PHARMACEUTICAL ENGINEERING®

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REGIONAL FACILITIES

Research Triangle: Building a Foundation for Pharmaceutical and Biotechnology Excellence

CMC Requirements for New Drug Registration in Latin America

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39 SPUMONI: ENHANCING PHARMA DATA QUALITY THROUGH SMART TECHNOLOGIES

Funded by the European Commission from 2019, the Smart Pharmaceutical Manufacturing Project (SPuMoNI) harnesses the potential of state-of-the-art technologies for the pharmaceutical industry. This article discusses the main SPuMoNI accomplishments.

DEPARTMENTS

PEOPLE + EVENTS

TECHNICAL

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By Michael L. Rutherford


Michael L. Rutherford

Meeting the Strategic Plan

It is hard to believe that by the time this column is published, my term as Chair will be half over. We've accomplished much, and I'm left wondering, "Where has the year gone?"

When this column is published, we will have completed two very successful international conferences—the Facilities of the Future Conference and the Aseptic Conference—and the European Annual Meeting in Amsterdam will likely be concluded. Several regional Affiliate and Chapter conferences and vendor shows will also have occurred.

The overwhelming majority of the Affiliates and Chapters will have signed the new 2023 Charter, and the nomination process and the ballot for the Board is almost finalized. Planning for the 2023 ISPE Annual Meeting in Las Vegas in October will be well along and is beginning to be finalized.

PE THEME: REGIONAL FACILITIES FOCUS

The pharmaceutical industry is truly a global one, but it's facing many challenges, including financial and ethical challenges, geopolitical considerations, supply chain pressures, talent shortages linked to wider labor market trends, and a swiftly changing product landscape. Inflation has risen to the highest levels in decades, leading to increasing costs for labor, raw materials, and transportation. This is on top of the price pressures the industry is already facing and the new and increasing government and protectionist trade policies on manufacturing networks that could drive increased regionalization.

ISPE is advancing our vision to shape the future of the global pharmaceutical industry.

North America and Europe remain the top global markets in pharmaceuticals, but the flattening of growth in pharma sales in developed countries have pharma companies increasingly looking to emerging markets—including Brazil, India, Russia, Colombia, and Egypt—for new sources of growth and revenue. These emerging markets, especially Latin America and the India subcontinent, are the ones that can see the most significant increase in pharmaceutical sales over the next three to five years. Hence the importance and focus on regional facilities in this edition of PE magazine.

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STRATEGIC PLAN: FOSTER PARTNERSHIPS AND COLLABORATION THAT ADVANCE ISPE'S MISSION

As stated, one of the challenges facing our industry is talent shortages. This challenge is not limited to a specific region, but it is more prevalent in emerging market regions that are becoming increasingly important to the pharma industry as they aim to grow and expand. An ISPE 2023–2025 Strategic Plan objective—foster partnerships and collaboration that advance ISPE's mission—is addressing this need through partnerships with the ISPE Foundation and industry supporters.

ISPE's Technology Without Borders program underpins the Foundation's Global Knowledge Exchange philanthropic pillar and supports our shared missions to provide global access to knowledge where needed. The Technology Without Borders program was created to expedite the process for availability of essential industry guidance documents and associated training to emerging economies, regulatory bodies, and organizations that would otherwise have limited or no access to the pharmaceutical industry's best practices and standards. Aided by significant funding, the program is currently being piloted in Brazil, as there is no single greater opportunity for ISPE and the Foundation to accomplish this goal than providing training that is translated into the local language of Portuguese.

As the pharmaceutical industry is leveraging new technologies and innovation—including advancement of digital and analytics tools—to grow the business, the need for qualified and knowledgeable talent increases, especially in emerging regions. Supporting initiatives and programs such as Technology Without Borders are synergistic and beneficial to both ISPE and the ISPE Foundation and will expand our footprint globally. ISPE, through the Foundation and this program, is advancing our vision to shape the future of the global pharmaceutical industry by providing solutions to complex challenges through manufacturing and supply chain innovation; member and workforce development; and technical, regulatory, and quality leadership.

I encourage all ISPE members to support the ISPE Foundation by going to their website at ISPEFoundation.org and making your contribution. If you have questions or would like more information about the ISPE Foundation or the Technology Without Borders program, contact Tori Johnson, Director of Development and Foundation Operations at tjohnson@ispe.org

Michael L. Rutherford is Executive Director, Computer Systems Quality and Data Integrity, at Syneos Health, and the 2022–2023 ISPE International Board Chair. He has been an ISPE member since 2003.

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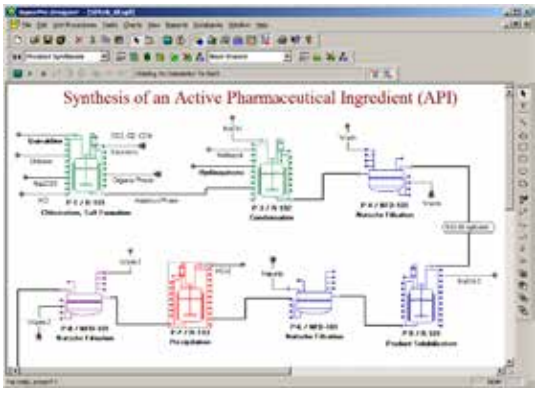

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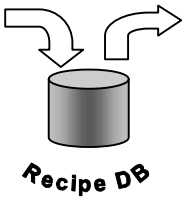

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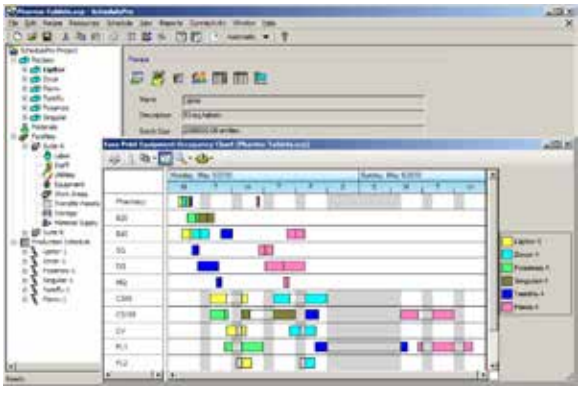

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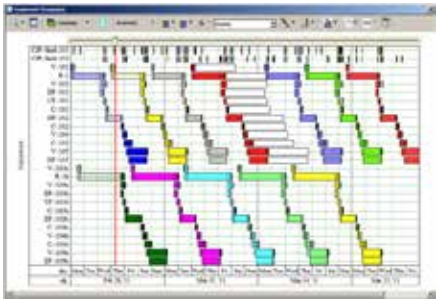

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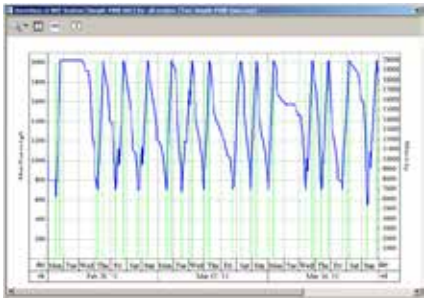

Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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By Miriam Kremer-van der Kamp


Miriam Kremer-van der Kamp

INDUSTRY GROWTH GENERATES OPPORTUNITY AND DIVERSE WORKFORCE

As a woman in the pharma industry, I have witnessed firsthand the growth of the industry in the Germany/Austria/Switzerland (D/A/CH) region and the opportunities it has brought for women like me.

The industry has been thriving thanks to the investment in research and development as well as the focus on the collaboration between industry and academia. The Novartis Campus that opened in Basel, Switzerland, in 2019 is an excellent example of the significant investments being made in the industry. The campus features cutting-edge technology and facilities, including a high-tech laboratory, research library, and digital hub for data analysis and modeling. These investments have resulted in the development of new drugs and treatments for a range of diseases, driving growth in the industry.

The D/A/CH region also leveraged its well-established regulatory framework for the approval and oversight of pharmaceuticals, ensuring that drugs are safe and effective before they are made available to patients. This helped build trust in the industry and promote further growth. An example of a new regulatory framework in the D/A/CH region is the Swiss Therapeutic Products Act (TPA), which was introduced in 2019. The TPA replaced the previous regulatory framework and introduced a range of new measures to improve the safety and efficacy of therapeutic products, including pharmaceuticals.

The growth of the industry has not only created a high demand for skilled professionals, but has also reinforced the need for diversity in thought, which has created space for greater gender equality. The growing recognition of women, and the value they bring to the workplace, has allowed so many to finally assume decision-making and leadership roles, allowing those in these roles, and those working toward them, the opportunity to make a true impact.

The Swiss government's support for promoting diversity and inclusion has also been a driving factor in the integration and embrace of female contributions. With the implementation of new initiatives—such as gender quotas on boards of directors and funding for programs that support women in the workplace—the D/A/CH region continues to raise awareness of the importance of gender equality.

With these recent developments, companies are recognizing the benefits of a diverse and inclusive workforce and are actively seeking out female talent. As a result, we've seen a rapid growth for ISPE's Women in Pharma® initiative, as women across the D/A/CH region are seeking networking and mentoring opportunities to continue to advance themselves.

Beyond Women in Pharma®, there are now more events and organizations focused on supporting women in the industry, which has allowed me to connect with other women and to learn from their experiences.

The growth of the pharma industry and the changing nature of the corporate landscape has led to the embrace of a new concept: the workforce of the future. This concept encompasses the evolving nature of work and the skills needed to succeed in a rapidly changing world. The investment in research and development and the emergence of the workforce of the future are exciting advances that offer many opportunities for women and other underrepresented groups.

Digital literacy, lifelong learning, flexibility and adaptability, collaboration and teamwork, and emotional intelligence are all key characteristics of the workforce of the future, and all delete of which are promoted by ISPE Women in Pharma® programming. As a member of the Women in Pharma® International Steering Committee and active Emerging Leader, I am excited about the possibilities that lie ahead.

