents regarding 3D printing have been reported in the US alone, and its industrial expansion is mainly due to support from open-source computer programs [35].

Big Data

Big data is computer science technology in which huge volumes of data belonging to a large variety of records are accessed at high velocity, which establishes the main dimensions that characterize a data management system initially architected on the Map Reduce mechanism [36]. This innovation has often been linked to the Internet of Things (IoT) when applied to manufacturing, because the records generated by this technology are large, varied, and quickly produced [16].

KEY BENCHMARKS IN ADOPTING INNOVATION

For each technology, four dates were extracted from the literature: year of discovery or invention, year first used in the industry, year first used in the pharmaceutical industry, and year it was considered by regulatory bodies. Table 1 contains the raw dates and the references from which they were extracted.

Figure 1 shows the adoption lead times of the selected technologies: first, the date of discovery or initial use, followed by adoption by nonpharmaceutical industries and then pharmaceutical industries, and finally inclusion in regulatory references. Although the periods vary depending on the technology, there is a consistent delay for all technologies regarding their adoption in the pharmaceutical industry, indicating later endorsement of the innovations in drug manufacturing and inclusion in regulations as well (taking the first implementation in other sectors as reference). The technologies have been grouped by field: chromatography, Industry 4.0 (AI, big data, 3D printing), lyophilization, and spectroscopy.

To establish indicators that may reveal inferences between the pharma industry and industry in general, regulations and gaps between the considered dates are used. Therefore, the following factors will be calculated, all measured in years:

- The time between adoption of these technologies by the pharma and nonpharmaceutical industries (GapPharmaNonPharma)
- The time between the pharmaceutical industry adoption and the first regulatory reference to a specific innovation (GapRegulationPharma)
- The time between invention of discovery of the technology and its adoption by nonpharmaceutical industries (NonPharmaIndustryAdoption)
- The time between invention of discovery of the technology and its adoption by the pharmaceutical industry (PharmaIndustryAdoption)
- The time between invention of discovery of the technology and the first regulatory reference to a specific innovation (RegulationAdoption)

These factors normalize the measurements. The statistics calculated for each, represented by the box plots in Figure 2, indicate the

Figure 1: Evolution of different technologies (grouped by field) since discovery or initial use until adopted by nonpharma industries and by pharma, and included in regulatory references.

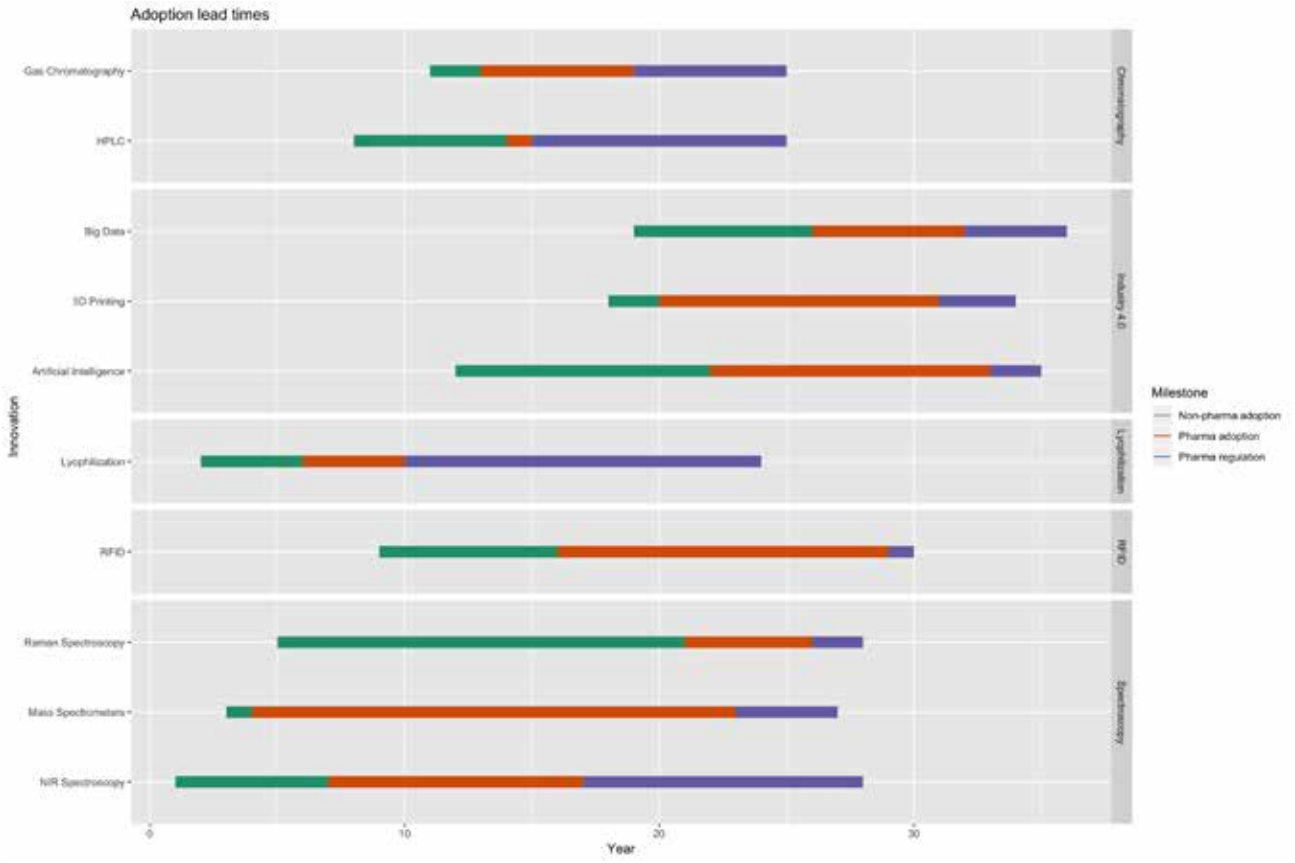
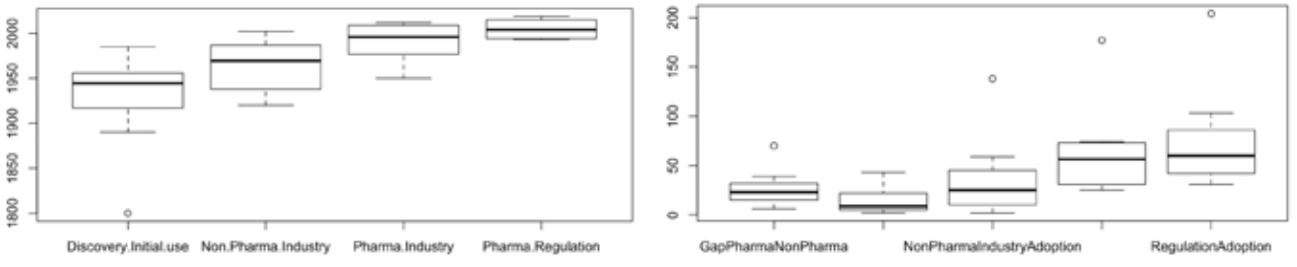


Figure 2: Box-plot representation of time distribution, in years.



presence of a clear outlier. Applying the Dixon test for outliers over the values corresponding with the discovery/invention date (displayed as Discovery.Initial.use in the box-plot of the Figure 2), produces a p value = 0.087 for the hypothesis that the NIR's invention date is an outlier.

In Figure 2 are Dates (left) when technologies were (a) discovered/invented (Discovery.Initial.Use); (b) adopted in pharmaceutical industries (Non.Pharma.Industry); (c) adopted in biotechnology/pharmaceutical industries (Pharma.Industry); and (d) referenced by regulatory bodies (Pharma.Regulation). On the right in Figure 2 are differences in technology adoption between (a) pharmaceutical and nonpharmaceutical industries (GapPharmaNonPharma); (b) pharmaceutical industry adoption and first regulatory reference (GapRegulationPharma); (c) technology discovery and nonpharmaceutical industry adoption (NonPharmaIndustryAdoption); (d) technology discovery and pharmaceutical industry adoption (PharmaIndustryAdoption); and (e) technology discovery and regulatory reference (RegulationAdoption).

Due to this evidence, the outlier is removed from the data set [63]. Only the gaps between pharmaceutical and nonpharmaceutical industries and between the pharmaceutical industry and regulatory bodies are kept for the NIR technology, because both measures are calculated by means of increments between the observations and therefore, the impact on the small data set is minimized. Applying this rule, the calculated factors take the values described in Table 2.

Considering this configuration, the results indicate that although there are records referencing the initial usage of technologies in the industry generally 24 years after their discovery or invention, on average the pharmaceutical industry assimilates initial usage 48 years later (±6 years). Furthermore, technology implementation by early pharmaceutical adopters was led mainly in R&D, not in manufacturing. Regulatory bodies included the sampled technologies an average of 12 years after they were implemented in pharmaceutical activities. Beyond this figure, a reaction can be observed in the agencies when drug companies prove the feasibility of innovative systems in their internal structures. Two indexes can be created for comparing the pharmaceutical innovative adoption:

The measurement of the pharmaceutical early adoption (PEA) provides the ratio among the pharmaceutical field and the industry implementation of a specific innovation. The smaller the index, the faster the innovative adoption is in the pharmaceutical industry compared with other industries. Values for PEA greater than 1 indicate a slower process of incorporating innovation in the pharmaceutical industry. For the set of technologies discussed in this approach and represented in the Table 1, the value of PEA = 1.99.

$$PEA = \frac{PharmaIndustryAdoption}{NonPharmaIndustryAdoption} = 1.99$$

Comparing how quickly regulation includes new technologies compared to companies, the ratio among the difference of time needed by regulatory agencies and pharmaceutical companies and the time required for companies introducing these technologies, gives a measure of the innovative attitude of the administrations. This coefficient can be identified as REA (regulatory early adoption) and is calculated taking the pharmaceutical company as reference and not the industry because for the regulatory bodies, the implementation of new technologies only make sense once they have been accepted by pharmaceutical companies. For the set of technologies considered here, REA = 0.28, which means that the regulatory bodies are faster than pharmaceutical companies in integrating innovative applications inside their mechanisms of control.

$$REA = \frac{GapRegulationPharma}{PharmaIndustryAdoption} = 0.28$$

Pharma's Delay

Sorting the technologies by their invention date and observing the adoption speed by nonpharmaceutical industries (using the NonPharma IndustryAdoption factor) and by pharma (using the PharmaIndustryAdoption factor), a systematic delay is observed along the history experimented by the drug manufacturing. Furthermore, the trend evidenced in Figure 3, confirmed by both categories (pharmaceutical and nonpharmaceutical industries), can be interpreted as an acceleration in the adoption of new technologies in more recent decades.

Creating sets of technologies which cluster similar innovations or keeping the specific invention as a standalone, there are five groups that can be compared by means of the PEA and REA indicators to measure the differences between the pharmaceutical industry and regulatory bodies in terms of the innovative attitude.

The spectroscopy group contains the NIR, Raman, and mass spectroscopy techniques; the chromatography group includes the HPLC and the gas systems; the Industry 4.0 group includes AI, big data, and 3D printing; lyophilization and RFID technologies constitute two independent measures that cannot be aggregated with any other innovation. The results of calculating the PEA and the REA values, based on the average of the elements for each category or using the individual values for the classes with only one element, are shown in Table 3.

Table 2: Distribution in years of the mean and the standard deviation values for innovation adoption considering the gaps between the pharmaceutical sector and the rest of sectors, the gap among the administrations and pharmaceutical companies, the needed time for the industry in general, the period of time required the pharmaceutical industry, and the elapsed time used by regulatory bodies.

Values in Years	Mean*	Standard Deviation	Mean Variation
Gap Pharma-NonPharma	25.60	18.54	5.86
Gap Regulation-Pharma	13.70	13.20	4.17
Nonpharma Industry Adoption	24.22	19.04	6.35
Pharma Industry Adoption	48.33	19.73	6.58
Regulation Adoption	60.55	24.16	8.05

* The mean variation ($\alpha\backslash\wedge\mu$)) is calculated considering N including the outlier associated to the NIR technology only for the Gap Pharma-NonPharma and Gap Regulation-Pharma variables.

CONCLUSIONS

The pharmaceutical industry can be deemed a key sector in the industrialized world for several reasons. From an innovation perspective, drug production is recognized as an industry that invests huge amounts of economic resources in R&D, where technology is a main constituent in development strategies. On average, 10% of sales is invested in the area that establishes the approach and deployment of sophisticated systems, aiming to control the production process and the facilities [64].

Figure 3: Adoption time in years experienced by nonpharmaceutical and pharmaceutical industries since the technologies were invented/discovered.