Though there is still so much work to do as it applies to accelerated equality for women and other marginalized groups, I am optimistic about the future of our industry, and specifically the promising developments that lie within the D/A/CH region's workforce of the future.

Miriam Kremer-van der Kamp is a Process Engineer at PM Group. She is the Emerging Leader Liaison for the Women in Pharma® International Steering Committee, Co-Chair in the Engineering, Automation & IT/OT Subgroup within the Biotechnology Community of Practice (CoP), and on the Leadership team of the Emerging Leaders D/A/CH. She joined ISPE in 2022.

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By Zen-Zen Yen


Zen-Zen Yen

EMERGING LEADERS SEEK TO INSPIRE, CONNECT, AND ELEVATE

ISPE's Emerging Leaders (EL) Steering Committee is taking time to get our foundation right so that we can help drive change and empower young pharmaceutical engineering professionals to pursue their dreams. Our vision and mission will serve as the pillar for how we engage with Emerging Leaders and students around the world, stay true to our goals, and adapt to regional requirements.

As a member of ISPE for a number of years, I have seen the organization grow and change, adapting to industry trends, scientific advancements, and pharmaceutical needs. Recently, the EL Steering Committee refined its vision and mission to better encompass what we do. As we continue to grow, we seek to inspire, connect, and elevate, and we can't wait to show you what those terms mean to us.

INSPIRE

The EL Steering Committee believes that the future of the pharmaceutical industry lies in the hands of the talented individuals who are committed to making a difference. We're here to inspire and guide those future leaders toward achieving their goals and realizing their full potential.

If you're looking for inspiration or have an idea to make a positive impact, this is the place to be. In 2017, we organized our first Hackathon. What began as a random thought quickly evolved into an exhilarating new concept that connects Emerging Leaders and students across the globe and encourages them to think creatively about real-life industry challenges. The Hackathon has become an integral part of ISPE conferences and attracts a growing audience every year. Without the support of ISPE, the Communities of Practice, and many experts who volunteer their time, this would have never become reality.

We want to inspire students to pursue a career in pharma. It may not be the first option they consider, but for those passionate about making a difference and saving lives, a career in the pharmaceutical industry can provide a sense of purpose and fulfillment that is difficult to find in many other fields.

CONNECT

In the world of pharmaceutical engineering, connection helps us answer the big questions and produce out-of-the-box results. By connecting leaders at all levels, we've built a sounding board for ideation, collaboration, and new perspectives. As Emerging Leaders ourselves, we recognize the importance of building and nurturing connections. This network has provided many of us with exceptional opportunities we might not have had otherwise, and as our network continues to expand, so do our possibilities.

While it may be easy to connect with peers in the same industry and company, our network goes beyond this by facilitating connections across various functions, companies, and locations. A regulatory professional, for example, offers valuable insights to a pharmaceutical manufacturing specialist, but these collaborations might not happen. To address this challenge, ISPE created a framework to facilitate connections and empower our members to make the connections required to thrive.

ELEVATE

Elevating the quest for knowledge is essential for personal and professional growth. In today's fast-paced and ever-changing world, it is crucial to keep up with the latest trends and developments. Additionally, learning new skills and knowledge can help individuals broaden their perspectives. Through ISPE's conferences and educational sessions, I have been able to learn about innovations within the pharmaceutical industry.

Elevating education is also crucial for societal progress, with ISPE's new Technology Without Borders initiative, knowledge documents, and trainings being made available in the areas of the world where there's a need.

NEW VISION, SAME ISPE EMERGING LEADERS

Being part of ISPE and meeting so many amazing leaders has been the opportunity of a lifetime. As we continue to inspire, connect, and elevate, we will work together to propel this community into the future of pharmaceutical engineering.

Zen-Zen Yen is Head of Engineering for Bayer AG and the 2022–2023 ISPE International Emerging Leaders Chair. She has been an ISPE member since 2016.

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RESEARCH TRIANGLE:

Building a Foundation for Pharmaceutical and Biotechnology Excellence

By Scott Fotheringham, PhD

North Carolina's Research Triangle is the largest of its kind in the US. Thanks to years of effort from industry, pharmaceutical professionals, and education institutions, it is synonymous with pharmaceutical and biotechnology excellence.

The Garment District. The Diamond District. The flower markets blooming on 28th Street. In Manhattan, each of these neighborhoods specialize in one thing. These areas raise the question: How does an area become a hub for competing businesses?

This phenomenon is repeated on a much larger scale in pharmaceutical manufacturing in regions around the globe, such as Boston, the San Francisco Bay Area, San Diego, and others in the US; BioValley and D/A/CH in Europe;and clusters in South Korea, China, and India in Asia. These regions are known for their concentration of pharmaceutical manufacturers, contract development and manufacturing organizations (CDMOs), excellent life sciences educational institutions, and supporting trades and companies. Although many of these regions are also home to other industries, one is synonymous with pharmaceutical and biotechnology excellence—North Carolina's Research Triangle.

THE RESEARCH TRIANGLE

North Carolina has 790 life sciences companies employing 70,000 people within 94 biotechnology and pharmaceutical manufacturing sites—including heavy hitters like Eli Lilly, Pfizer, GlaxoSmithKline, Novartis, Thermo Fisher Scientific, FUJIFILM Diosynth Biotechnologies, Biogen, Novo Nordisk, and bluebird bio. It's estimated that the life sciences industry generates more than $88 billion every year for the state's economy [1]. The heart of this booming environment is Research Triangle, an area bounded by three cities with exemplary life sciences universities: Durham, with Duke University; Chapel Hill, with the University of NC Chapel Hill; and Raleigh, with North Carolina State University.

Origin of the Research Triangle

In the 1950s, North Carolina had a struggling economy, the second lowest per capita income in the US, and was largely dependent on tobacco farming and industries requiring manual labor. There was a brain drain as university graduates looked for opportunities outside the state. Government and business leaders came together with a plan to meet these challenges and, in 1959, created Research Triangle Park (RTP). Its goal—to attract high-tech companies to the state—was successful, as companies like IBM and Burroughs Wellcome opened research and development (R&D) campuses.

Surrounded by universities and community colleges with life sciences programs, companies in RTP were able to access highly

skilled graduates, increasing employment in the state. By the 1990s, pharmaceutical companies were looking to partner with contract research organizations (CROs) for drug development and clinical trials. By 2000, 61% of new businesses in the area were involved with drug discovery and the development of medical devices [2]. Today, this 7,000-acre research park is the largest of its kind in the US. It includes 300 companies in biopharmaceutical and other life sciences and technology. The RTP Foundation, which runs the park, supports collaboration between universities in the Triangle, fosters cooperation between universities and biopharmaceutical companies, and works to improve the state's economy.

The Triangle has become well-known specifically for cell and gene therapy (CGT), in part due to the long history of CGT in the region—the UNC School of Medicine Gene Therapy Center in Chapel Hill was founded in 1993 by one of the pioneers of gene therapies, Dr. Jude Samulski. Jaguar Gene Therapy is building a $125 million facility in RTP to manufacture adeno-associated virus (AAV)-based gene therapies, Beam Therapeutics is constructing an $83 million plant to develop precision medicines, and IQVIA, a CRO, opened an innovation lab in the park in 2021, focusing on bioanalytics, vaccines, biomarkers, and genomics. This is by no means an exhaustive list: other companies in RTP include Pfizer, Novartis Gene Therapies (formerly AveXis), and Audentes (an Astellas company).

SUCCESS AND EXPANSION

The phenomenal growth of Research Triangle, with long-standing companies expanding their footprints and new companies constantly entering the region, is made possible by one of the strengths of the region, a characteristic that differentiates it from more built-up hotspots—there is room to grow.

For a company like FUJIFILM Diosynth Biotechnologies, which already has deep roots in the Triangle, continued expansion is an easy decision. It is one of many companies building out existing facilities—such as an expansion of its BioProcess Innovation Center in Morrisville that will double the company's process characterization and clinical process development capacity—as well as opening new facilities outside the Triangle.

The following are a few of the many places that contribute to the success of the industry beyond the Triangle.

Holly Springs

Only 23 miles from RTP, Holly Springs has become a vibrant extension of the Triangle. It's now home to numerous biotech companies, including CSL Seqirus, which completed

Addressing the shortage of skilled workers

The success of the biopharmaceutical industry and the expansion of manufacturing facilities, of both existing companies and newcomers, has put a strain on the number of temporary and permanent skilled workers needed to fill many positions in the Triangle.

"Fifty years ago, the focus was much more on research and innovation partnerships than providing a talent pipeline for future employees," said Christopher Chung, CEO, EDPNC. "The talent piece is actually more important now to pharma companies."

"We have people coming to North Carolina every day," said Bo Crouse-Feuerhelm, Vice President, Client Solutions, J.E. Dunn Construction Company. "All of these companies have openings, including ours—we are always looking for technical talent in construction." She noted that, historically, the Triangle has not had to deal with workers jumping from one company to another the way this happens in places like the San Francisco Bay Area, which has a nucleus of companies. But it does now. "It's become a challenge for existing companies to keep talent, with all the new companies coming to the region. We are also seeing it happen in the design and construction space too."

As is the case with so much in the Triangle, solutions to this challenge are coming from many angles. Recently, the NC Biotech led a diverse coalition of companies, universities, community colleges, government agencies, and organizations that was awarded a $25 million grant from the US Economic Development Agency, for a program they call "Accelerate NC - Life Sciences Manufacturing."

"This grant will allow us to build a collaborative program to increase life science manufacturing career opportunities for traditionally underserved communities," said Bill Bullock, Senior Vice President, Economic Development and Statewide Operations, NC Biotech.

Crouse-Feuerhelm sees the need to recruit from outside the region in pharmaceutical stronghold metropolitan areas like San Francisco, Philadelphia, New York City, Boston, Los Angeles, San Diego, DC, and Chicago to diversify the talent pool a necessity. She noted the example of Eli Lilly, which is investing nearly $1.5 billion in two manufacturing plants: one in Concord, near Charlotte, and one in RTP. "There isn't yet the same concentration of pharmaceutical talent in the Charlotte area, which is currently known for banking and commercial businesses. Lilly's going to change up that space with its campus and will have to retrain and recruit."

"We assure companies that while talent is not easy to find anywhere in the current environment, it will be easier in North Carolina because of our population growth, as well as thanks to assets like our community college system, which essentially pioneered the concept of customized training for a specific employer," said Chung. "There's no place where there's 5,000 skilled biopharmaceutical manufacturing employees sitting around unemployed waiting for the phone to ring."

Instead, he sees part of the solution being to help workers transition into this industry. North Carolina has the advantage that, every year, as many as 20,000 military personnel from Fort Bragg and Camp Lagoon exit active-duty service and re-enter civilian life. "That's a relatively untapped tranche of talent available for employers that are expanding in North Carolina," said Chung.

Student training is also important, through such programs as ISPE's Student Chapters. "We are cultivating talent from the regional universities, as well as providing ISPE student memberships at no cost to interns on the client side," said Bud Watts, President of CaSA. "We are undertaking an aggressive expansion of our student chapter outreach program, working with more than a dozen universities and tech schools."

As with so much in Research Triangle, it is a combined effort that will help solve this challenge.

construction of its cell-culture flu vaccine manufacturing plant in 2008; Amgen, which began construction of a $550 million drug substance manufacturing plant in 2022; and FUJIFILM Diosynth Biotechnologies, which is currently building a $2 billion expansion facility for mammalian cell culture, complete with 20,000-L bioreactors.

Sanford

This city is home to Abzena, a CDMO specializing in mammalian cell-based biologics and bioconjugates, which is building a 120,000-sq.-ft. plant containing eight 2,000-L single-use bioreactors; Pfizer, which has a 230-acre site focusing on vaccine intermediates and gene therapies that also includes microbial

fermentation, purification, conjugation, and cell banking; and Astellas, which opened its 135,000-sq.-ft. AAV gene therapy plant in 2022.

Clayton

Southeast of Raleigh, Clayton hosts Grifols, which has a blood fractionation facility that won an ISPE Facility of the Year award in 2014 [3] and Novo Nordisk, with its well-established injectable finished products plant and recent $2 billion expansion into active pharmaceutical ingredient (API) production.

Eastern North Carolina

In Rocky Mount, Pfizer has a 1.4-million-sq.-ft. manufacturing site on 250 acres that produces almost one-quarter of all sterile injectables used in US hospitals. Greenville, home to East Carolina University, has Thermo Fisher Scientific, a contract manufacturing organization (CMO) manufacturing solid dose drug products and sterile injectables, and Catalent, a CDMO that recently acquired a 333,000-sq.-ft. solid oral dose manufacturing plant that produces more than one billion units per year.

REASONS FOR THE TRIANGLE'S SUCCESS

The Triangle has been successful as a hotspot for pharmaceutical R&D and manufacturing due to the confluence of four resources:

- A skilled, well-educated, and trained workforce
- Robust infrastructure, including transportation networks, business development supports, and tax incentives for businesses
- Presence of tradespeople and companies providing design, engineering, construction, and validation services
- Amenities for an attractive quality of life

Access to a Pipeline of Skilled and Well-Educated Workers

"The number one benefit to being in the Triangle is the talent pool," said Charles Crosier, Associate Director, Engineering Science, FUJIFILM Diosynth Biotechnologies. "There are so many other biotech and pharma companies in this region that all the necessary departmental needs are here, including manufacturing technicians, facility mechanics, process and automation engineers, supply chain, validation specialists, and those experts in QA and QC."

This pool is filled with graduates from the numerous educational institutions in the Triangle and throughout North Carolina. Many of these colleges and universities have established specific programs, certifications and degrees structured around a pharmaceutical and bioprocessing core curriculum. These local universities and colleges provide the various talent and skill sets required to operate a complex biopharmaceutical facility, Crosier estimates that "6 out of 10 people that come to us are graduates from these local universities and colleges."

For example, FUJIFILM Diosynth Biotechnologies and NC State recently enhanced their strategic partnership with programs to focus on research and facility design related to sustainability goals and to create new bioprocessing techniques [4]. NC State also contains the Golden LEAF Biomanufacturing Training and Education Center (BTEC), which provides education and training for students and industry professionals at a GMP biopharmaceutical manufacturing facility. Also, on the campus is ASSIST, an engineering research center that develops nanotechnology-powered wearable medical monitoring devices.

North Carolina Central University (Durham) has the Biomanufacturing Research Institute and Technology Enterprise, which funds health-related research and workforce training.

Wake Tech Community College has seven campuses running numerous programs to train students to work in the pharmaceutical industry. These include its associate of applied science degrees in biotechnology (for CGT and R&D roles) and biopharmaceutical technology (for drug manufacturing and protein therapeutics), and the BioWork certification program for process technicians with a high school diploma. The college also runs the NC BioNetwork Capstone Center, at NC State University's BTEC facility, to teach new skills, technologies, and regulatory requirements to those already working in the pharmaceutical industry.

"We teach real-world applications when it comes to making medicine, from the innovation to create novel cures to large-scale manufacturing processes," said Leslie Isenhour, Dean, Biotechnologies Division, Wake Technical Community College. "Our programs are designed to provide the best hands-on technical education you can get outside of an actual company. Industry supports us in our efforts to purchase new equipment, as well as elevate the skills of our faculty. Our students are choice candidates for so many local companies that job opportunities are plentiful even before they graduate."

Wake Tech's campus in RTP houses the Lilly Science and Technology Center, as well as the FUJIFILM Diosynth Biotechnologies Early College Suite, which encompasses the Wake Early College of Information and Biotechnologies. The Early College Suite supports high school students interested in earning college credits in the life sciences. Once it's full, the suite will enroll as many as 100 high school students for each grade level.

Campbell University College of Pharmacy & Health Sciences was the first university in the Triangle to offer an educational program in the pharmaceutical sciences. Its Pharmaceutical Education & Research Center (PERC) is a US Food and Drug Administration (FDA)-registered, cGMP-compliant, single-source CRO equipped with the latest equipment and technologies, for most dosage forms, found in the pharmaceutical industry. PERC provides R&D for the pharmaceutical industry while also training students on analytical testing, drug development, manufacturing, clinical protocol development, animal screening, and FDA compliance.

"We work with smaller companies and startups because we are nimble," said Dr. Charles Carter, Chairman of Pharmaceutical & Clinical Sciences at Campbell University. "PERC has the

Students at Campbell University College of Pharmacy & Health Sciences.

resources and experienced personnel to help our clients with formulation development, as well as analytical and stability testing."

Making the high school connection

"Developing your workforce is good, but only if you have people to train," said Bo Crouse-Feuerhelm, Vice President, Client Solutions, J.E. Dunn Construction Company. Crouse-Feuerhelm is an active member of ISPE, sits on the ISPE Women in Pharma® and ISPE-CaSA Technology Show Committees, and is a former president of ISPE's CaSA Chapter. "This is why it's beneficial to go into middle schools—and even elementary schools—to create STEM programs." She and her colleagues have spoken at these schools about the design and construction job opportunities available in the industry.

Whether a student wants to work in architecture and construction, as a process engineer, in quality control, or in a skilled trade, they likely will need a strong background in science and math. As automation and Pharma 4.0™ continue to transform biopharmaceutical manufacturing, it will be important to have workers capable of operating automation systems and robotics.

"I cannot overstress the importance of STEM programs at the middle school and high school levels," said Carter. "PERC offers hands-on workshop opportunities for schools and at our lab facilities to allow students to see what pharmaceutical manufacturing is all about. Not only does this help generate a pipeline of good workers, but it also teaches the teachers, who stay to guide future classes of students."

Another training program is at the Workforce Development Center, a public–private partnership between Novo Nordisk and Johnston Community College in Clayton. This 30,000-sq.-ft. educational and skills training facility works with students from elementary school through postsecondary education who are considering careers in the life sciences, particularly biotech. STEM RTP, an initiative that provides access to education and training, has grants for programs aimed at supporting those who are traditionally underserved in STEM education, including women and girls, minorities, and people from low-income backgrounds.

CaSA Chapter supports students throughout the Triangle and beyond

ISPE's Carolina-South Atlantic Chapter (CaSA) is active in six states, including North Carolina. In addition to hosting the annual Sciences Technology Conference—which celebrated 30 years of innovation this past February at the Raleigh Convention Center—CaSA runs student chapters that afford opportunities to network with professionals and develop skills to those looking to enter the pharmaceutical industry. It also awards the Jane Brown Scholarship to select CaSA Student Chapter members wanting to enter the life sciences industry who are enrolled in an undergraduate or graduate program. In Research Triangle, there are Student Chapters at Campbell University, NC Central University, NC State University, and UNC Chapel Hill.

"The centerpiece of our Tech Conference this year was the career fair," said Bud Watts, CEO, Hygenix, and President of CaSA. "We gave manufacturers center stage to create an environment in which student talent could identify companies that are hiring. Several major manufacturing organizations contributed to our student growth programs and were speakers for each education segment of the conference."

ROBUST INFRASTRUCTURE AND ECONOMIC DEVELOPMENT PARTNERS

North Carolina consistently ranks among the best states in which to do business. It has a lower cost of living than many other biomanufacturing hotspots and tax incentives—such as the state's Job Development Investment Grant (JDIG)—that are based on the number of jobs a company creates. For example, the local governments in Holly Springs and Wake County awarded job development grants worth a total of more than $35 million to Amgen based on the number of jobs its new manufacturing site will provide.