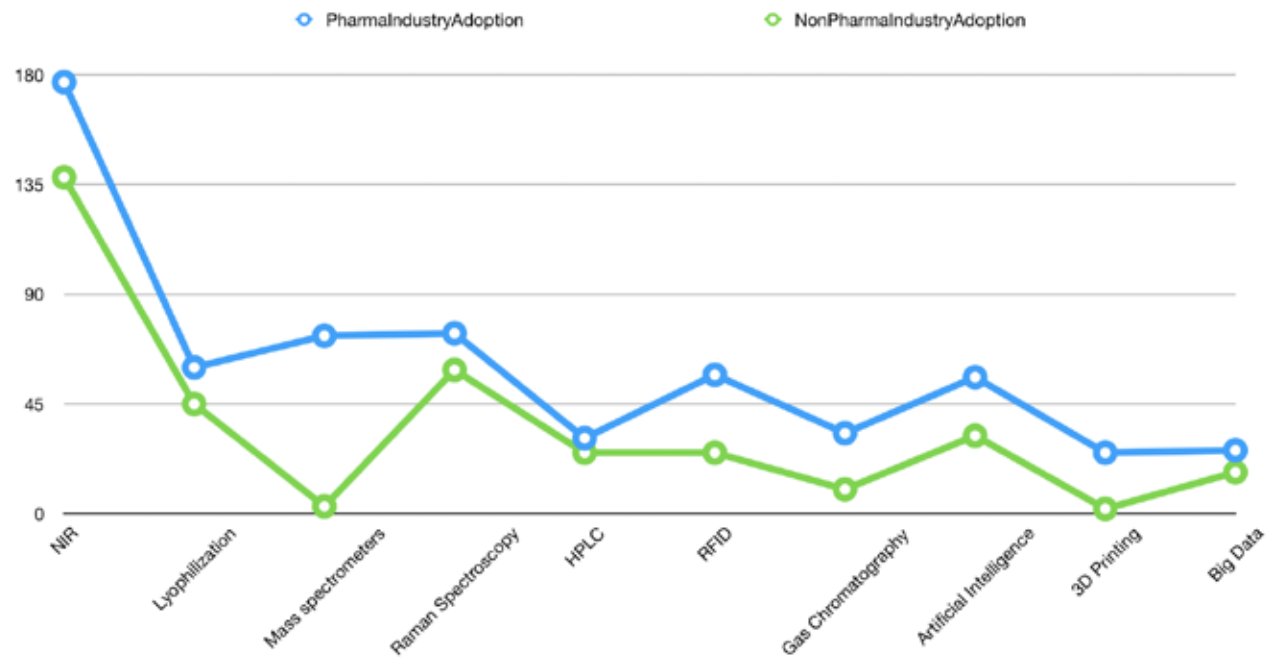


Table 3: Measurements of the PEA and the REA indicators calculated for the established categories defined by the observed innovations.

	Spectroscopy	Chromatography	Lyophilization	RFID	Industry 4.0
PEA	1.62	1.83	1.33	2.28	2.10
REA	0.13	0.48	0.72	0.04	0.18

Finally, drugs have been designed to provide positive outcomes for patients and to improve the welfare of the population, even though there is an undeniable risk of unfortunate episodes (where people died or the treatment did not provide the expected outcome). Although some recent opinions regarding a relaxing attitude in regulatory agencies could be misunderstood [65], the reality is pointing a different direction. Health authorities are providing tools to enable more flexible drug manufacturing operations, but a demonstrated indepth knowledge of robust process and product development is required before adopting the measures introduced by regulators. The implementation of these opening rules is only accepted because they provide safer manufacturing for the benefit of the end patient.

From a patient-centric perspective, the slower innovative attitude in drug manufacturing in comparison to other industries (see Figure 3) is justified by the required control of the fabrication process to preserve the safety of patients. As regulatory agencies have repeatedly shown, they act quickly in front of critical episodes such as the coronavirus pandemic. The innovation delay cannot be explained by regulatory obstructions.

On the other hand, the introduction of new technologies in compliant guidance has been always faster than their implementation in the pharmaceutical industry, as can be observed by the REA and PEA factors in the Table 3.

Notice that the innovations linked to equipment requiring physical contact with drugs during the manufacturing operations (spectroscopy, chromatography, and lyophilization) present a PEA lower than those technologies not used to directly manage the product. However, the regulatory agencies are slower to include those techniques in their guidance than innovations not physically in contact with the drug (for example, big data or AI). The 3D printing technology is an exception in the Industry 4.0 group

(PEA = 12.5, REA = 0.24), which could be related to the intrinsic relationship between the physical process creating drugs by this technology and the Industry 4.0 basis.

Finally, an acceleration can be ascertained from the regulatory agencies, including technologies developed under the umbrella of the Industry 4.0 (REA = 0.18), whereas pharmaceutical manufacturing is keeping a similar pace (PEA = 2.10) than observed for other innovations.

To ensure more rapid adoption of novel technologies, we recommend the pharmaceutical industry work more closely with all the actors involved in the community, including regulators and suppliers, to speed up the regulatory framework of these technologies, as the pharmaceutical industry can play a critical role in this process.

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DRIVING BIOPHARMA SOLUTIONS

With Digital Technologies

By Martin Mayer

Developing comprehensive digital solutions is crucial for the entire value creation process for pharmaceuticals. A holistic view of the interrelations of product, production process, and plant is becoming increasingly significant. In this context, the application of model-based technologies provides support in drug development, process scale-up, and manufacturing. Furthermore, it accelerates time to market. The prerequisites: adequate software solutions and the willingness to break down silos and bridge gaps between disciplines.

Several often interrelated trends are driving change in the pharmaceutical industry and not only because of the COVID-19 pandemic: achieving quicker production of new drugs, accelerating time to market, and delivering affordable patient treatments. These trends make unprecedented demands in terms of agility, flexibility, and adaptability and must be addressed by science and technology—and this is where digitalization can contribute significantly.

By using digitalization strategies—which contain innovative approaches to discover, develop, and manufacture new drugs—agility is increased and overall development and production time is reduced. The full potential of available technologies, such as simulation or data analytics, could be even better realized by uniting them in a smart way. This would require combining and using data that results from all aspects and phases of the life cycle of a drug, from its development, clinical studies, and production process all the way up through to the responses of patients to their treatments (e.g., desirable side effects).

DIGITAL TWINS

A key aspect of the large change process based on digital technologies, also known as digital transformation, is the digital twin. The digital twin is the most exact virtual representation possible of a real system, with all its components, their properties, and functionalities. In the pharmaceutical industry, everything starts with the patient's needs and the goal is to develop a drug targeting those needs. A process capable of delivering a stable product and engineering a plant that is fit for the process must be established. This is why we speak of several twins—the digital twin of the patient, product, production process, and production plant.

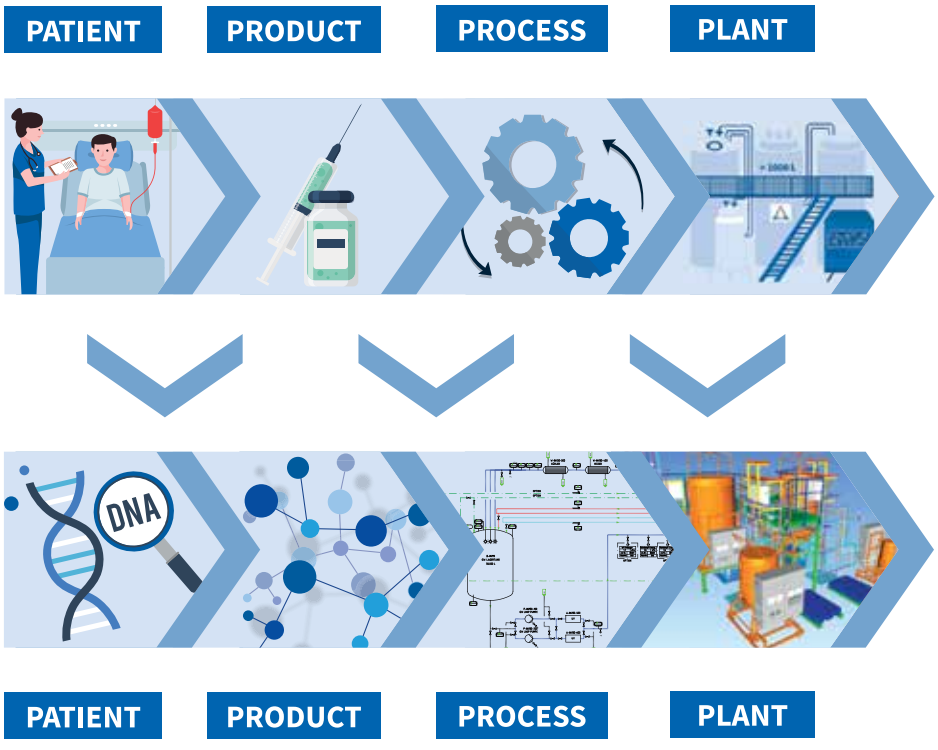
A key challenge for companies active in drug development is to shorten the lead time from early-stage development in the clinical phase to the commercial production scale. Smartly applied digitization is crucial for the entire value creation process. It is no longer enough to just optimize individual steps in the value chain: a holistic approach is required.

THE 4 PS OF THE VALUE CHAIN

The pharmaceutical value chain is based on four fundamental and strongly interconnected elements: the patient, an effective product, an approved production process for that product, and a functioning plant to make that product, all of which work according to the regulations of the authorities. Each of these "4 Ps" can find its virtual representation in a digital twin (see Figure 1).

The trend toward personalized medicine makes patient data increasingly important. The patient's digital twin would include their genetic properties and personal medical characteristics like metabolic fluxes or drug reactions. The digital twin of a product tailored to the patient's needs contains information about its molecular structure and properties, its critical quality attributes (CQAs), and its design. The production process—with its individual steps, required equipment, critical process parameters (CPPs), and control and simulation systems—can also be depicted by its

Figure 1: The 4 Ps of the pharmaceutical value chain are interconnected. Each element finds its virtual representation in a digital twin (figure © Zeta).



own digital twin. The virtual representation of the production plant on which this process is run is based on data regarding building layout; the respective equipment, utilities, modular structures and their properties; piping; and technical building equipment.

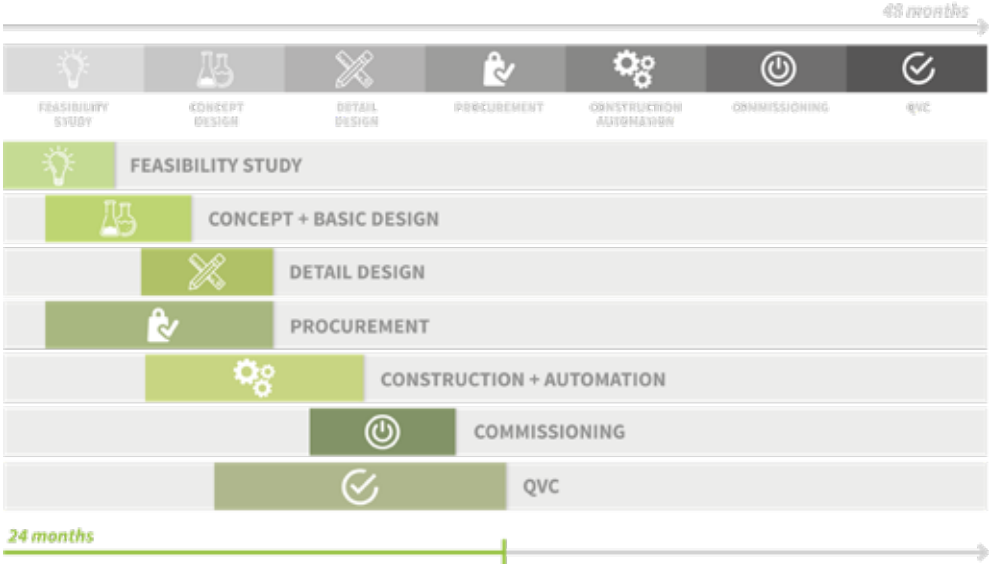
INTEGRATED ENGINEERING FOR PROCESS AND PLANT

In the pharmaceutical industry, digital platforms allow for aggregation of massive amounts of data from a variety of sources. During production, for example, data on the current state of the plant and product are generated by metrological instrumentation and the records required by GMP are made digitally in the electronic batch record to safeguard the product's quality. Data from operations alone are often not sufficient for an efficient and reasonably usable digital twin of a system for maintenance, energy, or production optimization. Data that have already been generated in the course of system planning (e.g., 3D data, extensive information from piping and instrumentation diagrams [P&IDs], component specifications, and electrical planning data), so-called metadata, serve as a valuable addition here.

The integration of data derived from process monitoring and engineering results in a digital twin that is useful for a number of applications. The prerequisite for this integration of the virtual, digital world into the real, physical world is uniform data from all engineering disciplines through all project phases (concept, basic, and detail engineering).

However, the creation of harmonized data—the digital twin—is impossible as long as the data only exist in silos, as is still very often the case. During investment projects to create a manufacturing facility for a new drug, a number of project partners are included and many aspects have to be covered—engineering, process scaling, applying the needs of cGMP—and multiple disciplines have to be integrated, such as process engineering, 3D design, electrical engineering, automation, and qualification. Although state-of-the-art technology may be used (e.g., computer-aided design software for creating P&IDs, 3D models, or electrical wiring diagrams), the respective tools are usually operated separately by the project partners and do not blend data with each other. By using digital, integrated engineering, such data silos are avoided and uniform data are generated. Specific product life-cycle management solutions cover the workflows from concept design of a plant to basic and detail engineering (P&ID, electrical engineering, 3D design, electronic qualification and allow all project partners to deliver harmonized data from all disciplines. These tools serve as one common software landscape for all project partners and enable data input, data management, and data use. All engineering workflows and user-oriented front ends are covered.

Figure 2: A high degree of parallelization of project phases significantly reduces time from 48 to 24 months.