"Since 2017, Holly Springs has been a certified entrepreneurial community, which recognizes our support for small business development," said Irena Krstanovic, Economic Development Director for Holly Springs. "Every year we encourage new entrepreneurs through our policies and grants for small businesses."

The types of infrastructure specific to biopharmaceutical manufacturing—which requires great quantities of water and electricity, while also generating considerable wastewater—make it important to have access to the type of affordable, reliable utilities that are available in North Carolina. Additionally, the Triangle has good access to highways, airports, rail, and ports, all of which are essential for any pharmaceutical facility.

In addition to government incentives and support, there are a number of nonprofits and foundations that have been important to the economic development of the life sciences in the Triangle. The following are a few notable examples.

North Carolina Biotechnology Center

The North Carolina Biotechnology Center (NC Biotech) was established in RTP in 1984 and is, in some ways, the nerve

center of the Triangle. This independent nonprofit collaborates with a range of partners to create employment, enhance educational programs in the life sciences, and entice new companies to the region.

"Our work is aimed at creating an environment to develop, attract, and retain talent," said Bill Bullock, Senior Vice President, Economic Development and Statewide Operations, NC Biotech. "Our portfolio of workforce and talent development programs work in collaboration with community colleges, universities, HBCUs [historically Black colleges and universities], K-12 schools, companies, and communities to provide targeted solutions to workforce development needs."

With the goal of making North Carolina a national and global hub for biotechnology, its mission includes:

- Strengthening university research
- Fostering collaboration between government, businesses, and academia
- Supporting biotechnology business development and the creation of new companies
- Educating the public about biotechnology

"Combined with the North Carolina Department of Commerce, the NC Biotechnology Center was the foundation that set North Carolina up for success as a pharmaceutical manufacturing hub," said Crouse-Feuerhelm. "It ties into the great universities and medical schools surrounding Research Triangle Park, as well as the community college system."

Golden LEAF Foundation

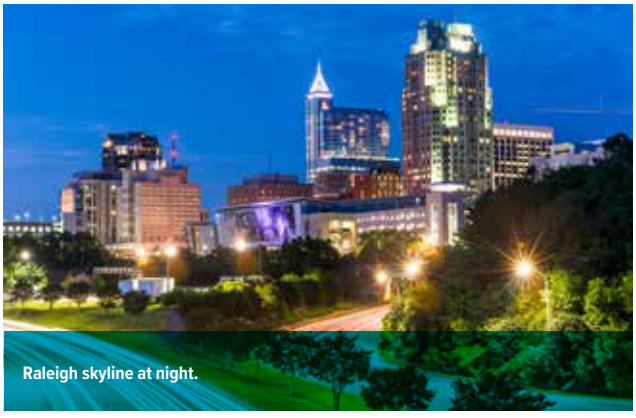
With the decline of tobacco farming—one of the mainstays of the NC economy for centuries—there was a concerted effort to diversify the state's economy. The Golden LEAF Foundation, established in 1999, kickstarted this effort, providing grants and other forms of support to communities adversely affected by the loss of the tobacco economy. For example, Golden LEAF awarded $1.9 million in 2021 to support the burgeoning biopharmaceutical industry in eastern North Carolina.

Economic Development Partnership of North Carolina (EDPNC)

The EDPNC is a public–private partnership that functions to attract new businesses to North Carolina while supporting those already there, including those in biotechnology and pharmaceuticals.

"Every day we're in conversation with companies thinking about where their next expansion is going to occur, and we're lucky that they're considering North Carolina," said Christopher Chung, CEO, EDPNC. "We try to capitalize on the area's success and leverage it to attract even more growth in the industry."

As one example of the type of partnerships it forges, the EDPNC worked with the NC Biotech to win a federal Build Back Better award worth $500,000 to encourage the life sciences industry in traditionally distressed communities in the state.



Raleigh skyline at night.

PHOTO CREDIT: MICHAEL ROBSON/VISITRALEIGH.COM

ANCILLARY SERVICES, CONTRACT FIRMS, AND TRADESPEOPLE

The Triangle also has a surfeit of contract firms, skilled tradespeople, and equipment vendors with experience working with the pharmaceutical industry. There are as many as 2,500 companies supporting the biotechnology and life sciences industry in North Carolina. The availability and quality of design; architecture; engineering, procurement, construction management, and validation (EPCMV) consultants; and utilities contractors in the Triangle has evolved, boasting companies like CRB, BE&K, DPR Construction, and JE Dunn.

"When I first came to North Carolina in 1993, you could name on one hand the companies to go to for design or construction services," said Crouse-Feuerhelm. "Now, there is far more competition in the life sciences space, including companies capable of managing a $2 billion program, as well as commissioning, qualification, and validation services."

"These services require a different knowledge base and skill set specific to our industry," said Crosier. He points to more stringent heating, ventilation, and air conditioning (HVAC) requirements, the fit and finish of all cleanroom surfaces, the need for differential pressures and proper airflow rates, and the ability to generate and distribute hygienic utility systems such as for water for injection (WFI), clean compressed gases, and pure steam generation. "There's a lot more engineering involved in terms of the design, functionality, and continuous monitoring of our manufacturing suites."

Crosier states that, "The RTP area is well represented with numerous specialized trades, equipment vendors, general contractors and engineering firms that focus on the life sciences industry. These unique companies continue to support the RTP area and its partners to provide rapid, turn-key solutions in the stringent timelines and budget allocated while meeting all of the client's requirements in terms of safety, quality, and sustainability."

"There are companies that have heavy rigging equipment, such as industrial cranes for setting structural steel, and a strong talent pool of skilled workers who can build facilities with GMP cleanrooms," Crosier said. "They understand what an ISO 8 cleanroom is and how it differs from building a box store."

Having local skilled tradespeople, contract firms, and equipment vendors also reduces expenses and increases the speed of building a new facility. "If we want a standard or custom heat exchanger or diaphragm valve, for example, we have local representation for all those main products," Crosier said. "Companies that support the biotech and pharma industry—including processing equipment and components, raw materials, and consumables—are well represented in this environment."

AMENITIES FOR AN ATTRACTIVE QUALITY OF LIFE

In addition to the availability of talent, an excellent education system, government incentives, and business development partners that make North Carolina a good place to do business, cities in the Triangle are routinely ranked among the best places to live and work in the US. *US News & World Report* ranks Raleigh and Durham the sixth best place to live in the US, based on the Triangle's educational and employment opportunities and access to green spaces and entertainment [5].

"The popularity of the Triangle applies to both businesses and individuals," said Crosier. "While the cost of living here has gone up, it's still lower than a place like Boston and Philadelphia. We also have available land to develop, unlike some of those other regions."

Environmental sustainability, which is of ever-growing importance to pharmaceutical companies, also contributes to the quality of life in the Triangle. For example, companies within RTP can only build on a fraction of the land they own, preserving the remainder as greenspace.

"The town of Holly Springs has long put sustainability as a priority," Krstanovic said. "We have one of the most robust reclaimed water systems in the county, which is a major reason we've attracted global companies who have championed sustainability goals. Also, we received grant money to fund public electric vehicle charging stations in our growing downtown and are always pursuing additional partnerships to increase our green initiatives."

REPLICATING THE TRIANGLE'S SUCCESS

Those wanting to replicate Research Triangle's success—Crouse-Feuerhelm listed Virginia, South Carolina, and Austin, Texas, among them—need to keep in mind that the region didn't win a lottery and can't be duplicated simply by hanging up an "open for business" sign. It took an original idea, visionary leadership, decades of effort, and continued attention and care to make it the vibrant hub of biopharmaceutical research, development, and manufacturing that it is today.

"It's hard to emulate," said Chung. "It's hard to get the resources marshaled even to take some of those first steps. If you're an executive needing to defend the decision to put your manufacturing in this part of the country versus another, North Carolina's going to be seen as a hotbed and a safer bet—more business friendly and much more cost competitive."

"You have to have informed and engaged champions and leadership, appreciate the importance of talent, and build sustainable programs to develop and sustain a workforce across the entire education continuum," Bullock said. He then adds sobering recommendations for anyone looking for quick results. "It's important to be aspirational, but pragmatic and patient. RTP and its evolving economic impact on the Triangle and the state has been more than 60 years in the making. And you'll need to sustain the investment. Remember that the NC Biotech Center has been funded by the State of North Carolina for 38 years."

CONCLUSION

Like so many in the pharmaceutical industry, Crosier expresses genuine enthusiasm for the work his company does, and the way even different firms work together. "I have colleagues at other companies and, even though we work for different life science companies, we're all trying to make things better for everyone and the industry. If one of us comes up with a good idea or finds a great product or solution to a common industry problem, we're often willing to share it, as long as it's not proprietary or specific intellectual property such as information regarding batch recipes, source code and/or processing techniques."

When FUJIFILM Diosynth Biotechnologies was looking to install roll-up doors at the RTP facility, a local life sciences firm with the same doors was willing to give Crosier feedback and guidance so he could better understand their performance and reliability. "We installed the same doors and then someone from a third company asked the same favor of us. We were willing to give them a tour so they could see the doors in operation. By scratching each other's backs, we're able to achieve the goal we're all aiming for—to create life-saving medicines while improving the quality, safety, and cost of these products. That's why the life sciences industry matters, and that's why firms like ours exist."

One could expand this to say that's why Research Triangle exists. "There was a lot of foresight among elected officials and business leaders in North Carolina 60 years ago," Chung said. "It's much harder these days for public officials to make those kinds of long-term visionary bets. The governors at the time were willing to make a bet that what they planned would help North Carolina in 30, 40, or 50 years. And they were right."

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CMC REQUIREMENTS for New Drug Registration in Latin America

By Aicha Otmani, PhD, RAC, and Flávia C. Firmino

The global pandemic has demonstrated that now, more than ever, we need to work toward a global solution and prioritize the harmonization of technical requirements. Positive improvements have been observed in the acceptance and implementation of international standards by various regulatory agencies in Latin America. This article offers an overview of the chemistry, manufacturing, and controls (CMC) requirements for the small molecules product registration process in Latin America and highlights the divergence of some requirements from harmonized standards like the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

In an era when the world is accelerating the development of drugs and targeted medicines using innovative technologies, pharmaceutical companies still face registration hurdles for well-characterized molecules because of redundant or additional local regulatory requirements. There is a concerted effort from multinational pharmaceutical companies in developing countries to embrace regulatory convergence with international standards, primarily ICH, and to implement these standards to meet the increasing needs for and to expedite patient access to specialized and targeted medicines.

Improvements have been observed by various regulatory agencies in Latin America for the acceptance and implementation of international standards—for instance, the ICH Common Technical Document (CTD) format. However, existing, or new local regulatory requirements still present hurdles and the regulators' intention to embrace ICH guidelines or to accept alternate risk-based, scientifically supported approaches may be interpreted negatively by global pharmaceutical companies.

When companies pursue drug registration in these markets, the need for additional country-specific documents—such as certificates of pharmaceutical products (CPPs), Good Manufacturing Practice (GMP) certificates, site master files, and various types of declarations—may deter or delay progress and prevent timely patient access to drugs. These various local regulations inhibit the pharmaceutical industry from achieving its goal of harmonized international guidance documents and a single global dossier with harmonized terminology, regulatory standards, and evidence requirements.

Alternate approaches to meeting local requirements emerged during the COVID-19 pandemic: one example is the acceptance of electronically generated regulatory documents (e.g., CPPs). Regulatory agencies can learn from the transformative experience required by COVID-19 pandemic restrictions. And beyond that, they should willingly improve regulatory frameworks to streamline processes and global harmonized requirements (e.g., ICH) and to consider the adoption of reliance procedures that benefit patients via faster access to quality medicine.

This article offers an overview of the CMC requirements for the small molecules product registration process in Latin America. The information results from the authors' experience working in a global company and managing successful drug registrations in the Latin American region. The Latin American region defined here includes the following Central and South America countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, the Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras,

Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela. Caribbean markets are excluded from this analysis.

REGIONAL REGISTRATION PROCESSES

In the absence of a harmonized regional process for drug registration in Latin America, local regulations and processes set by each individual country are established. Some of these are more stringent than ICH requirements (e.g., Brazil requires specific forced degradation studies and analytical validation requirements) [1] and require more detail, which may ultimately restrict flexibility for drug supply, at initial registration, and during product life cycle management related to postapproval changes.

In the past few years, improvements in regulatory systems have been observed in Latin America, showing a stepwise harmonization of local regulations with international standards such as ICH. Despite the complex and challenging process of creating or reviewing a regulation in the region, many draft and new regulations have been published, illustrating regulatory agencies' willingness to improve their regulatory frameworks. A few examples of new or revised regulations include the Chile Institute of Public Health (ISP) adopting the CTD format for Module 3 for new drug registration [2], creating new timelines for agency review and approval of regulatory submissions, and the Colombian Ministry of Health creating new timelines for agency review and approval of regulatory submission and publishing newly established reporting categories for postapproval changes [3].

When the Brazilian Health Surveillance Agency (ANVISA) gained ICH membership in 2016, it also received an important perspective into global harmonization efforts. Since then, ANVISA has been an active member in several forums for reliance and harmonization initiatives, and its role as an ICH Management Committee member has reinforced the agency's focus on regulatory convergence with ICH guidelines. Unfortunately, among the 19 standing members of ICH, only two are Latin American regulatory agencies—ANVISA (Brazilian Health Surveillance Agency/Agência Nacional de Vigilância Sanitária) in Brazil and COFEPRIS (Federal Commission for the Protection against Sanitary Risks/Comisión Federal para la Protección contra Riesgos Sanitários) in Mexico—and only three are observers: ANMAT (National Administration of Drugs, Food and Medical Technology/Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) in Argentina, CECMED (Regulatory Authority for Medicines, Equipment and Medical Devices of the Republic of Cuba/Autoridad Reguladora de Medicamentos, Equipos y Dispositivos Médicos de la República de Cuba) in Cuba, and INVIMA (National Institute for Food and Drug Surveillance/Instituto Nacional De Vigilancia de Medicamentos y Alimentos) in Colombia. This means that the registration process in these markets depends heavily on local regulations.

Note that a country's membership in ICH does not translate into immediate adherence to the guidelines: ICH implementation plans are used generally to determine the transition. However, implementing ICH guidelines in these markets requires additional time and resources to both properly interpret the guidelines and to work them into local rules by revising, creating, or eliminating regulations.

In the absence of a harmonized regional process for drug registration in Latin America, local regulations and processes set by each individual country are established.

Until full transition is achieved, even the two ICH members (Brazil and Mexico) must still use local redundant documents for initial drug registration. Latin American countries widely recognize the US and EU as reference markets—or country of reference (COR)—as part of the drug registration process. However, drug product approval in a COR doesn't necessarily mean local registration requirements are harmonized with dossiers submitted and approved in the COR, or that the local drug review process is accelerated as a result of the COR. The request for far more data than originally required or approved in the COR should be anticipated, including where the data are generated (e.g., the site where development occurs versus where commercialization is intended). Additional required information beyond ICH guidelines, or non-value-added documents (e.g., declarations), require companies to prepare and maintain multiple versions of the registration dossier across the region. These situations can lead to filing and approval delays for new medicines and can create additional burden on product life cycle management.

Companies often must manage divergent and complex regulatory requirements due to differences in local postapproval regulations and requirements since additional registration submissions are required for low-risk changes. This, in turn, can lead to drug stock outs and shortages. One example of such complexity is that Latin American health authorities cannot accommodate minor changes that require a simple notification in US [4] and/or EU [5] (the "do and tell" procedure) but are considered instead a major change (e.g., Colombia) [6] that requires a minimum of 6- to 12-month review and approval timeline.

COUNTRY-SPECIFIC REGISTRATION REQUIREMENTS

Despite the evolving growth of local drug regulations and increased global harmonization efforts in Latin America, it is reasonable to state that the registration process is still highly country-specific. Although Latin American regulators seek global harmonization, they struggle with the right balance of local versus global requirements, which leads to an increased demand for country-specific documentation.

Table 1: Appendices and drug substance Module 3 required sections.

Section	Argentina	Bolivia	Chile	Colombia	Ecuador	Paraguay	Peru	Uruguay	Costa Rica	Dominican Republic	El Salvador	Guatemala	Honduras	Nicaragua	Panama	Venezuela
3.2.A.1			X													
3.2.A.2			X					X								
3.2.A.3			X													
3.2.S.1.1		X	X	X				X	X	X	X	X	X	X	X	*
3.2.S.1.2		X	X	X				X	X	X	X	X	X	X	X	
3.2.S.1.3			X				X		X	X	X	X	X	X	X	
3.2.S.2.1			X					X								*
3.2.S.2.2			X					X								
3.2.S.2.3			X													
3.2.S.2.4			X													
3.2.S.2.5			X													
3.2.S.2.6			X													
3.2.S.3.1			X													*
3.2.S.3.2		X	X													
3.2.S.4.1	X	X	X	X	X		X	X	X	X	X	X	X	X	X	*
3.2.S.4.1			X				X									
3.2.S.4.2	X	X	X		X		X	X	X	X	X	X	X	X	X	
3.2.S.4.3	X	X	X		X		X	X								
3.2.S.4.4			X													
3.2.S.4.5			X													*
3.2.S.5			X													*
3.2.S.6			X													X*
3.2.S.7.1		X	X													X*
3.2.S.7.2			X													
3.2.S.7.3			X						X	X	X	X	X	X	X	X*

* Corresponding Quality Overall Summaries (QOS) sections 2.3.S.1, 2.3.S.2, 2.3.S.3, 2.3.S.4, 2.3.S.5, 2.3.S.6, and 2.3.S.7 are required.

Most countries in Latin America, except Brazil and Mexico, do not require a full Module 3 CTD dossier to register a drug. Table 1 and Table 2 list the CTD sections that are needed in the registration dossiers where a full Module 3 is not required. The content of regional sections is not listed because this section differs significantly from country to country. Depending on the country, dossiers require CMC/Quality documentation that isn't usually included in the global CTD dossier. Examples of such documentation include:

- Certificates of analysis (COAs) of all formulation components from both the drug product manufacturer and supplier
- Executed batch records, including packaging records
- Chromatograms from analytical testing for batches on stability
- Analytical validation protocols and reports
- Specific stability information provided in a specific format such as statements, declarations, and memos
- CTD sections signed by the manufacturer, even when the manufacturer is not necessarily the marketing authorization holder
- Local testing/release

This article discusses the most common requirements that may impact dossier preparation and registration: approval in COR/country of origin (COO), CPP, stability studies, ancillary documents, and other requirements.

Table 2: Drug product Module 3 required sections.