Combining data input of all project partners in real time delivers a harmonized data set: the digital twin of the process and the plant. This harmonization of data significantly reduces project risks due to 100% transparency for all project partners at all times. This transparency results in benefits in many areas, such as change management. Unavoidable changes of equipment at later stage of engineering require massive effort, as they affect all disciplines: Changing a pump in its dimension causes impact, from the 3D design all the way to electrical and automation engineering and qualification workflows. Communication of the changes to all disciplines are time-consuming and error-prone. Integrated software landscapes allow better management of these changes, because consequences of changes become transparent before the change is approved, and all project partners can follow up on the change in real time in their own domain.

A refinement of the digital twin of the process by including a process simulation offers further advantages in qualification and validation. An example: the possibility to revert to a simulation of plant and process during automation software commissioning allows testing of functionalities (like recipes, control strategies, and interlocks) within a short timeframe and independent of equipment. This results in shorter commissioning times during factory acceptance and site acceptance tests (FATs and SATs). Furthermore, this simulation can serve as the basis for operator training simulations.

Finally, this harmonized data are the basis for future applications in the field of augmented or virtual reality, as it contains all the information about the 3D dimensions, the equipment (tag numbers, spare parts), and its location on the manufacturing site.

Recently, the approach to apply one centralized digital toolchain delivered remarkable results at a project in Vienna, Austria. The project covered the engineering and construction of a downstream processing facility for vaccine production, in accordance with already existing facilities. The scope included civil construction, electrics, HVAC and cleanroom, process equipment, utilities, automation, qualification, and commissioning. To ensure market supply for the human papilloma virus vaccine, the targeted project lead time was 24 months from feasibility study to first production run. To meet the ambitious timeline, the engineering phases were parallelized (see Figure 2).

To handle the complexity increase that resulted from concurrent work, a centralized digital platform was applied. This platform allowed efficient management of the different disciplines and project partners during all project phases. Collaboration between project partners and the end customer was supported, and efficient reviewing of P&IDs and 3D design, including real-time access to the 3D model, was ensured via a collaboration platform. As the project progressed, all documents, specifications, 3D models, wiring diagrams, and automation applications contributed to the digital twin of process and plant. At the end of the project, a comprehensive digital twin of process and plant was available and was used for commissioning tasks as well as for later operations.

This digital twin served as a tool for communication between the project partners and the end customer, and it helped ensure plant usability, a maintenance-friendly design, and appropriate ergonomics. All equipment (including actuators, sensors, and vessels) and their locations were digitally specified and managed, and a complete list of spare parts was available. This data was combined in a mobile application running on smart devices for supporting the maintenance tasks (see Figure 3).

Figure 3: Combining digital data on a smart device for maintenance support.

PROCESS DEVELOPMENT AND SCALE-UP

Data are also digitally recorded and documented in product and process development. Modeling and computer simulation techniques are increasingly being used. The process, which was initially developed on laboratory scale, is mapped digitally and the result is used for technology transfer. For clinical development, a scale-up is necessary, as larger quantities of product are required, which must be manufactured meeting GMP criteria.

During product and process development, when process conditions are specified on a scientific basis using quality by design (QbD) principles, valuable information is generated and essential criteria are worked out. The CPPs are defined, which has a decisive influence on the CQAs of the product. This implies it is reasonable to develop and optimize the product or process and at the same time derive valuable information for engineering the scale-up (pilot scale) and the manufacturing plant (production scale). Following the approach of FDA industry guidance [1], this data should be used beyond the development stage, which is still not widely applied.

Fermentation in a bioreactor is an example: design parameters have a decisive influence on product quality. On a one-liter scale, a large amount of data that affects the interaction between the product and the process is determined in the laboratory: gassing rates, temperature, pH value, and occurring pH jumps. These parameters (design of experiment [DoE]) span a space in which many variations are possible and optimum conditions are evaluated (bioprocess modeling) [2]. In the next step, a set of parameters is assigned to the design of the production plant. A determined oxygen input, for example, can be achieved in different ways, such as by adjusting the shape and geometry of the agitator or by the design of the gassing device [3].

Model-based technologies, as part of the digital process twin, are the key to simulations and many optimization measures. Experimental time is reduced by model-based DoEs during process development and characterization. A further benefit of the models is the possibility of using them in the context of closed-loop process control [4], operator training, or for virtual sensing techniques (soft sensors) that are used to provide alternatives to costly or impractical physical measurement instruments.

MODELS FOR CLOSED-LOOP PROCESS CONTROL

The bioprocess model can be described as the digital twin that results from combining data on the production process and the product itself. On account of the QbD approach, DoE-based bioprocess models have been applied in process development for over a decade. In the manufacturing stage, however, process models are not yet applied, even though the exploit of the power of mathematical models was recommended by the FDA in the PAT guideline [1]. Following the PAT guideline, future submissions may include new control strategies, such as model predictive control (MPC). MPC resorts to the bioprocess model based on the QbD/DoE approach. To provide a proof of concept, the applicability of DoE-based mathematical models for closed-loop control of a manufacturing process was explored and demonstrated. Using this approach completes a major step in closing the gap between process development and manufacturing.

Closed-Loop Process Control

In the proof of concept previously outlined, a closed-loop control strategy, as depicted in Figure 4, was elaborated. In closed-loop control systems, also known as feedback control systems, process variables are automatically regulated to a desired state. Such systems possess the ability to self-correct without human intervention. Closed-loop control in manufacturing processes is supposed to become even more relevant when moving toward continuous processes.

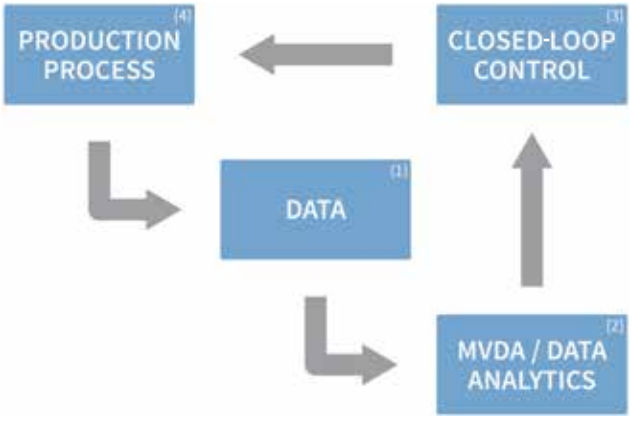
Establishing Closed-Loop Control Technology

To establish closed-loop process control, a number of software tools are applied. Several workflow steps have to be taken until the application can start:

Modeling/DoE

An applicable process control strategy has to cover the interdependencies of the CPPs and the resulting CQAs. In the experimental setup for a fed-batch cultivation of E. coli in a 60 L GMP-compliant bioreactor equipped with an industrial automation system (DCS), temperature, feeding rate (growth rate), and induction strength were assigned CPPs, and the CQAs were biomass and soluble product titer. For modeling of these interdependencies, a novel software tool was used. This tool combines a parametric model, covering the basic principles within the process (mass and energy balance, for example) with a nonparametric model (machine learning algorithm, artificial neuronal network) [2, 5–7].

Figure 4: Closed-loop control strategy: (1) During the production process, data are generated by sensors, actuators, and the methods of process analytical technology; (2) Data analytics based on a mathematical model; (3) Elaboration of a closed-loop control strategy based on the gained know-how; and (4) Connection to the process via PCS.



MPC

The MPC is a software that further uses the established model and combines it with an objective function. In principle, it is like a GPS navigation system in a car: the model is the map, the MPC is the device, and the objective function allows for different strategies to follow—shortest route, fastest route, cheapest route. After defining objectives and constraints, the setup is used for optimization. The optimization algorithm calculates the optimal values for the manipulated variables (in this case, temperature, feeding rate, inducer). The software receives the references for these manipulated variables, as well as the current values for the controlled variables (product titer, biomass) from the process control system (PCS). It further calculates the next values for the manipulated variables and transmits them for execution to the PCS.

MPC approach benefits

With the scientific-based approach using intensified DoE, the process is explored in an advanced way. A robust model of superior performance in terms of robustness, accuracy, and reproducibility is generated. The reuse of this elaborate model for closed-loop process control enables the process to run in perfect conditions regarding titer and quality of product.

Starting the building of the model early in process development phase enables model transfer along scale. With minor adaptations, models can be used from small scale up to large scale. Hence, the implementation of MPC ideally starts in development phase when process variations for model calibration are available. This reduces risk, improves plant performance, and assures the intended quality. Furthermore, flexible operation strategies are supported, as changing of boundary conditions while safeguarding the quality of the product is facilitated.

With the scientific-based approach using intensified DoE, the process is explored in an advanced way.

From a cost perspective, it can be concluded that applying MPC at production facilities will significantly improve plant efficiency by improving yield/time and yield/space ratios. It can counteract out of specification (OOS) production and potentially save full production batches.

CONCLUSION

It is important to overcome the siloed thinking that exists among lab, pilot, and industrial scales. If the appropriate digital twin of the biological process (bioprocess model) has been developed at the small scale, it can be accessed in the planning for the next larger step and has the potential to greatly increase the accuracy of the CPPs at larger scales. Simulated test runs can be performed and fewer test runs at production scale are necessary, which can significantly reduce time to market. Furthermore, the bioprocess digital twin can be used to address a variety of questions about the influence of process parameters, equipment, conditions, safety, and competitiveness.

Plant constructors focus on the technical process and the plant itself. In product development, the focus lies on the bioprocess model combining the product and the process. To get a comprehensive picture, it is necessary to go one step further and combine these approaches. Blending the digital twins of the bioprocess and technical processes together in one simulation environment or platform results in an improved understanding of the interactions between process, product, and plant. It permits the acquisition of information, for example, on energy and mass balances, vessel sizes, and buffer quantities, even before the plant is constructed. This software platform supports the engineering and manufacturing procedures to provide a commercially attractive production process at final scale.

Using a comprehensive picture of the interdependencies of plant, process, and product and an early understanding of their interactions, improved engineering results and a whole range of further advantages are obtained. Model-based technologies allow the sharing of knowledge needed for scale-up, support the implementation of the QbD approach, and allow the application of

advanced process control techniques. A significant reduction in time for process development is the result.

Individual digital twins, or process models for single-unit operations, are incorporated into a comprehensive digital twin, a fully integrated process model. An adequate software environment with the respective IT platforms is required for this approach. A comprehensive toolchain, in terms of systems, software, and methodological support in combination with sound engineering expertise, is essential. The challenge lies in creating an overarching concept and architecture. A climate of co-creation between stakeholders, suppliers, partners, and experts is the prerequisite to break up silos and to support fast-track biopharmaceutical drug development and manufacturing. Not least because of the COVID-19 crisis, we have learned how essential the bundling of competencies is to be able to quickly respond to patients' needs.

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About the Author

Martin Mayer has held a wide variety of senior roles from business development to research and development responsibility to general management. Martin was responsible for a number of projects in chemical industry, pulp and paper, and in the biotech/biopharma industry mainly in the field of digitization, data management, data analytics, and mode-based optimization. At Eppendorf, he was responsible for driving digitization towards new solutions from smart devices to cloud-based services. At ZETA, he is responsible for business development in the field of smart engineering services and digitalization. Martin is a member of the Steering Committee for the Plug & Produce activities within the ISPE Pharma 4.0™ program. He joined ISPE in 2020.

Celebrating the 2021–2022 ISPE International Board of Directors and Award Winners

The traditional passing of the gavel took place in person at the 2021 ISPE Annual Meeting & Expo on 2 November. The ISPE International Board members were seated, and ISPE distributed awards for both 2020 and 2021 since the 2020 awards were postponed due to the pandemic.

Joanne Barrick, RPh, the 2020–2021 ISPE Board Chair and Advisor–Global Validation at Eli Lilly and Company, passed the gavel of the Chair to Jörg Zimmermann, Vice President, Vetter Development Service, External Affairs at Vetter Pharma-Fertigung GmbH & Co. Zimmermann served as Vice Chair during 2020–2021.

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Board Emerging Leaders Representative (Non-voting)
Project Manager/ Engineer
ACCO Engineered Systems

Awards were announced for both 2020 and 2021 at the 2021 ISPE Annual Meeting & Expo since 2020 awards were postponed due to the pandemic.

2020 AND 2021 AWARDS

Affiliate and Chapter Excellence Award

- **2020:** The Greater Los Angeles Area, San Francisco Bay Area, and San Diego Chapters received the award as a group due to their efforts to ensure members stayed informed and engaged through the pandemic, while adding 12 more events and 36 webinars; some done jointly, some individually, some with other industry groups.
- **2021:** Philippines Affiliate, which engaged in multistakeholder activities to address a variety of areas during the pandemic including supply chain, vaccine development and regulatory requirements, and pharmacovigilance and adverse event monitoring, as well as increasing student and Emerging Leaders participation.

Committee of the Year

- **2020:** ISPE Aseptic Conference Program Committee, which pivoted to a fully virtual event and exceeded attendance expectations, and ISPE Brazil Affiliate and the Women in Pharma® Brazil COVID-19 Project, which received a $2,500 support match grant to fund efforts to create hygiene kits and provide portable showers for the homeless of Sao Paolo.
- **2021:** Emerging Leaders Virtual International Hackathon, because the committee demonstrated strong leadership in creating the fully global, virtual Hackathon, which had 60 participants, 10 coaches, and 5 judges, making it the biggest Hackathon to date.

Pharmaceutical Engineering® Article of the Year

- **2019:** "Regulating Online Pharmacies and Medicinal Product E-Commerce" (November–December 2019) by Sia Chong Hock, Mervyn Ming Xuan Lee, and Lai Wah Chan.
- **2020:** "Implementation of a Formal Energy-Efficient Design Process" (March–April 2020) by Aoife Hamill, BE MSc, John Hanley, PhD, MPhil, CEng, and Vincent Lane.

Max Seales Yonker Member of the Year Award

- **2020:** Eamon P. Judge, Global Engineering Advisor–European FM Leader, Eli Lilly and Company, in recognition of his work with the Ireland Affiliate for over 17 years, and his work as President of the Affiliate to form and lead the Irish COVID Alliance beginning in April 2020.
- **2021:** Eleanor F. Small, PhD, Principal Scientist, Johnson & Johnson Consumer, Inc., for her leadership and commitment to the Delaware Valley Chapter, where she helmed the financial management and move to fully virtual programming, started subchapter initiatives, and the Chapter maintained the highest member retention of any US Chapter through the pandemic.

Richard B. Purdy Distinguished Achievement Award

- **2020:** Christopher John Potter, PhD, CMC Pharmaceutical Consultant, for his years of service to ISPE, first as a member and now as an advisor and consultant; his contributions included building PQLI®, raising ISPE's profile with global regulators, work on ICH Q8, 9, 10, and 11, work on the quality metrics, ICH Q12, Advancing Pharmaceutical Quality (APQ) program, and regulatory programs on ATMPs and breakthrough therapies.
- **2021:** Mario Brenga Giampietro, ISPE Brazil Affiliate, who was the Brazil Affiliate President and a member of the GAMP Global Steering Committee; he made significant contributions with these initiatives and fostering relationships with regulators, interactions with other Chapters and Affiliates, and built Communities of Practice within the Affiliate. The award was given posthumously as he passed away in 2021.

Company of the Year Award

- **2020 and 2021:** The award recognizes the entire industry including ISPE membership for their unprecedented level of collaboration, dedication, tireless efforts, innovation, and speed; not only companies directly contributing to COVID-19-related vaccines, detection, and treatments, but all companies and regulatory authorities who supported and continue to support all pharma- and patient-related needs during the pandemic.

Facilities of the Year Awards (FOYA) Overall Winner

- **2021:** Janssen Sciences Ireland, Ringaskiddy, Ireland, BioCork2–Large Scale Fed Batch Facility, a project initiated to add new drug substance fed batch capacity at 15,000 L scale to the existing biologics facility.

ISPE CaSA: Attracting New Talent to the Pharmaceutical Industry

By Marcy Sanford

ISPE's Carolina-South Atlantic (CaSA) Chapter serves members from six different states in the US: North and South Carolina, Tennessee, Alabama, Georgia, and Florida, each with their own unique contributions to the pharmaceutical industry.

The region has significant pharmaceutical industry activities. With more than 735 life science companies employing more than 66,000 people and 80 biopharma manufacturing sites across the state, North Carolina is home to one of the largest concentrations of biologics and pharmaceutical manufacturers in the world. These companies produce a wide array of products, including small-molecule therapeutics, monoclonal antibodies, industrial enzymes, and vaccines, and the industry continues to expand as cell-and-gene-based therapies move from the research lab to commercial manufacturing [1, 3]. One factor in North Carolina's success is Research Triangle Park (RTP), the largest research park in the United States and home to hundreds of companies including science and technology firms, government agencies, academic institutions, startups, and nonprofits [2].

South Carolina has 670 life sciences companies providing jobs to 43,000 people and the life science industry is thought to be one of the fastest growing sectors in the state. In 2020, companies in the state exported more than $812 million of medical instruments and pharmaceutical products [4]. Pharmaceuticals companies employ more than 3,000 in Georgia [5]. Florida is home to the second-largest medical device manufacturing industry, second-largest pharmaceuticals manufacturing industry, and the fifth-largest biotech R&D industry in the US [6].

Tennessee ranks second in the US in exports of medical equipment and supplies, with a total of $4.0 billion in 2020. Tennessee's largest export partners in this sector include Japan, Singapore, Belgium, the Netherlands, and China, accounting for 65 percent of exports [7]. Alabama's bioscience industry has an estimated annual economic impact of $7.3 billion, as well as a track record for breakthrough discoveries [8].

Bringing members together from this very diverse and expansive geographic area covering more than 300,000 square miles is one of the biggest challenges for the CaSA Chapter.

A GROWING CHAPTER

When it was founded in 1991, the Carolinas Chapter encompassed North Carolina and South Carolina. In 1997, Georgia, Alabama, and Florida joined the group and in 2004, the Chapter added Tennessee to its membership base and geographical territory. CaSA is now one of ISPE's largest and most active chapters, has been awarded the prestigious Chapter Excellence Award many times, and has been recognized by ISPE with the Affiliate–Chapter Award for Innovation and Society Support.

CaSA President Chris Small, Hanbury Architecture Planning, said the Chapter is working hard to better serve all members and that getting individuals to take on leadership roles will be instrumental to that success. From the beginning, he said, CaSA success has been due to its members and the network of support they provide to each other.

"We have a really good cross section of folks that are interested and invested in the people side of the pharmaceutical industry," Small said. "I became involved with the chapter 10 years ago when I attended a networking event. As I continued to go to more events, I thought ISPE was giving me more than I was giving it, and when I

Quick Facts about ISPE Carolina-South Atlantic Chapter

Founded: 1991
Region: Alabama, Florida, Georgia, North Carolina, South Carolina, and Tennessee
Membership: More than 1,300

Officers

- **President:** Christopher Small, Hanbury Architecture Planning
- **Vice President:** Bud Watts, Hygenix
- **Past President:** Rich Stanfield, CAI

Committee Chairs

- **Women in Pharma® Chair:** Jessica Cochran, JacobsWyper Architects
- **Treasurer:** Alma Montemayor, Flad Architects
- **Secretary:** Hadassah Eley, Biogen Idec
- **Membership Chair:** Christopher Smith, CAI
- **Emerging Leaders/Student Affairs Chair:** Haley Durbin, Sequence, Inc.
- **Education:** Wes Champion, Pharmaceutical Calibrations & Instrumentation
- **Networking:** Miles Chamblee, R.E. Mason
- **Technology Conference:** Shelly Preslar, Azzur Training Center
- **IT/Media:** Gina Thompson, Werum IT Solutions
- **Chapter Managers:** Nancy Lowe and Teri Saylor

was asked to step up and lead the chapter, I said, 'yes.' We have a good mix of vendors, suppliers, and people from across the entire industry. ISPE gives its members a network of trusted people you can lean on."

In a typical year, CaSA hosts four to six educational events, a major technology conference, and monthly social events. "The networking aspects are phenomenal. The best life sciences networking group in this area is ISPE's CaSA Chapter," Small said. "Our chapter historically has focused on the education and networking. Our technology conference includes education tracks and exhibits. We try to stay focused on what our owner/operator companies need and have found that our most successful events happen when we reach out to them and ask what they need and the topics that are keeping them up at night. Now that we have a lot of new players coming in, we need to determine how to engage the new companies."

TALENT IS KEY

Small says one constant they hear from all companies in the industry is that new talent acquisition and workforce development is an ongoing issue. CaSA has made that the focus of their Technology Conference this year. "Our technology conference is going to focus on how to train the workforce of the future and how to access different programs. We are going to help link them to colleges. We're very education focused but the topics really jibe with what our companies need."

The ISPE CaSA 2022 Life Sciences Technology Conference–Aligning Technology, Talent, and Transformation will be held 15 February at the Raleigh Convention Center. Conference sessions will focus on technology including new innovations for research, development, and manufacturing, where to find skilled employees, how to train and retain employees, and how to have continued success in an ever-changing landscape.

While the workforce of the future is a main topic of this year's Life Sciences Technology Conference, CaSA members have been focused on helping students interested in joining the industry for years. "In 2015, the CaSA Chapter established the ISPE CaSA Jane Brown Scholarship to encourage students seeking a career in the life sciences industry," said Wendy Haines, PhD, PharmEng Technology. Jane Brown was a Past President of the CaSA Chapter and past ISPE chair who helped establish the first CaSA ISPE Student Chapters at North Carolina State University and Campbell University in 1995. The scholarship is open to CaSA Student Chapter members enrolled in an undergraduate or graduate field of study at an accredited university or college. "Over the years, we have awarded one to two scholarships to deserving candidates based on their scholarship application, ISPE involvement and contributions, academic achievement, letters of recommendation, and essay," Haines said.

CaSA also has a very strong Women in Pharma® (WIP) group. "We established WIP as a separate committee two years ago," said Small. WIP has education topics at the technology conference that are focused on WIP and WIP events from book club to golf outings.

Small predicted pharmaceutical industry growth in the region will mean even more professionals will rely on the networking and educational opportunities that ISPE and the CaSA Chapter provide. "We have other markets that are tapping resources, everything from supply chain to talent, as companies in the tech industry have begun planning major facilities in the area. How do we make the pharmaceutical engineering industry attractive to incoming employees? In this thriving market, that will continue to be a challenge."

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About the Author

Marcy Sanford is the Publications Coordinator for ISPE.

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

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

Revision to GEP Guide: A Link to QRM-Based C&Q

Since the first edition of the *ISPE Good Practice Guide: Good Engineering Practice* (GEP) was published in 2008, the pharmaceutical industry and regulators developed industry standards, best practices, and regulatory guidance around topics that relate to GEP, culminating in particular in the *ISPE Baseline Guide: Commissioning & Qualification* (Second Edition). The revised C&Q Baseline Guide incorporates ASTM E2500, EU GMP Annex 15, ICH Q8, Q9, and Q10, and applicable regulatory guidance.

The new *ISPE Good Practice Guide: Good Engineering Practice (Second Edition)* incorporates the revision to the C&Q Baseline Guide and defines and clarifies GEP as an enabling process for quality risk management (QRM)-based integrated C&Q. The revised guide also expands on content in the first edition and places more focus on operational engineering.

"Running a business efficiently requires working practices that will deliver optimum value for a given scope of work," said Guide Co-Lead Chip Bennett, Associate Director, Global C&Q, CAI. "The adoption of GEP can lead to a balance of expenditure and activity in relation to benefits. Benefit is most likely gained when finite resources are focused on identified higher risk aspects or when high-risk aspects are more intensely controlled to enable reliable delivery and seamless production. Specific potential benefits include facilitation of speed-to-market of regulated products through efficient delivery of manufacturing facilities and systems and an optimized level of quality oversight, commensurate with the maturity of established GEP."

"This guide considers the entire range of pharmaceutical engineering activity and identifies key attributes of GEP within it, including how GEP relates to and interfaces with GxP," said Guide Co-Lead Joerg Block, PhD, GMP Compliance Engineer, Bayer AG PH-PS Engineering. "This guide defines GEP that supports and enables the design, delivery, and operation of engineered systems."

The guide was developed through the collaboration of representative professionals from various sectors and geographic regions of the pharmaceutical industry with the intention of determining a common understanding of the concept and principles of GEP. Visit the Guidance Documents site at ispe.org/publications/guidance-documents for more information.

—Marcy Sanford, Publications Coordinator

MEET THE ISPE STAFF

ELMARIE HERLOFF-PETERSEN

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Elmarie Herloff-Petersen, Director of Events, Conferences & Digital Engagement

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

As the Director of Events, I am involved in the planning, logistics, and program management of ISPE global events. My days are regularly consumed by meetings, but I try to manage this carefully to avoid frustration and meeting fatigue. My mornings are blocked to "get things done" and when the US wakes up (I am based in Belgium), I am available for meetings and direct follow-up with colleagues.

What do you love about your job?

The people, the absolute madness to deliver an event and, seeing the end-product delivered successfully, with everyone still intact. In this position, I am challenged enough to learn, and feel comfortable applying the skillset that I have developed, which in turn builds confidence. The confidence that the job gives me is priceless.

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

With three teenagers, and lots of animals, my husband and I sometimes feel like we are living on the edge☺. We are fortunate to live in the countryside, which allows for lovely lunch runs. From March to August, you will find me in our vegetable garden, rotavating, digging in compost, seeding, planting, and harvesting the bounty. The delight and abundance of our home-grown vegetables honestly makes me feel like a proper farmer. Whenever possible, I escape to my work room to design and produce leather bags to quench my creative soul.

CASE STUDY:

Water for Injection Plant AI-based Maintenance

By David F. Nettleton, PhD, Javier Rodríguez Vega, Lavanya Mandadapu, Alejandro A. Rosales Lavielle, Miguel Romero Carol, and Ivan Paquico Rodriguez

This article presents the results of applying artificial intelligence (AI), such as machine learning algorithms, to identifying and predicting anomalies for corrective maintenance in a water for injection (WFI) processing plant. The aim is to avoid the yearly stoppage of the WFI plant for preventive maintenance activities, common in the industry, and use a more scientific approach for the time between stoppages, expected to be longer after the study and thus saving money and increasing productivity.

The case study describes how we preprocessed data from sensors, alarms, and water quality attributes indicators for 2018 and built predictive models based on identified "anomalies" during this period. Next, we preprocessed the same data captured for the first six months of 2020 and applied the 2018 models to see if they were still valid two years on. The initial results show the models are robust and are able to identify the chosen anomaly events. Also, the rule induction machine learning approach (a technique that creates "if-else-then"-type rules from a set of input variables and an output variable) is "white box," which means the models are easily readable by humans and can be deployed in any programming language. Data volumes of around 4 GB per year, generated from 31 sensors, 14 alarms, and four water quality indicators, were successfully processed.