Section	Argentina	Bolivia	Chile	Colombia	Ecuador	Paraguay	Peru	Uruguay	Costa Rica	Dominican Republic	El Salvador	Guatemala	Honduras	Nicaragua	Panama	Venezuela
3.2.P.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*
3.2.P.2.1		X	X				X									*
3.2.P.2.2		X					X									
3.2.P.2.3		X					X									
3.2.P.2.4		X														X
3.2.P.2.5		X					X									
3.2.P.2.6		X	X				X									
3.2.P.3.1	X	X	X	X	X	X	X	X								*
3.2.P.3.2	X		X	X		X		X								
3.2.P.3.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
3.2.P.3.4	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
3.2.P.3.5	X	X	X			X	X	X								
3.2.P.4.1	X	X	X	X	X	X	X		X	X	X	X	X	X	X	*
3.2.P.4.2	X		X			X	X									
3.2.P.4.3	X		X		X	X										
3.2.P.4.4			X						X	X	X	X	X	X	X	
3.2.P.4.5			X	X				X								
3.2.P.4.6			X													
3.2.P.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*
3.2.P.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3.2.P.5.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
3.2.P.5.4			X		X											
3.2.P.5.5		X	X													
3.2.P.5.6			X						X	X	X	X	X	X	X	*
3.2.P.6			X													
3.2.P.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*
3.2.P.8.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3.2.P.8.2			X			X										
3.2.P.8.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Corresponding Quality Overall (QOS) sections 2.3.P1, 2.3.P.2, 2.3.P.3, 2.3.P.4, 2.3.P.5, 2.3.P.6, and 2.3.P.7 are required.

Approval in Country of Reference (COR)/Country of Origin (COO)

The drug registration process in Latin American countries depends heavily on first approval in a well-recognized country with competent regulatory agency, known as the COR. Therefore, the US and EU are widely recognized as COR markets. The fact that the US and EU follow ICH guidelines does not really dictate the registration process, nor does it drive the requirements for a harmonized registration process in Latin America.

In addition to the COR, some Latin American markets require approval in the COO, which is defined as the country where the drug is manufactured, packaged, or exported from. Therefore, when planning submissions in a specific market in Latin America, it is important to take this requirement into

Table 3: Certificates and licenses required for initial registration.

	Manufacturing License	GMP Certificate	CPP
Argentina	✓	✓	✓
Bolivia	✓	✓	✓
Brazil	✓	✓	✓*
Chile	Not required	✓	✓
Colombia	✓	✓	✓
Costa Rica	Not required	✓	✓
Guatemala	Not required	✓	✓
Honduras	Not required	✓	✓
Mexico	✓	✓	✓
Panama	Not required	✓	✓
Peru	Not required	✓	✓
Venezuela	Not required	✓	✓

* Approval letter accepted in lieu of a CPP; not required at the initial submission but before ANVISA approval.

Table 4: Stability requirements for initial registration submissions in Latin America.

Countries	Climatic Zone*	API Stability Required? (Y/N)	In-Use Stability Required? (Y/N)	Photo-Stability Required? (Y/N)	Minimum Required Data at Submission
Argentina	II	N	N	N	6 months accelerated / 12 months long term
Bolivia	IVA or IVB	Y	Y	N	6 months accelerated / 6 months long term
Brazil	IVB	Y	Y	Y	6 months accelerated / 12 months long term
CAC**	IVB	N	Y	N	6 months accelerated / 12 months long term
Chile	II or IVA	Y	Y	N	6 months accelerated / 6 months long term
Colombia	IVB	N	Y	N	6 months accelerated / 12 months long term
Ecuador	IVA or IVB	N	Y	Y	6 months accelerated / 12 months long term
Mexico	II	Y	Y	Y	6 months accelerated / 12 months long term
Paraguay	IVA or IVB	N	Y	N	6 months accelerated / 12 months long term
Peru	IVA or IVB	N	Y	N	6 months accelerated / 6 months long term
Uruguay	II	N	N	Y	6 months accelerated / 12 months long term
Venezuela	IVB	Y	Y	N	6 months accelerated / 12 months long term

* II: 25°C/60% RH; IVA: 30°C/65% RH (hot and humid); IVB: 30°C/75% RH (hot and very humid)

** Central American countries (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, and Panama).

account [7]. A review of COR/COO requirements in Latin America shows that most markets mandate that the product is first approved in the COR—and it is tied to the availability of a CPP to be able to submit a new marketing application and to the product being approved in the COO before submission or approval [7].

Certificate of Pharmaceutical Product (CPP)

The CPP is intended to facilitate regulatory review and to replace a full dossier evaluation of the quality, safety, and efficacy of the requesting country. When effectively used, this accelerates approval and early patient access to innovative medicine. The CPP is required in Latin American regions to support a regulatory submission at the beginning of or during the health authority review. According to the World Health Organization (WHO) Scheme, CPPs should not be required in countries that require full ICH CTD dossiers and that have the capability to conduct full quality, safety, and efficacy reviews [8].

When developing a regional submission strategy for Latin American countries, CPP requirements are considered early in the planning phase. If required, national regulatory authorities should be open to discussion in advance of the regulatory submission to give advice and agree on the content of the submission, including the CPP, to move forward as quickly as possible [9, 10].

In practice, all Latin American countries conduct detailed evaluations of drug registration applications, even if they require and receive a CPP. For markets with fast-track, simplified, and/or reliance procedures (e.g., Argentina [11]), the decision is based on the recognition of certain regulatory authorities and not on the CPP. In these markets, the registration procedure for small molecules medicines is quite simple and requires minimum CMC information. For example: the approval process in Argentina is short (4 to 6 months).

Most Latin American countries do not require full CTD dossier evaluation (see Tables 1 and 2) but do require a CPP. These markets will perform a thorough dossier assessment of the submitted information with follow-up questions and information requests to applicants. Moreover, because the CPP confirms GMP status, additional GMP certificates should not be necessary. Table 3 describes the markets that require both documents (CPP and GMP certificates). Given that the

CPP is a legal document, additional certification and/or legalization should not be requested. This is not what is currently observed as the CPP document is either certified or legalized.

Stability Studies

Latin America is a diverse region with different climatic zones. For instance, Chile, Argentina, and Mexico are Zone II markets (25°C/60% RH), whereas Brazil and Paraguay are Zone IVB markets (30°C/75% RH). Despite that, the most restricted climatic zone (i.e., Zone IVB) when available, is usually provided to all Latin American market registration submissions, considering the stability of the product and the proposed shelf life. Table 4 describes a high-level overview of the stability requirements in Latin America.

Three drug product stability batches are required for initial registration and ICH Q1A (R2) Stability Testing of New Drug Substances and Products [12] is largely accepted in the region. Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Mexico, and Peru accept stability data from pilot/development batches manufactured at development sites, whereas the other Latin American countries, except Argentina [11], require stability data from the proposed commercial sites. Additionally, Mexico requires real-time commercial stability data to grant the drug product shelf life if the development site is not being registered as part of the drug product commercial supply chain. Also, COFEPRIS in Mexico doesn't allow extrapolation of shelf life considering the long-term, real-time commercial stability data that are amenable to statistical analysis, which is allowed by ICH Q1E, Evaluation of Stability Data [13].

Although the principles of ICH Q1A (R2) are widely accepted and recognized by most Latin American health authorities, some markets still require a significant customization of the stability data by means of stability declarations and other ancillary documents: these additional requirements are discussed in the next paragraphs.

Ancillary Documents and Other Requirements

Although some ancillary documents are needed to support drug registration even in a well-established market, some ancillary documents in Latin American markets go beyond what would be expected for inclusion in the dossier and sometimes these documents contain redundant information already covered in the CTD sections. Ancillary documents required to support registration in these markets include COAs, GMP certificates, test chromatograms, a batch numbering system, stability declarations, and signed declarations.

Certificates of Analysis (COAs)

Drug product COAs are required in most Latin American markets. Sometimes, COAs for the drug substance, the excipients used in the formulation, and the primary and nonfunctional secondary packaging material are requested. Most markets accept COAs from the registration batches (pilot or commercial scale) or commercial batches, if available. In Mexico, COAs from development batches can only be accepted if the site where the product was manufactured is also registered for commercial supply. In Central American markets, COAs of the samples submitted for testing are needed.

Sample Requirements

Samples of the finished product and/or standards are required in some markets in Latin America at or during the marketing application review. The challenges with providing samples are around their availability, arranging for their shipment, and preparing the appropriate regulatory documentation for custom clearance. Finished product samples are required in the following countries: Uruguay, Panama, Bolivia, the Dominican Republic (only product photos required for fast-track pathway), Guatemala (not required for fast-track pathway), and Nicaragua (for presentation only).

Compendial Monographs

Most formulations use common ingredients (excipients) and most of these excipients are of compendial grades. Additionally, quality control testing of these compounds is conducted using standard testing following applicable pharmacopeia—such as United States Pharmacopeia (USP), European Pharmacopeia (EP), and Japanese Pharmacopeia (JP)—that was current at the time of testing.

Registration dossiers in most Latin American markets require copies of the pharmacopeial monographs. Although copies are included in the dossier, they may no longer be valid when reviewed by the regulatory authorities due to ongoing updates to the compendia. Countries that require copies of excipient monographs and/or general testing monographs include Bolivia, Brazil, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, and Venezuela.

Miscellaneous Declarations

Some of the documents that are required in the initial registration dossiers in Latin America include various declarations that serve different purposes.

Batch numbering system declaration or memo: The batch numbering system declaration or memo is a document that describes how the drug product and sometimes the drug substance batches are numbered. This information should be produced by the manufacturing site and should describe how the lot numbers are issued and assigned. The batch numbering system declaration is required in Bolivia, Chile, Ecuador, Panama, Paraguay, and Peru.

Signature declarations or memos: Although the principles of ICH Q1A (R2) are widely accepted and recognized by most of Latin American health authorities, some markets still require a significant customization of the stability data, by means of stability declarations and other ancillary documents. The declarations/memos are required individually for the drug product and reconstituted drug on stability as applicable. The information required in these declarations include product information (name, strength, dosage form), manufacturer, packager and license

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holder, and drug product manufacturing site name and country. Most important, this documentation also includes stability batch information such as batch size, type, manufacturing and expiry dates, packaging configurations, start and end date of the stability studies, analysis dates, storage conditions, quantities of samples on stability, and conclusions with specific wording. Sometimes the stability chamber type and the material and the color of the container closure system are required. Signature memos are required in Peru, Ecuador, and Central American markets. Additional declarations to describe how the drug is described/referred to in the CTD components (generic molecule name/code) versus the proposed trade name or how a test result is reported on the COA versus how it is described in the specification (e.g., how the attribute "appearance" is described in the specification document specifically for pass/fail or complies type of reporting) all need to be explained. These declarations are needed in Central American markets.