THE WFI PLANT

Figure 1 shows the general schema of the WFI plant, consisting of four main zones (1 to 4). The pretreatment system is located in Zone 1; the WFI manufacturing by distillation via thermocompressor is in Zone 2; Zone 3 contains the hot water for injection loop (at 85°C) plus 10,000 liter tank; and Zone 4 contains the ambient temperature water for injection loop (manufacturing loop). In Zone 3, there is a 10,000 liter WFI tank, which is maintained at 85°C, and the main loop, which runs at 85°C, has three points of use. One of these points delivers WFI to the manufacturing loop with 12 use points, which are cooled down to ambient temperature to be used by operators.

The IT infrastructure includes automatic control by programmable logic controller (PLC), human machine interface (HMI) panel for starting/stopping and changing set up values in the system, and system of control and data acquisition (SCADA) for data of critical values storage under electronic record rules (CFR 21 part 11). Critical values include loops temperatures, total organic carbon (TOC), conductivity, pressures, and flows. The system has been running for more than five years.

The following critical variables and alarms in the plant sensors have been recorded for the different circuit loops every 30 seconds for more than four years:

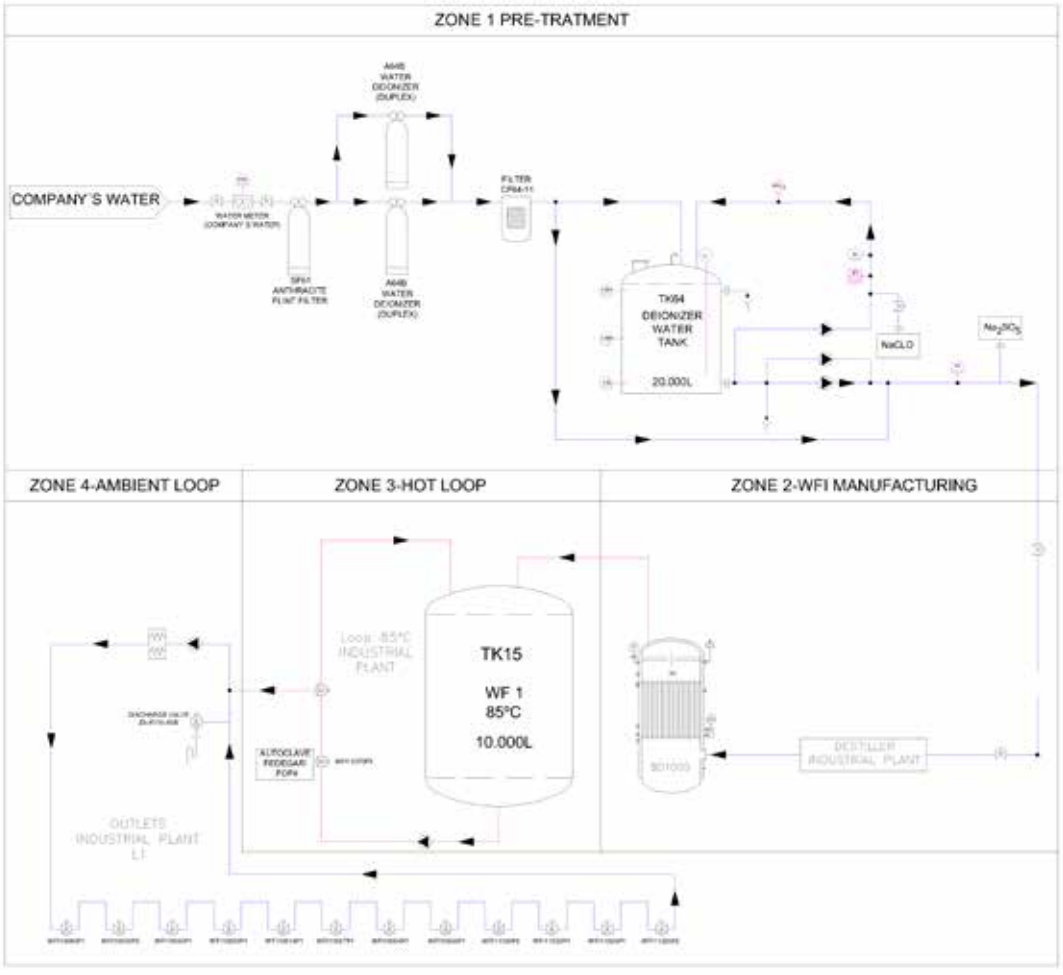
- 85°C loop: conductivity, TOC, loop return temperature, temperature downstream of the heat exchanger, temperature in the 10,000 liter tank, flow in the return, pressure downstream of the pump, temperature in the outlet of the distiller, and conductivity in the distiller
- Ambient loop: conductivity, TOC, loop return temperature, temperature downstream of the heat exchanger, temperature in the vent line, temperature in the vent filter, flow in the return of the ambient loop, and pressure downstream of the pump

Each variable has been stored as follows: 2 values per minute x 1.440 min per day x 365 days per year x 4 years = 4.204.800 values per variable + metadata stored in comma separated value (CSV) format under CFR 21 part 11 requirements.

The sampling frequency is every 30 seconds because this is the default value needed to supervise parameters like temperature, conductivity, and TOC. After statistical evaluation, it was found that one minute was too long and 15 seconds was too short. Temperature, conductivity, and TOC variations are not expected within a range of 30 seconds.

In the unlikely event that a use point is added or removed in the WFI system, the conductivity, TOC, or temperature in the loop would not be expected to change. Such a change would have a high cost for stoppage and validation.

Figure 1: Schema of the plant, distinguishing four main zones.



The files were acquired in CSV format for data scrubbing with 26,453 files between 2016 and 2020, representing 115 million parameters values together with 10,000 alarm messages, occupying a total volume of 22 GB.

Two alarm types are used: type 1 alarms stop the system such that the user cannot extract WFI from the use point. All use points are automatic and in case of any type 1 alarm, the use point does not open. All other alarms, type 2 alarms, are informative.

Cleaning and consolidating of this information with a personal computer was found to be unfeasible, so a big data hardware and software infrastructure (on-premise) was used:

- Distributed data processing
- High performance computing (HPC)

The CSV files were automatically exported from the original database to meet CFR 21 part 11 requirements for authorization, authentication, and electronic record management. Any modification in any CSV file can be detected by a special application in the system that detects any file modification that has been created. If a sensor "goes bad," an alarm type 1 or 2 is raised.

Information that refers to network working notifications, network speed, and internal data used by the programmers but not related to date, time, or value was removed as part of cleaning and consolidation of the data files.

Note that we adopt a more practical definition of big data, which reflects the real situation when doing data processing: if the data cannot be processed in conventional hardware (e.g., laptop/desktop computer) and software (e.g., Excel), then it is big data. For example, Excel in 64-bit Windows and 16 GB RAM stops running for files more than around 500 MB. Both the length (number of rows) and the width (number of columns) can be a determinant: for example, a file with 7,000 rows and 12,000 columns will be very difficult to process with conventional hardware and software.

AI APPROACHES

In a previous project by Rodriguez et al. [1], neural networks (unsupervised learning system autoencoder) were applied to the 2018 data of the WFI processing plant to identify outlier anomalies

in the sensor data. Stored data were used to feed the autoencoder, and outliers were considered as values out of range or affected by some kind of electrical interference. For example, a temperature that cools down 50ºC in 10 seconds or a temperature of 150ºC, are not possible (our heat exchanger has a limit of 135ºC).

This study confirmed the viability of applying machine learning algorithms to identify underlying trends and thresholds in the water plant sensor data. In our project, we adopted a methodological approach [2] and took into account the time series data type by deriving statistical metrics for specific time windows [3]. This approach has previously been successful for predicting rice blast disease from a complex array of meteorology sensors [3]. We also used our experience in applied research in the process industry [4] to solve data processing and modeling issues for sensor data. In contrast to our previous work using neural networks [1], we chose rule induction [5, 6] as the machine learning algorithm, which was shown to be equally precise while providing human readable rules as the data model, which then can be easily deployed. The large data volumes were processed using Python and the scikit-learn machine learning library using online resources. In the scikit-learn library, we have mainly used preprocessing, tree, and linear model libraries for big data processing, preparation, and modeling. In addition, we used the Matplotlib library for data visualization and the DateTime library for working with time fields columns.

The machine learning approach uses a "tree/rule induction" algorithm [6], which generates a decision list for regression problems using a "separate-and-conquer" approach. In each iteration, it builds a model tree and makes the "best" leaf into a rule. Its reported performance makes it one of the best state-of-the-art algorithms for rule induction where the output (predictive/classifier) variable is of numerical continual type.

A key part of the algorithm is the "information gain measure" [7], based on Shannon's definition of "information entropy" [8]. In order to partition the training data set, the heuristic uses an information gain calculation to evaluate which attribute to incorporate next, and where to incorporate it in the induction tree.

BIG DATA PROCESSING

Big data volumes of around 4 GB per year, generated from 31 sensors, 14 alarms, and 4 water quality indicators, were successfully processed. The data was preprocessed using cloud services and Python analytics.

Data Preparation

Initially, the entire 2018 data was loaded into the Python data frame and the date/timestamp was converted into a Python date/time data type and separated as "date" and "time." After cleaning, the data consists of the 31 sensor data values recorded with 30-second time intervals between subsequent records. The cleaned data frame structure contained repetition of the timestamp as the sensor values were distributed in a row fashion. Reorienting the data frame to contain unique values was done by creating a new column for every sensor to facilitate further processing of each individual sensor and knowing its effect on the underlying trends in the data. This process is called "pivoting." The pivoted data frame structure was used for both 2018 and 2020 data. Once the sensor data was prepared, the alarm data was also treated in the same way. However, the alarm data distribution over time was stochastic (involve probability) and these were therefore matched to the closest 30-second timestamp.

On one hand, we wanted to test the latest data (2020); on the other hand, we wanted to use data to train the models that had a more significant time difference (2018) to evaluate if there was any significant change over time in the sensor calibrations. The one year of data (2018) was considered sufficient to train the models in this current evaluation, thus 2019 data was not used.

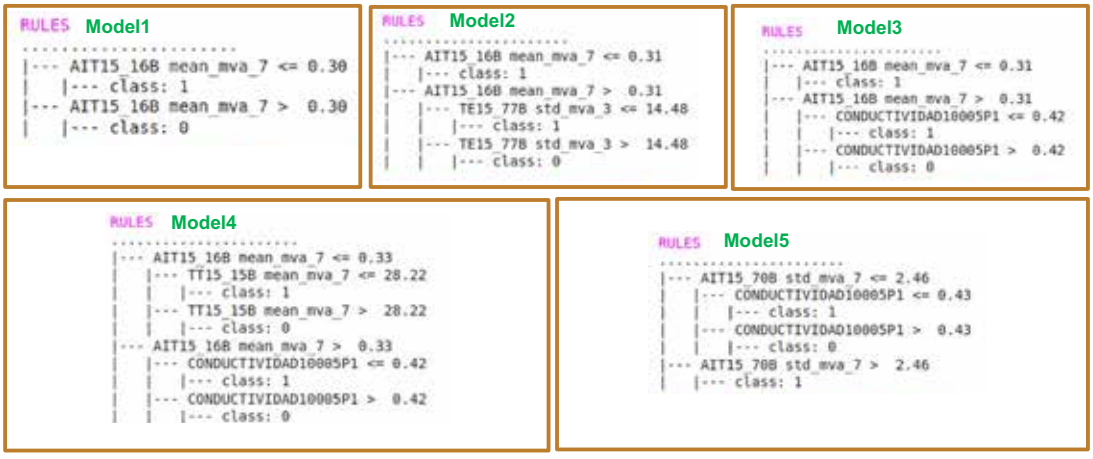
The 2018 data preprocessing time was benchmarked by identifying specific sub-steps, and the following provides the details of the time taken for each data preparation process sub-step. Most of the initial steps such as loading the entire sensor data and conversion and selection operations have linear time complexity $O(n)$, as the data size is directly proportional to the processing time required by the operations. However, for pivoting and merging the alarm data based on nearest timestamp, the original complexity was $O(n2)$. Applying optimization techniques such as divide and conquer, especially in the merging of alarm data with sensor data, yielded a final complexity of $O(nlogn)$. The total number of records in all steps except the last was 1 million, which corresponds to 4 GB of data. The last step processed 365 records, one for each day of the year.

Approach

First, corrective maintenance events (or situations/problems) were initially identified with the water plant experts for the year 2018. Complementary data (over the same time period, e.g., one reading per day) was obtained for the system quality indicator (e.g., WFI, required pharmacopoeia parameters). Next, non-supervised techniques, such as *k*-means and DBSCAN, were used for unsupervised clustering. Note that DBSCAN is a clustering algorithm that defines clusters as continuous regions of high density. It works well if all the clusters are dense enough and well separated by low-density regions. The overall objective was to build an "anticipatory model" for which the machine learning algorithm is able to identify trends in the data in the run-up period (e.g., 14 days) to a corrective (or preventive) maintenance event or a given situation requiring attention and thus predict the event/situation.

Following on from the analysis and modeling of the 2018 data, in a next step we apply the models trained with the 2018 data on the 2020 data (1/1 to 30/6). For each day, the mean and standard deviation of sensor readings were calculated, followed by the 3- and 7-day moving averages, and the water quality alarm (conductivity) was aggregated. In the analysis step, we generated plots and statistics of the sensors to compare 2018 values with 2020. This was followed by a clustering of the 2020 data using DBSCAN, *k*-means, and density-based algorithms, to identify clusters of anomalies and nonanomalies in 2020. These statistics help us to validate the

Figure 2: Model rules (trained on 2018 data).



anomalies identified by the predictive models. Finally, the 2018 models were applied to the 2020 data to identify anomaly periods.

Data Analysis

The data analysis step prepares the basis for the data modeling that follows. Visualization of the sensor and alarm data over time via plots was a key technique used to understand the physical variables and alarms and identify outliers. This was combined with correlation analysis and clustering techniques. For example, key correlations were found between sensors AIT15_70B (return TOC in the ambient loop) and AIT15_16B (return conductivity in the ambient loop); TT15_15B (temperature cold return loop) and AIT15_16B, TT15_15B (return 85°C loop temperature); and TT15_77B (temperature in the ambient loop) and TT15_15B. A consensus approach applied to different density-based clusters (2–6 clusters) indicated the following potential "anomaly" groups: Feb. 14–24, Mar. 5–22, Mar. 24–Apr. 15, Apr. 18–27, May 6–9, May 26–30, Jun. 6–8. Note that in order to select the optimum number of clusters for a given data set, the clustering algorithm has a metric to indicate "goodness" of the clustering (low intra-cluster distance and high inter-cluster distance), together with the data analyst and domain expert evaluations to be sure the groupings make sense in terms of the data analysis objectives.

A 3D study was made of the normal cases and the anomaly cases, using three axes representing the temperature and water conductivity sensors TE15_77B (temperature in the ambient loop), AIT15_70B (return TOC in the ambient loop), and AIT15_16B (return conductivity in the ambient loop). From the study it was clear that these three sensors were able to distinguish normal cases from anomalies.

PREDICTIVE MODELING

The following describes how the data models were trained and tested on the 2018 data. Then we describe the results of applying these models to the 2020 data.

Building Data Models

As mentioned above, different rule models were generated from the 2018 data. Figure 2 shows the rule models trained from the 2018 data. From the rules, it can be seen that the main sensors included are AIT15_16B (return conductivity in the ambient loop), TE15_77B (temperature in the ambient loop), AIT15_70B (return TOC in the ambient loop), and Conductividad1005P1 (conductivity water quality attribute measure of the sampled WFI in one point of use). Note that the 7-day moving average (mva_7) was preferentially chosen among the available attributes (which also included the 3-day moving average, the mean, and the standard deviation).

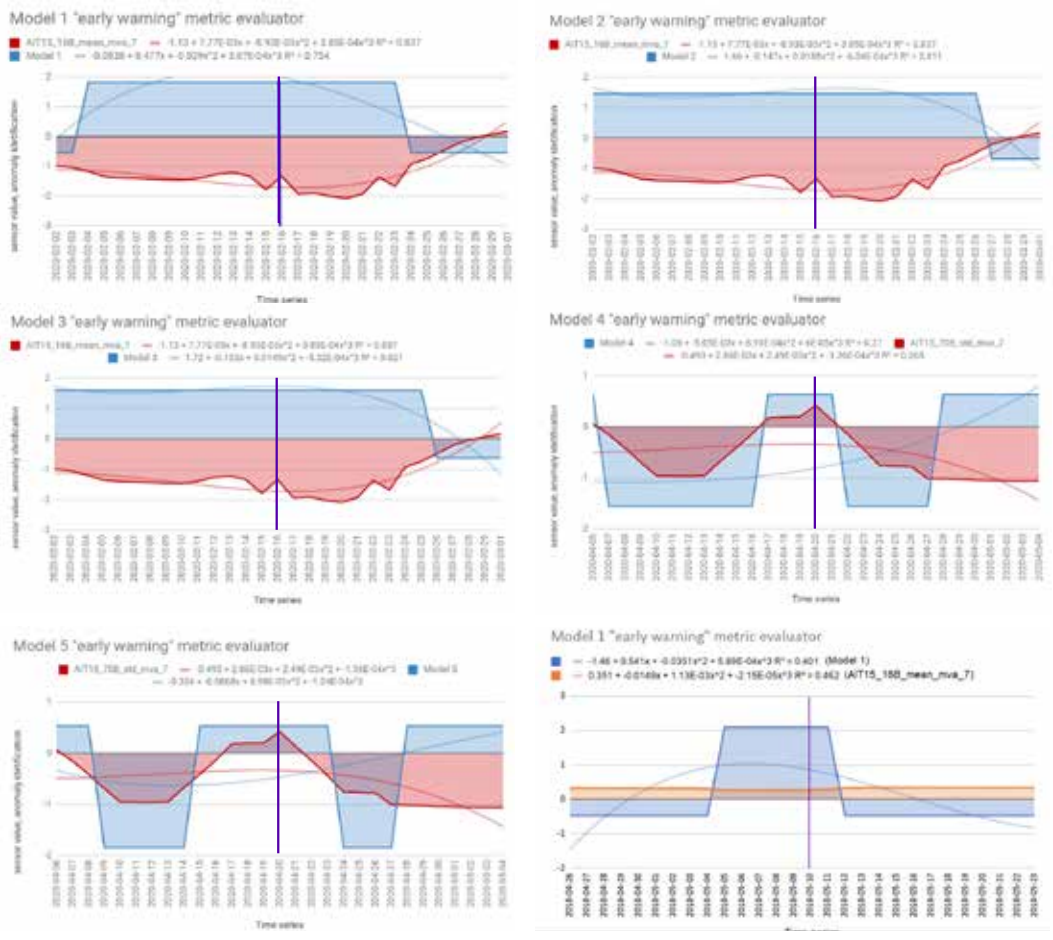
An example for interpreting the rule model for model 5 interprets the first branch as follows:

> IF AIT15_70B_std_mva_7 IS less than or equal to 2.46
> AND Conductividad1005P1 IS less than or equal to 0.43
> THEN class = 1 (anomaly).

With reference to the data normalization overall, it can be seen that the models maintain the same structure and attributes, which in some cases had switched between models. These rule models are generated after doing a preselection of the 2018 data. This preselection considered the most relevant events (4 nonanomaly days and 5 anomaly days) of the 2018 data where the 14 days before a relevant day had a direct impact on deciding if the day contained an anomaly or not. Each 14-day period was considered as a "data group," with corresponding start and end data and a label if considered an anomaly (1) or not (0). For example, data group 1 had start/end dates of 1/1 and 14/1 and a label of 0 (no anomaly), while data group 6 had start/end dates of 26/4 and 9/5 and a label of 1 (anomaly).

It is relevant to note here that the anomalies are related to sensors, which are in turn related to alerts. The alerts have a ranking system of criticality (1 to 4, where 1 is the most critical). From this, the anomalies can be ranked and ordered on the DSS screen so the operator can clearly see the most critical ones and discretionally discard the least

Figure 3: AUC used as the metric evaluator for models 1 to 5 (2020 data) and model 1 (2018 data, bottom right).



critical ones. The anomalies chosen for train/test were major anomalies (level 1) that caused shutdown of the plant/zone.

After consulting with the WFI plant maintenance records, the anomaly/non anomaly events were associated with the following dates: May 10, Aug. 15, Sept. 10, Oct. 19, and Dec. 3.

The anomalies have a confidential aspect so we can only give limited details. The ones corresponding to 2018 were in the months of May (repair of sealings and re-calibration), September (TOC error/repair and pump replacement), and October (filter replacement and review tasks). The anomalies identified and used for training/testing of the models were associated with major alarms, requiring shutdown of part or all of the plant.

Nine data groups of 14 days were chosen in chronological order for training and testing. Then several data groups were chosen for training a model and one data group was chosen for testing the model. For example, model 1 was trained with data groups 2, 1, 3, and 5 and tested with data group 6. Two key aspects were that the test data group had to be chronologically posterior to all the train data groups, and the train data groups had to include a mixture of anomalies and non-anomalies. From the available combinations throughout the year 2018, this enabled us to train and test five different models, shown previously in Figure 2.

In order to evaluate the success of the predictions of the data models on the 2018 data, we have used the area under the curve (AUC) metric for the model trend curves. The AUC is a quantified value of the area under a given curve between two vertical points. A larger area can be interpreted as a more significant "signal" and a smaller area as a less significant "signal." The AUC metric used in this study served as an "early warning" alert where the model was able to flag the previous 14-day period before an anomaly event. Using this alert, it is possible to spot the start of an anomaly period and advise the maintenance manager of the WFI pharmaceutical plant installation so they can take preventive measures.

Figure 3 (bottom right) shows the AUC plotted for model 1 (blue) and corresponding time period in the 2018 data where model 1 was applied to the May 10 anomaly. The red trend shows the main sensor values, in this case for AIT15_16B.

Table 1: AUC for each model and test date – 2018 training data (Relative performance in parentheses).

	May 10	Aug. 15	Sept. 10	Oct. 19	Dec. 3	Average
Model 1	13.44 (1.0)	12.27 (1.0)	12.27 (0.92)	12.27 (0.75)	6.87 (0.53)	(0.84)
Model 2		0.00 (0)	0.00 (0)	0.00 (0)	5.08 (0.39)	(0.39)
Model 3			13.28 (1.0)	13.92 (0.85)	10.98 (0.85)	(0.90)
Model 4				16.36 (1.0)	12.88 (1.0)	(1.00)
Model 5					-0.02 (0)	(0.00)

Figure 3 (bottom right) shows for model 1 that the main sensor (present in the rules) is AIT15_16B and the value taken is the 7-day moving average of the mean (thus _mean_mva_7). The blue area represents the anomaly period identified by model 1. The AUC for model 1 is calculated with the following integration equation:

$$AUC = \int_a^b -1.46 + 0.541x - 0.0351x^2 + 5.89E - 04x^3 . dx$$

In the equation, a and b are the x-axis range of April 26 to May 23, 2018. This period is translated into a numerical sequential index =1.28 (14 days before and after the start date of the anomaly) to be evaluated and placed in the evaluation of the curve equation above. An anomaly event threshold period has been noted for each model. For model 1, May 10 is considered as the anomaly event start date. Therefore, the numerical sequential index of =1.14 is used to calculate the AUC of the model's output values for the period from April 26 to May 10, 2018, which gives a value (area) of 7.33 (see later baseline adjustment). This calculation was done after standardizing the model data values.

As mentioned previously, five anomaly start dates (May 10, Aug. 15, Sept. 10, Oct. 19, and Dec. 3) were identified from the statistical analysis and by verification of the WFI maintenance records for 2018. For each corresponding 28-day period, the AUCs for the polynomial curves of each model were fitted. The resulting values are in Table 1. Note that for the 2018 training data, models were only applied to dates that were posterior to the data they were trained on, thus avoiding including a priori information.

After the AUCs of the models were calculated, a "baseline" value is determined for each model. The baseline of the model (read from the y-axis) is a relative reference for the model's performance in an ideal state where it is not detecting any anomaly. The integral of the standardized model value in its ideal state (y-axis value) for each model is considered its baseline. By aggregating the model baseline AUC with the overall AUC of the model, we can get the true capability of the model to detect an anomaly period.

Table 1 shows the AUC results of the models after aggregating the original AUC with the baseline AUC. For model 1, the calculated baseline AUC was -6.11 and the AUC of model 1 for the May 10 anomaly event was calculated as 7.33. After aggregating the baseline AUC value, we get 13.44 for model 1 and May 10. This calculation was performed for all the models and dates, giving the resulting AUC values.

Table 1 also shows the relative performance values in parentheses. To obtain a normalized relative performance between models and anomaly dates, the AUC values were normalized with respect to the greatest value per column (when there were at least two values in a column). For example, in column 5 (Dec. 3), model 4 had value of 1.00 because it was normalized as the maximum value in column 5 (12.88/12.88). Model 5 had a value of 0 because it was normalized as the minimum value in column 5 (-0.02/12.88). Finally, the average for each row of all columns is calculated and given in the last column. It can be seen that models 1, 3, and 4 were the best overall performers for the anomaly dates and model 2 and 5 obtained the lowest average values. For individual dates, model 4 can be seen to be the best performer for Oct. 19 and Dec. 3, model 1 is the best for May 10 and Aug. 15, and model 3 performed well for Sept. 10.

Model Testing on 2020 Data

Here are the results of applying the 2018 models to the first six months of 2020 data. To evaluate the models on specific events, two "anomaly" periods were chosen: Feb. 16–18 and April 20–26. These periods were chosen because they coincided with real maintenance tasks that significantly affected the sensor data and were confirmed by checking the WFI plant maintenance records.

We evaluated the application of the models to each anomaly event, using the AUC metric described above.

As seen previously, Figure 3 shows the AUC plotted for each model and corresponding time period in the 2020 data. In Figure 3, models 1, 2, and 3 are applied to the Feb. 16–18 anomaly period and models 4 and 5 are applied to the April 20–26 anomaly period. The red colored trends show the main sensor values and the blue colored trends show the model values.

The anomalies have a confidential aspect so we can only give limited details. The ones corresponding to Feb. 14–17, 2020 refer to a major stoppage for repair: change of membranes of valves, probe calibration, and sterilization of circuits after calibration. The anomalies identified and used for training/testing of the models were associated with major alarms, requiring shutdown of part or all of the plant.