Chromatograms: The chromatograms for testing methods performed by high performance liquid chromatography, gas chromatography, or infrared spectroscopy are required for drug substance (Chile, Mexico) and/or drug product (Ecuador, Mexico, and Uruguay). The chromatograms for the drug product stability testing from the initial analysis (time zero) and all subsequent time points—at least for the identification, assay, and dissolution tests— are required for all registration batches on stability tested under long-term (Ecuador, Mexico) and accelerated conditions (Mexico). The chromatograms must include the blanks and standards (Mexico) and must be clearly identified with the batch number, the time point, and storage conditions. The chromatograms must show date, time, volume of injection (Ecuador, Mexico), and the area under curve (Mexico). The same is required for the drug substance in Mexico. In Uruguay, the certificate of analysis of a recent manufactured lot of a drug product with its chromatograms or spectrums (sample, reference standard, and blank) should be provided.

Process validation: Brazil and Paraguay require the process validation report if section 3.2.P.3.5, Process Validation and/or Evaluation, does not provide the summary of the validation report, including acceptance criteria results and conclusions.

REQUIREMENTS BEYOND ICH

ICH's mission is to achieve greater harmonization worldwide to ensure safe, effective, and high-quality medicines are developed and registered. Harmonization is achieved through the development of ICH guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final guidelines [14].

As described previously, ANVISA in Brazil and COFEPRIS in Mexico (recent member) are the only ICH members in the region, thereby, the perception described next will focus on ANVISA's adherence to ICH requirements. Although ANVISA has been an ICH member since 2016, the implementation plan of ICH guidelines is still ongoing. It is expected that some local regulations beyond ICH will continue to exist. It is well-understood that the process of updating or creating regulations takes time and effort and that it must be done while juggling other priorities of reviewing and approving new drug applications and, more recently, fighting a serious health pandemic.

ANVISA's analytical method validation [15] and forced degradation [1] requirements are examples of those local regulations that bring additional technical requirements and make a Brazil dossier different from a US or EU dossier (both ICH member countries) and drive the divergence between harmonized global registration process.

In-Country Testing of Imported Medicines

The requirement for in-country testing for imported medicines has been in place in several Latin American markets for a while. Argentina, Brazil, Chile, Mexico, and Uruguay require in-country testing and perform the analytical method transfer or validation locally, which means that dossier submissions in these countries are sometime delayed due to logistics, something that was heavily experienced during the COVID-19 pandemic when there were extreme challenges to shipping samples, reference standards, and reagents to conduct transfer/validation exercises locally. In addition, a method transfer protocol and report also need to be generated and included in the dossier, as appropriate [16].

In Brazil, partial quality control tests are allowed when certain criteria are met including, but not limited to, the number of batches imported or the temperature and humidity monitoring and recording during transportation [17]. Companies often do not request the waiver of the quality control testing because it is difficult and more costly to execute these measures.

In Chile, it is required to include specific tests in the local drug product specification, depending on the dosage form [18]. The local specification must be followed for the testing and release process in the Chilean market. Among the additional tests required are

in-process control tests and primary packaging type and material. Although there is no technical basis to perform in-process control tests in the finished drug product, the Chile regulatory agency, ISP, has not been accepting the scientific justifications to waive those additional tests required by the local regulation.

In general, in-country testing of imported medicines causes delays for the batch release, reduces the remaining shelf life on the product, and delays patient access to medicine while increasing the risks for potential drug shortages. It is a misuse of resources that also negatively impacts the environment [19].

Considering that drug manufacturers have appropriate controls throughout the production process and supply chain to ensure product quality in line with recognized good manufacturing and distribution practices, the regulatory agencies should consider waiving the import testing requirement and focus on establishing risk-based approaches that are commensurate with the level of risks in accordance with ICH Q9 Quality Risk Management [20].

REGULATORY FLEXIBILITIES DURING THE COVID-19 PANDEMIC

Like many regulatory agencies around the world, the Latin American health authorities implemented several regulatory flexibilities during the COVID-19 pandemic to (a) increase manufacturing capacity for COVID-19-related medicines, (b) accept globally generated documents in lieu of local requirements, and (c) rely on (full or partial) assessment reports from other regulatory agencies, with the aim of enabling more efficiency and agility in the approval/authorization of medicines and without compromising regulatory standards, patient safety, and product quality.

Another valuable trend that emerged from the COVID-19 pandemic was the acceptance of electronically generated regulatory documents, including CPPs. At the break of the COVID-19 pandemic, a backlog of issuing CPPs was observed. The European Medicines Agency (EMA) responded to this backlog by implementing a new system to issue electronic certificates of medicinal products. As of 30 March 2020, EMA no longer provides printed certificates: only electronically signed and authenticated certificates will be issued. The WHO endorsed the EMA's decision and encouraged the various boards of health to accept this approach [21]. Similarly, the FDA Center for Drug Evaluation and Research (CDER) began issuing electronic CPPs (eCPP) starting December 2021 [22].

This was positively received by all countries in Latin America and expanded to other types of documents where an expected "original" document or a document with wet signature would be required.

On a positive note, there are ongoing discussions at the WHO on the revision of its scheme and the value of the CPP in national regulatory authorities, with the aim of adopting more unified and efficient regulatory approaches/processes. A series of modifications have occurred to respond to the changing regulatory environment where the recommendation is that the CPPs should not be requested in countries that have the capability to conduct full quality, safety, and efficacy reviews unless they have a rationale to request one [9].

The authors' opinions are that some of the flexibilities allowed by the Latin American regulators should continue when the impact of the pandemic decreases, such as acceptance of electronically signed documents, flexibility on importing testing, either allowing for late submissions of the local analytical validation data or waiving the requirement, acceptance of risk-based approaches to streamline CMC packages and/or to justify the absence of local requirements, and ultimately the national regulatory authorities following ICH guidelines.

The key message spread during the pandemic is that the industries and regulators should apply the learnings from this unprecedented global experience to streamline their current processes and seek opportunities for greater international collaboration, either through reliance procedures and/or collaborative review initiatives such as the International Coalition of Medicines Regulatory Authorities (ICMRA) [23].

CONCLUSION

The global pandemic has demonstrated that applying regional solutions is inadequate and inefficient. More than ever, we need to work toward a global solution, prioritize the harmonization of technical requirements, and eliminate the ones that do not add value to product quality or safety but instead delay product availability in the region. Such a harmonized approach via the adoption of ICH should be considered as a foundation for a global process.

The positive learnings from the transforming experience of COVID-19 pandemic should be applied to the regulatory processes in the Latin American region moving forward. Risk-based approaches to CMC data and to local specific requirements, with patient-centric focus should be permitted, to ensure the timely supply of life-saving medicine to the patients in the region.

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A PROPOSAL FOR a Comprehensive Quality Overall Summary

By Roger Nosal, Connie Langer, Beth Kendsersky, Jennifer L. Brown, Megan McMahon, and Timothy J.N. Watson

When working with the common technical dossier (CTD), the structure of Module 2 "follows the scope and outline of the Body of Data in Module 3" [1], which can reduce review efficiency. This structure does not allow explanation of justification for the control strategy [2], particularly when a quality by design (QbD) approach is employed. The authors propose using Module 2.3 to effectively convey the control strategy and clearly identify the established conditions (ECs) or regulatory binding elements that "are considered necessary to assure product quality and therefore would require a regulatory submission if changed post approval" [3].

This novel approach to Module 2 uses a structure that shows how enhanced process knowledge, product understanding, and risk assessments are linked to the control strategy. Application of this innovative approach will quickly orient regulators to the content of Module 3, "present product quality benefit-risk considerations, summarize the pharmaceutical development, present an overall understanding of the product quality," [1] and facilitate continuous improvement.

As part of the US Food and Drug Administration (FDA) QbD pilot [4] in 2005–2006, the need to convey how the control strategy is linked to the target product profile (TPP) and quality target product profile (QTPP) was discussed. One possible solution raised was a Module 2 that integrates the product development story, links the product attributes to the drug product (DP) and drug substance (DS) manufacturing processes to demonstrate a holistic drug product control strategy, and demonstrates how the control strategy supports the TPP.

Ultimately, the summary was not adopted during the QbD pilot, but was reintroduced in 2014 when a Pharmaceutical Research and Manufacturers of America (PhRMA) team prepared a white paper describing the content and format of an improved Module 2. A draft of the paper was shared with several regulators, and it was agreed that there would be value in an overview of the product to familiarize reviewers with the comprehensive development story and control strategy prior to examining a particular element of the CTD. The proposal for the Quality Overall Summary (QOS) resembled what constituted the Expert Report [5] in Europe prior to the adoption of the CTD.

This proposal is also somewhat aligned with the concise, logical framework of the Japanese Gaiyo, but is further intended to provide assessors with a well-articulated introduction to key aspects of the overall control strategy and narrative of how the data contained in Module 3 and associated risk management justifications are reflected in the regulatory binding elements described in the Japanese Application Form [6].

Based on the framework that was developed by the PhRMA team, Pfizer piloted an approach to Module 2 that was referred to as the "comprehensive Quality Overall Summary (QOS)." While a comprehensive QOS is not currently defined by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), it is a Module 2 summary document that contains a QTPP, a TPP, a development narrative and resulting control strategy, and a listing of regulatory commitments/ECs.