Note that the operator will not have to interpret the graphics of Figure 3 or the model of Figure 2 (which are internal to the system). The operator will just see a list of potential events ranked by criticality and probability.

Table 2: **Performance of 2018 rule models on 2020 data in terms of "early warning success" using AUC metric.**

	AUC models		Relative performance		Average
	Feb. 16	Apr. 20	Feb. 16	Apr. 20	
Model 1	29.63	-0.07	1.00	0.00	0.50
Model 2	27.47	-0.02	0.93	0.00	0.46
Model 3	28.89	-0.02	0.98	0.00	0.49
Model 4	11.85	33.29	0.40	1.00	0.70
Model 5	16.93	31.34	0.57	0.94	0.76

The AUCs for the polynomial curves fitting the models 1, 2, and 3 to the first time period (Feb. 2 to Mar. 1) and anomaly start date (Feb. 16) are 22.61, 18.63, and 20.83, respectively. The AUC of the model's output values helps us to understand how well the 2018 model works with the 2020 data. Also, considering models 4 and 5 for the second time period (Apr. 6–May4) and anomaly start date (Apr. 20), the AUCs for the polynomial curves are 13.14 and 7.42, respectively. Table 2 also shows the AUC values of the models after aggregating the baseline AUC value. For example, the integral of the baseline AUC value for model 1 is -7.02 and aggregating this value with 22.61 gives the final AUC of 29.63 as seen in Table 2, column 1. This calculation is repeated for all the models, and their respective results are presented in Table 2.

The first column of results in Table 2 shows the AUCs for each model applied to the Feb. 16 anomaly. In general, a larger AUC will give a bigger "alarm" signal, so for the Feb. 16 anomaly, models 1 to 3 are giving the strongest "signals" (29.63, 27.47, and 28.89, respectively). Also, the second column of results shows the AUCs for each model applied to the Apr. 20 anomaly. This shows that models 4 and 5 give the strongest "signals" of 33.29 and 31.34, respectively.

The normalized relative performance between models and anomaly dates (Table 2, columns 3 and 4) was calculated as previously described for the 2018 results (Table 1). For individual dates, model 4 can be seen to be the best performer for Apr. 20 and model 1 for Feb. 16.

The results in Table 2 show the strength of "signal" that the models trained on the 2018 data provide for the anomaly periods identified in the 2020 data, and how they coincide with the anomalies.

For deployment, as we do not know beforehand which models will give the best performance for which dates, we must run all models and then can use a threshold τ to choose the ones to apply. The threshold would have to be calibrated from further testing, but if we initially set $\tau = 0.75$, for example, it can be seen that for Feb. 16, models 1 to 3 would give output values greater than τ (and thus would trigger an alarm) and for Apr. 20, model 4 and 5 would give output values greater than τ and would thus trigger an alarm. But, if the maximum AUC value is not good (e.g., instead of 29.63 it was to be 8.3 for Feb. 16), then the relative threshold will not work. So we also need a value σ (a minimum AUC which has to be achieved), which is factored into the threshold to trigger the alarm. The value σ would have to be calibrated for the data.

Note that the human operator does not have to interpret the models (Figure 2) or the AUC (Figure 3), which are internal to the system. The operator will just see a list of potential events ranked by criticality and probability. There is a 14-day prediction window that was agreed on with the operations manager as practical for planning remedial actions.

CONCLUSIONS

We have presented an approach for condition-based maintenance in a WFI plant, using data driven modeling based on extensive sensor data. The predictive data models use a 14-day period as input and give as output an indication if an anomaly event will occur in the following 14-day period. Data models have been trained on data from the year 2018 and tested on data from the first six months of 2020. The AUC metric provides a realistic measure of the "signal" produced by a predictive model during the lead-up period to an anomaly, which can be used in deployment.

For the 2018 data, predictive models based on 14-day periods were able to predict events later in the year, thanks to patterns that existed in the 14-day lead-up periods that indicate that an anomaly will or will not occur. The corresponding rules can be interpreted as "nuggets" of information which could be used, for example, to give special maintenance attention to the sensors. For deployment, the data models could serve as a back end to a decision support front end.

For the 2020 data, some differences were detected in sensor values and behavior with respect to the 2018 data, so it was decided to standardize the data (between 0 and 1). Note that "normalization" typically means rescaling the values into a range of [0, 1], whereas standardization rescales data to have a mean of 0 and a standard deviation of 1 (unit variance).

This is a typical issue for deployment of data models: how AI using machine learning will improve and get "smarter" over time for decision making and data interpretation. A "quality metric" is necessary to periodically "benchmark" the data model against new data batches to quantify precision. If the precision goes below a given threshold (which is calibrated depending on the application), this triggers an alert. Based on the alert, offline retraining with new (latest) data samples can be performed, or automatic online retraining can be performed. The former is recommended at present because the model should be verified by a human expert before going online, for example, to evaluate potential issues such as noise/data quality and bias, among others.

Overall, the current approach is promising and follows a systematic methodology for data processing, analysis, and modeling with specific time series features built into the data. The AUC metric is proposed as a key metric for measuring the "signal" produced by the predictive models. It could be said that the approach is limited given that it is not designed to predict events in an unseen period further than 14 days in the future. On the other hand, the approach has a wide scope as it identifies any anomaly and not specific faults (for example, by zones of the plant or for specific components). Preventive maintenance requires flexibility by its nature so the current work will serve as a basis for the predictive time window and identify specific key components that can most affect the production and downtime of the WFI plant.

For now, the data produced in the process is only used for informational purposes. In the next phase, we will be able to take action and perform maintenance based on the AI information. The second phase will also consider validation of the algorithms to confirm if they should be the basis for GxP decisions. Evaluation of return on investment (ROI) for implementing the approach will also be considered in the next phase.

For the WFI plant in general, we are on the way to having an application that will allow us to decide when preventive maintenance is needed based on the likelihood of anomalies rather than on a set annual schedule.

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Risk-Based Continued Test-Method Performance VERIFICATION SYSTEM

By Ronald D. Snee, PhD

Good data are a characteristic of good science. Quality data are arguably more important today than ever before and are considered by many to be a corporate asset because they are used to develop products and processes, control our manufacturing processes, and improve products and processes when needed [1]. Quality data also reduce the risk of poor process performance and help prevent defective pharmaceuticals from reaching patients.

The US FDA and USP have provided guidance for developing, validating, and verifying effective test methods that will deliver quality data [2–4]. Their guidance calls for continued method performance verification (CMPV) to verify a test method's performance over its life cycle. At the same time, there has been renewed interest in developing risk-based methods of all types [5]. Fortunately, we have concepts, methods, and tools available to build assessment and mitigation of risk into a test-method performance verification system [6].

The FDA calls for CMPV [2, 3]. However, there are three critical risks associated with the long-term use of the method.

- First, the method's precision in terms of reproducibility and repeatability decreases over time. (Note: Although the pharmaceutical industry often uses the term "reproducibility" to describe *between-laboratory* variation in measurement results, this article addresses *within-laboratory* reproducibility, which measures variation due to different analysts, instruments, and other factors at a given laboratory.)
- Second, the method does not meet acceptance limits (specifications).
- Third, management does not pay sufficient attention to method performance.

This article discusses CMPV methods that effectively reduce these critical risks.

BLIND CONTROLS TO ASSESS METHOD PERFORMANCE STABILITY OVER TIME

An effective way to assess the long-term stability of a test method is to periodically submit "blind control" samples (also referred to as reference samples) from a common source for analysis along with routine production samples. Blinding the samples ensures that the analyst cannot determine the difference between the production samples and the control samples, and, as Nunnally and McConnell have stated, "There is no better way to understand the true variability of the analytical method" [7].

The control samples are typically tested two or three times (depending on the test method) at a given point in time. The sample averages are plotted on a control chart to evaluate the stability (within-lab reproducibility) of the method. The standard deviations of the repeat tests done on the samples are plotted on a control chart to assess the stability of the repeatability of the test method. The deviations of the sample averages from the overall mean measure the within-lab reproducibility of the method. The standard deviation of the test results from the sample mean measures the repeatability of the method.

Weitzel and colleagues described a six-year study in which control samples were used to monitor an assay measurement process [8]. The blind control samples were drawn from a common master control batch and periodically submitted for lab analysis. Six analysts (A, B, C, D, E, and F) tested the 48 samples in duplicate over the six-year period. See the Appendix (online at https://ispe.org/potency_assay_blind_control_data_appendix) for a summary of the results.

Figure 1 shows the control chart for the 48 samples. The first 23 samples were tested by analyst A, and the remaining samples were tested by the other analysts. In Figure 1, we see:

- Analyst A has more within-lab reproducibility issues; several sample averages are outside the control limits.
- There are some within-lab reproducibility issues around samples 37–41; these are principally attributed to analyst C (see the results for analyst C in the Appendix).
- The variation for the other analysts is smaller than that of analyst A.
- The overall average is essentially the same for all analysts.
- Analyst A has larger test-to-test variation (repeatability) than the other analysts.

As we will discuss later, the overall method variation was found to be within the goal of the method.

"Sensitizing rules" are often used in conjunction with control limits to detect nonrandom patterns of variation (level shifts, trends, cycles, and so on), which may not be detected by the control limits [9]. These rules increase the sensitivity of the control charts to detect small shifts. One important type of nonrandom variation is out-of-trend results.

Other metrics, such as system suitability test (SST) failures and out-of-limits results, can also be used to assess continued verification. This article focuses on monitoring the results of blind control samples and product stability test results because these test results are widely used and reflect how the test methods are used on a daily basis. SST results have the limitation of measuring only instrument precision, which does not take analyst variation and other sources on variation into account.

TEST-METHOD STABILITY METRIC

The control chart analysis tells us whether we have a measurement stability problem for the particular method being studied. But a lab will have several methods to worry about. Some stability problems are more important than others. This raises the question, "When should we worry about method stability?" The answer is when long-term variation represents more than 20% of the total variation. Note that:

> Total variation = Long-term variation (within-lab reproducibility) + short-term variation (repeatability)

The analysis of variance (ANOVA) is used to separate the long-term variance from the short-term variance. ANOVA of the control sample data computes the percent long-term variation, which measures the stability of the test method over time (within-lab reproducibility). Long-term variation variance components less than 30% are generally considered good, with larger values suggesting the method may have within-lab reproducibility issues [10]. Collins and associates also discuss the use of long-term variation to assess process stability [11].

Control limits may be based on the replicate variation, and this may be an issue when looking for trends. In such a case, the run averages should be subjected to an individuals' moving average control chart [9], which uses the short-term between-sample variation to calculate the control limits, as discussed by Snee [12].

The process stability acceptance criteria for long-term variance are:

- Less than 20% variance indicates measurement process stability is not a problem
- Variance between 20% and 30% suggests that measurement stability may be a problem
- Greater than 30% variance indicates that corrective action may be needed

Figure 2 shows stable (top) and unstable (bottom) measurement processes. The top chart shows a stable process: The long-term variation is 21%, and all points are within the control limits. The variation is random, without trends, shifts, or cycles. This measurement process shows good within-lab reproducibility.

The bottom control chart shows an unstable measurement process: Five of the sample averages are outside the control limits, and the long-term variation is 58%, well above the 30% threshold for corrective action. This measurement process has poor within-lab reproducibility.

Figure 1: Potency assay blind control Xbar-S chart.

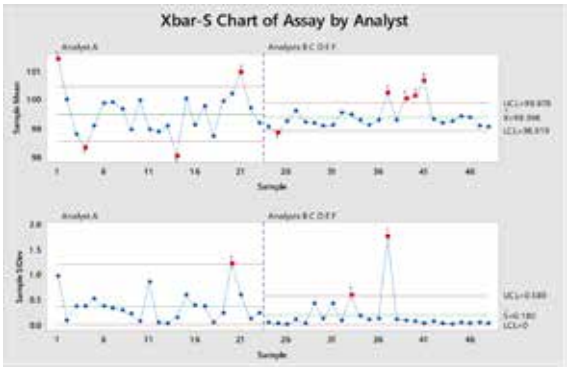


Figure 2: Examples of stable (top) and unstable (bottom) measurement processes showing good and poor within-lab reproducibility.

Control limits may be based on the replicate variation, and this may be an issue when looking for trends.

Table 1: Analyst A's control sample test results: ANOVA and variance components analysis.

ANOVA					
Source of Variation	**Degrees of Freedom**	**Sum of Squares**	**Mean Square**	**F Ratio**	***P* Value**
Sample	22	27.4654	1.2484	5.565	0.000
Replicate tests	23	5.1598	0.2243		
Total	**45**	**32.6252**			
Variance Components Analysis					
Source of Variation	**Measurement Characteristic**	**Variance Component**	**% of Total**	**Standard Deviation**	
Sample	Within-lab reproducibility	0.512	70	0.716	
Replicate tests	Repeatability	0.224	30	0.474	
Total	**Method variation**	**0.736**	**100**	**0.858**	

Table 2: Potency assay method repeatability and within-lab reproducibility by analyst.

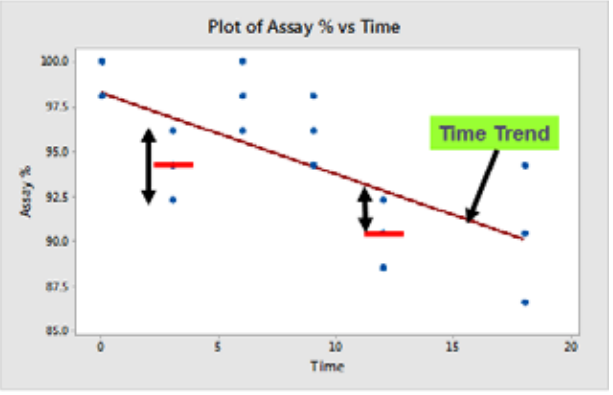
	All Analysts		Analyst A		Analysts B, C, D, E, and F	
Variation Type	**Variance Component**	**% of Total**	**Variance Component**	**% of Total**	**Variance Component**	**% of Total**
Within-lab reproducibility	0.294	61	0.512	70	0.105	40
Repeatability	0.188	39	0.224	30	0.155	60
Total for method	0.482	100	0.736	100	0.261	100
Goal for total	1.0		1.0		1.0	

The process stability acceptance criteria stated previously are recommendations that may be revised to suit specific applications. Also, when the criteria indicate that within-lab reproducibility and/or the total measurement variability may be a concern, one should look at how the variation in the test results compares to the acceptable limits (specifications) for the measurement method. This issue is addressed later, in the discussion of test-method performance capability indices.

ANOVA is used to calculate the portion of variation that is attributable to measurement repeatability and within-lab reproducibility [9]. Table 1 shows the ANOVA of the test results for analyst A in the potency assay study as well as the associated variance components. In Table 1, we see that the sample-to-sample variation (within-lab reproducibility) is statistically significant ($P = 0.000$). Within-lab reproducibility accounts for approximately 70% of the total variation in analyst A's test results, with the remaining 30% being due to repeatability variation.

Table 2 summarizes variance component statistics for all analysts, analyst A, and analysts B, C, D, E, and F. Here we see that variation for analysts B, C, D, E, and F is 40% of the total, a little above the 30% guideline. The good news is that the total variance goal of 1.0 is met by analyst A as well as the other analysts [8]. So, although within-lab reproducibility may be high for this method, the results are within the goal for the method, which is relatively tight (relative standard deviation = 1%).

Figure 3: Product stability study example 1: Assay versus time in months.



PRODUCT STABILITY DATA TO ASSESS METHOD PERFORMANCE

The use of blind controls to assess measurement stability may have drawbacks. The first concern is that resources are required to maintain the control sample and insert the blind controls with the routine production samples. Furthermore, try as you might to keep the controls blinded, there is a risk that analysts will identify the blind controls and their purpose.

Whereas blind controls are used to routinely test a common product over time and observe the variation in the test results, Ermer and colleagues have noted that product stability data are another source of such data [13]. In a product stability study, at least one batch of the product is typically tested using a common test method at various time points to assess the stability of the product.

In product stability studies, after the time trend has been accounted for, the variation remaining is due to the test method's repeatability and within-lab reproducibility. Figure 3 illustrates this by showing the relation between assay % and time measured in months for example 1 from Table 3. Repeatability is the variation around the sample mean, as illustrated by the data at three months. Within-lab reproducibility is the variation between the sample mean and the trend line, which is illustrated by the 12-month data.

Table 4 presents the ANOVA for example 1 (Table 3) as well as the associated variance components. In this case, reproduciblity accounts for 45% of the total measuremeent variation. The lack-of-fit *P* value (0.042) indicates that within-lab reproducibility is statistically significant.

Product stability study example 2 data show a more complicated data set (Table 5). Here, five lots have been put on a stability test. Duplicate test results were made at each of eight time points (0, 3, 6, 9, 12, 18, 24, and 36 months). Scatterplots of assay results versus time (not shown) identified linear trends for the different lots. The overall adjusted R^2 equals 80% for these relationships. An examination of these plots shows several instances where the duplicate points are both above and below the trend line, indicating within-lab reproducibility variation. Variation between pairs of duplicate results reflects the repeatability of the method.

The ANOVA and variance components (Table 6) show that within-lab reproducibility accounts for 34% of the total measurement variation, which is above the stability acceptance criteria (<30%) discussed earlier. The ANOVA model allows for the slopes of the trend line to vary between lots. The residual variation is due to the test-method variation: within-lab reproducibility (lack-of-fit) and repeatability (replicates). The lack-of-fit *P* value (0.017) indicates that within-lab reproducibility is statistically significant, although it is not large as measured by the criteria for long-term variation criteria (acceptable <30%).

ASSESSING TEST METHOD CAPABILITY

Measurement systems typically define acceptance criteria in terms of a goal standard deviation or upper and lower limits (USL, LSL), which are called "specifications" here.

Table 3: Product stability study example 1.

Test	Time, month	Assay %
1	0	98.08
2	0	100.00
3	0	98.08
4	3	92.31
5	3	94.23
6	3	96.15
7	6	100.00
8	6	98.08
9	6	96.15
10	9	96.15
11	9	94.23
12	9	98.08
13	12	88.46
14	12	90.38
15	12	92.31
16	18	90.38
17	18	94.23
18	18	86.54

Table 4: Product stability data example 1: ANOVA and variance components analysis.

ANOVA					
Source of Variation	**Degrees of Freedom**	**Sum of Squares**	**Mean Square**	**F Ratio**	***P* Value**
Time	1	130.32	130.32	15.72	0.001
Residual	16	132.66	8.29		
Lack-of-fit	4	71.02	17.76	3.46	0.042
Replicates	12	61.64	5.134		
Total	**17**	**262.98**			
Variance Components Analysis					
Source of Variation	**Measurement Characteristic**	**Variance Component**	**% of Total**	**Standard Deviation**	
Lack-of-fit	Within-lab reproducibility	4.21	45	2.05	
Replicates	Repeatability	5.14	55	2.67	
Total	**Method variation**	**9.34**	**100**	**3.06**	

Table 5: Product stability study example 2.

Time, months	Replicates	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
0	1	97.6	100.9	98.7	100.3	100.9
0	2	98.4	98.8	100.5	101.5	100.4
3	1	97.7	98.2	95.8	99.7	97.3
3	2	99.4	97.5	96.5	100.1	99.0
6	1	97.7	98.5	96.7	98.6	97.7
6	2	96.2	97.5	96.0	99.5	99.6
9	1	96.9	97.6	97.5	98.3	98.4
9	2	97.3	98.9	96.3	99.6	97.9
12	1	94.0	96.9	94.7	96.8	96.5
12	2	95.3	97.5	98.3	98.3	97.0
18	1	96.5	96.3	93.7	96.7	99.5
18	2	94.9	96.5	94.1	95.2	96.8
24	1	96.0	95.8	93.1	96.3	96.0
24	2	97.5	96.0	92.5	97.1	96.5
36	1	92.1	92.3	91.3	93.9	93.7
36	2	92.7	92.0	89.5	93.8	94.6

Table 6: Example 2 product stability data: ANOVA and repeatability and within-lab reproducibility variance components.

ANOVA					
Source of Variation	**Degrees of Freedom**	**Sum of Squares**	**Mean Square**	**F Ratio**	***P* Value**
Time	1	312.58	312.57	265.68	0.000
Lot	4	22.81	5.7	4.85	0.002
Time × Lot	4	10.5	2.62	2.23	0.074
Residual	70	82.36	1.18		
Lack-of-fit	30	49.9	1.66	2.05	0.017
Replicates	40	32.45	0.81		
Total	**79**	**474.08**			

Variance Components Analysis				
Source of variation	**Measurement characteristic**	**Variance Component**	**% of Total**	**Standard Deviation**
Lack-of-fit	Within-lab reproducibility	0.41	34	0.64
Replicates	Repeatability	0.81	66	0.90
Total	**Method variance**	**1.22**	**100**	**1.10**

The measurement system's performance can be assessed using the process performance capability index (Ppk):

Ppk = A/B
where A = minimum (USL – Average, Average – LSL)
and B = 3 (standard deviation).

A generally accepted minimum value for Ppk is 1.33, which is consistent with 0.006% of the test results being outside of the specifications. This calculation assumes that the measurement process is stable and the measurement variation follows a normal distribution. Process performance capability indices are applicable to measurement processes because measurement is a process.

Table 7: Potency assay measurement capability analysis.

Data Set	N	Average	Standard Deviation	P_{pk}	Lower P_{pk}	Upper P_{pk}
All analysts	96	99.4	0.69	1.18	1.00	1.36
Analyst A	46	99.5	0.85	0.98	0.75	1.20
Analysts B, C, D, E, F	50	99.4	0.51	1.57	1.25	1.90

Table 7 summarizes the Ppk index for the potency test method data (Figure 1, Tables 1 and 2). As expected, the Ppk value for analysts B, C, D, E, and F (Ppk = 1.57; 95% confidence limits 1.25–1.90) is higher than that for analyst A (Ppk = 0.98; 95% confidence limits 0.75–1.20). These results were confirmed when the test results were compared to specifications (target measurement uncertainty = 90–110) and the Ppk values and their 95% confidence limits were examined.

The capability analysis is useful because it compares the measurement variation to the specification limits (acceptance criteria) of the test method. The frequency of out-of-specification results is done as part of the analysis.

One of the outputs of the analytical target profile is a set of acceptance limits that are the same as specifications for the output of the measurement [4]. As noted previously, the acceptance limits in this case were 90–110.

The sample size used to estimate the Ppk capability index is a critical consideration. Capability indices require larger sample sizes than might be expected. From a practical perspective, the sample should contain data that represent the total range of product values that the method is expected to measure. For example, if the total range of values for a particular measurement typically seen for a product is 90–110 and the data set contains values that range from 92 to 98, the sample is not representative of the total range of values.

From a statistical perspective, capability indices are highly variable when estimated from small samples. Studies have shown that, at a bare minimum, the sample size should be larger than 30–60, with the preferred sample size being greater than 60–90 [14]. Additional data on the uncertainty associated with the capability indices can be found in reference 14. That analysis shows that the length of the confidence intervals is wide, even for a sample size of 60.

Reporting the lower confidence limit for the performance capability index is a conservative strategy that takes sample size into account. For example, consider a sample of size 30, for which Ppk equals 1.30. This is close to the preferred minimum of 1.33, but the confidence limits are wide (1.02–1.76). By reporting "performance capability index = 1.02 (lower 95% confidence limit)," we have reported a performance capability index that has taken the limited sample size into account. Of course, the lower confidence limit can be increased by increasing the sample size.

RISK OF LACK OF MANAGEMENT ATTENTION

We often hear the comment that test methods receive insufficient attention from management. If management put test methods higher on their priority list, more resources would be made available to support measurement systems, which would in turn increase the chances that better measurement systems will emerge. One way to get management attention for test methods is to include method performance data as part of the management review of production data. Such an approach is shown in Figure 4 [15]. This strategy seems reasonable because the test methods are used to produce the production data.

Figure 4: Production and test-method monitoring system.

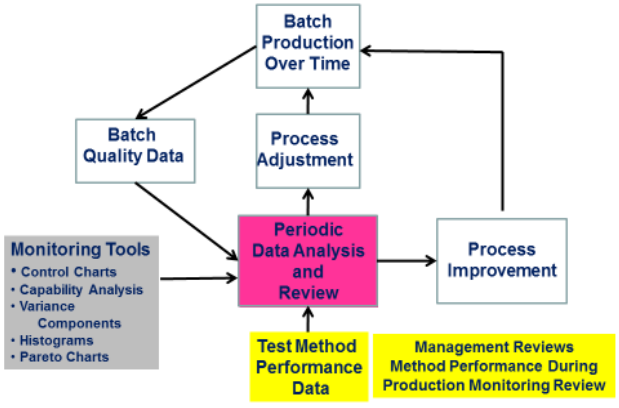


Figure 4 is a schematic of a system that links method performance data with the process, its data and analysis, management review, process adjustment, and process improvement. Process adjustments are changes made to bring the process back to target and/or within specifications. Process improvements are process changes made to correct problems in process performance. Process improvements typically result from team-led process improvement projects using an improvement framework such as define, measure, analyze, and improve and control (DMAIC) [16].

This results in a system for CMPV as well as continued process verification, as called for in the FDA guidance [2, 3]. When we add test-method performance data to the system, we achieve CMPV as recommended in the USP guidance [4]. Although this article focused on the monitoring of test-method measurements, out-of-specification, out-of-trend, and system-suitability-failure events can also be added to the metrics monitored.

I refer to management review as the "secret sauce." Requiring periodic management review of measurement systems is a giant step forward toward the long-term sustainability of effective measurement systems. Management review is a "team sport" done by different management teams at different times. These teams include process operators (daily/hourly), area management (weekly), site management (monthly), and business management (quarterly). The management review plan should be devised to suit the needs of the business. Test-method performance would typically be assessed less frequently (e.g., monthly or quarterly) than process performance. The schedule selected will, of course, depend on the specific needs of the organization involved.

TRUST BUT VERIFY

The admonishment to "trust but verify" applies to the monitoring of test methods. The tools described in this article provide an effective check on test-method stability and capability, and they reduce risk. The use of blind control samples is effective. The use of product stability data also works; this method is a broader and more robust verification check and reduces cost. Commercially available software can be used to carry out the calculations and analyses required for the proposed approaches. The proposed systems approach with integrated management review helps maintain the stability of test methods over time. This results in reduced risk of poor manufacturing process performance and defective pharmaceuticals reaching patients.

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