The objectives of the comprehensive QOS format are to describe the product development process in the context of assuring quality and mitigating risk to the patient, to provide a clear summary of the control strategy, and to guide the reviewer through the content of Module 3. The comprehensive QOS was successfully submitted to all global markets with the exception of Japan, where the Module 2 format is very specific. Direct feedback from the US FDA on this pilot is shared in the discussion.

This article summarizes an alternate and more functional way to format the QOS presented in Module 2.3. In addition, the ISPE

Regulatory Quality Harmonization Committee (RQHC) regional focus group is developing proposals on the content and structure of a risk-based Module 2 that could ultimately support standardization of chemistry, manufacturing, and controls (CMC) terminologies and submission standards for control strategy harmonization and cloud assessment [7, 8]. Both of these efforts could serve to provide options to the Expert Working Group (EWG) that is currently developing strategies for the revision of The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality–M4Q(R1), Quality Overall Summary of Module 2, Module 3: Quality [9].

Among other things, the M4Q(R2) EWG is working toward "organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management" [1]. The ICH M4Q(R2) concept paper sets goals for "better capturing the pharmaceutical development and the proposed control strategy, which should be the backbone of the revised M4Q structure. This should address key elements of the proposed pharmaceutical product, including the QTPP, manufacturing process, and control strategy" [1].

Considering the ongoing work within ICH to revise the quality section of Module 2.3 and the implementation of ICH Harmonised Tripartite Guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, which brings focus on the control strategy when reviewing postapproval changes, now is a good time to discuss the format of Module 2. A comprehensive QOS that clearly articulates the product link to the patient and that presents and justifies the product control strategy from beginning to end would be valuable.

CHALLENGES WITH THE CURRENT MODULE 2 STRUCTURE

The US FDA published a white paper in 2018 calling for a revision to Module 2 because, "there can be a disconnect between applicants and regulators regarding the communication of quality data and its impact on the assessment. Currently, it takes time and/or communications (e.g., information requests) to fully understand the quality data and its significance in an application" [10].

The FDA suggested that it would be valuable to connect the summary to the patient, describe the control strategy, and guide the regulator through the submission. Further, they indicated that there is an opportunity to present and discuss life cycle management plans for the product. Addressing these points would allow the regulator to "be prepared to best assess the applicant's own conclusions about potential risk to the patient, and the control of such, in the commercially manufactured product" [10].

The current use of Module 2 to summarize Module 3 creates challenges for both regulators and industry. The regulators are not provided with a coherent and complete description of a product control strategy or overview of the life cycle change management. Companies that are market authorization holders (MAHs) must manage inconsistency in regulatory assessments among global regulators [11], must provide additional information due to the lack of integration between inspections and assessments, and have no incentive to use enhanced development approaches for postapproval changes. Module 2 could serve as a location in the CTD structure to effectively describe the control strategy, which could lessen significantly the effort required to understand how the control strategy fits together and lay the foundation for MAHs to seek flexible regulatory approaches that support an efficient life cycle management plan [10].

Module 2 for a new drug registration application typically consists of individual summaries presented in the same order as those in the corresponding Module 3 section [8]. Because the story that underwrites the control strategy is not presented until the second major subsection of Module 3 (i.e., Section 3.2.S.2.6 or 3.2.P.2 for DS or DP, respectively), reading the dossier and/or summary in the sequential order of the CTD can reduce review efficiency, particularly when a QbD approach is employed. Furthermore, elements of the control strategy are spread across several sections of the CTD and are not easily linked to the development narrative and comprehensive risk assessments. This current Module 2 may not provide a holistic summary nor an insightful view into the control strategy or product development.

At present, there is a concerning trend away from global harmonization of Module 2. National regulatory agencies are requesting bespoke summary documents, such as the Canadian Certified Product Information Document, the Japanese Application Form, the Korean CMC Summary Document, and the South African Summary of Critical Regulatory Elements, as discussed in the article by Kendsersky and colleagues [8].

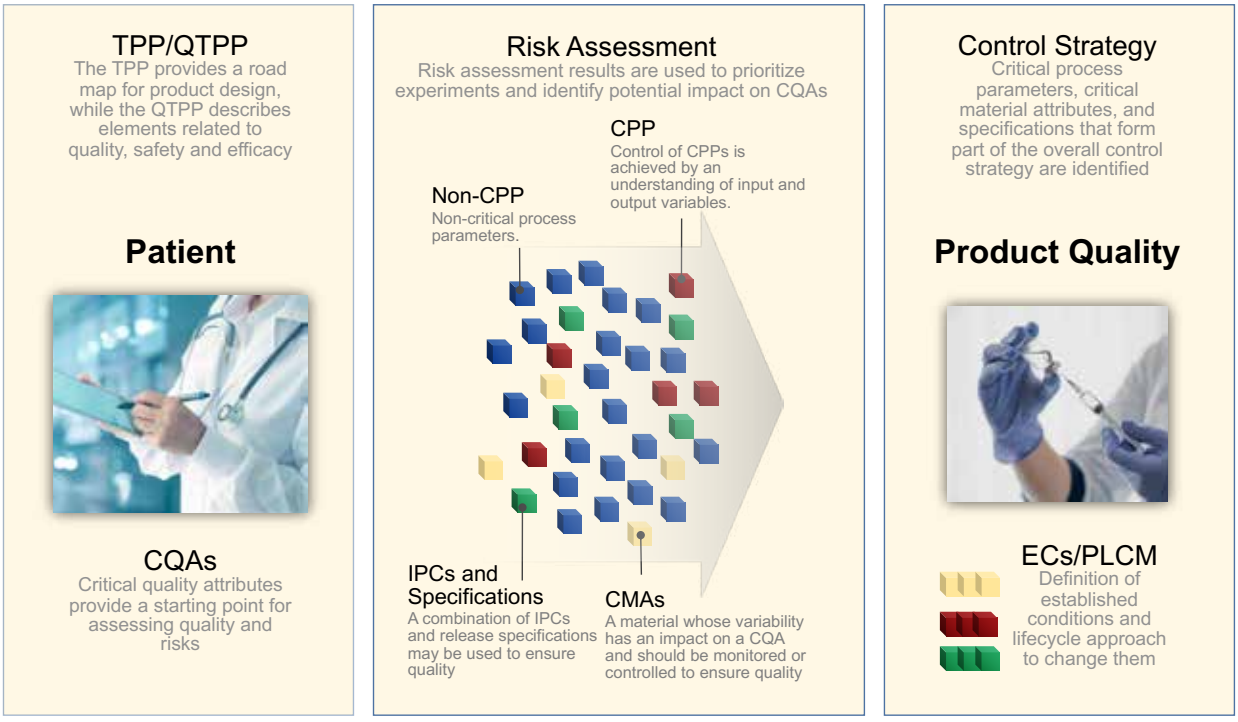
In that article, the authors outlined an opportunity to propose a summary document that "frames the drug development story by effectively conveying how enhanced process understanding, product knowledge, and risk assessments are linked to a comprehensive control strategy; links the drug substance and drug product critical quality attributes (CQAs) to target product profile (TPP) and quality target product profile (QTPP); summarizes the holistic control strategy, including links to more detail in Module 3, demonstrating how the proposed manufacturing process and controls (namely, critical process parameters, critical material attributes, and ECs) will provide assurance a drug substance and drug product will meet their respective CQAs; and declares and documents a summary of the ECs, and a proposed Product Lifecycle Management (PLCM) document [3], if applicable can also be leveraged" [8].

The proposed comprehensive QOS fulfills these conditions. If elements such as these are adopted during the revision of ICH M4Q, this could influence global regulatory agencies to eliminate the requirement for custom Module 2 commitment documents.

PROPOSED SOLUTION

The control strategy for each individual product will be unique, as it is based on the properties of the individual DS, formulation, and manufacturing processes and, if applicable, devices. The comprehensive QOS provides a single location to bring together the development

Figure 1: The QOS narrative is strategically organized based on the development data used to justify the control strategy and to illustrate the linkage between the patient and product quality.



narrative, the control strategy, the ECs, and a suggested life cycle approach to change them. The recommendations outlined within reflect the successful elements of the 2018 comprehensive QOS pilot strategy with the added objective of further streamlining the summary into a more concise and ordered format.

Figure 1 illustrates the interconnectivity of how the product is designed and quality is controlled to deliver the needs of the patient. A well-written, globally harmonized comprehensive QOS that includes a development narrative would provide regulators with a concise, science- and risk-based development story that highlights a product's control and life cycle strategies, thereby potentially decreasing review and approval timelines and enabling faster availability and sustained supply of critical medicines to patients worldwide.

TPP/QTPP AND DEFINITION OF CQAs

As illustrated previously, a development narrative briefly summarizes the quality elements of the product that are designed to meet patient needs (TPP and QTPP) and is organized based on the product understanding, risk assessments, and development data used to justify the control strategy. The information contained in the narrative will provide an integrated summary that shows how and why important aspects of the control strategy that are detailed in the ECs were selected.

Starting with an understanding of the needs of the patient and the TPP provides the reviewer a roadmap of the product design and development, while providing a clear linkage to the patient. The TPP defines the indication and patient population, describes usage of the product, provides dosage and administration details, explains dosage form and strengths, and lists packaging and storage requirements.

A preliminary list of the CQAs derived from the TPP provides a starting point for assessing the risks associated with product quality. The purpose of the QTPP is to link the attributes of the DP back through the TPP to the needs of the intended patient population. The QTPP describes elements of the product related to quality, safety, and efficacy, as shown in Table 1.

The patient considerations drive the product design considerations and target attributes. From there, a preliminary list of CQAs is identified. For purpose of illustration used throughout this article, labels have been assigned to each CQA. This list of CQAs provides a starting point for assessing the risks associated with product quality.

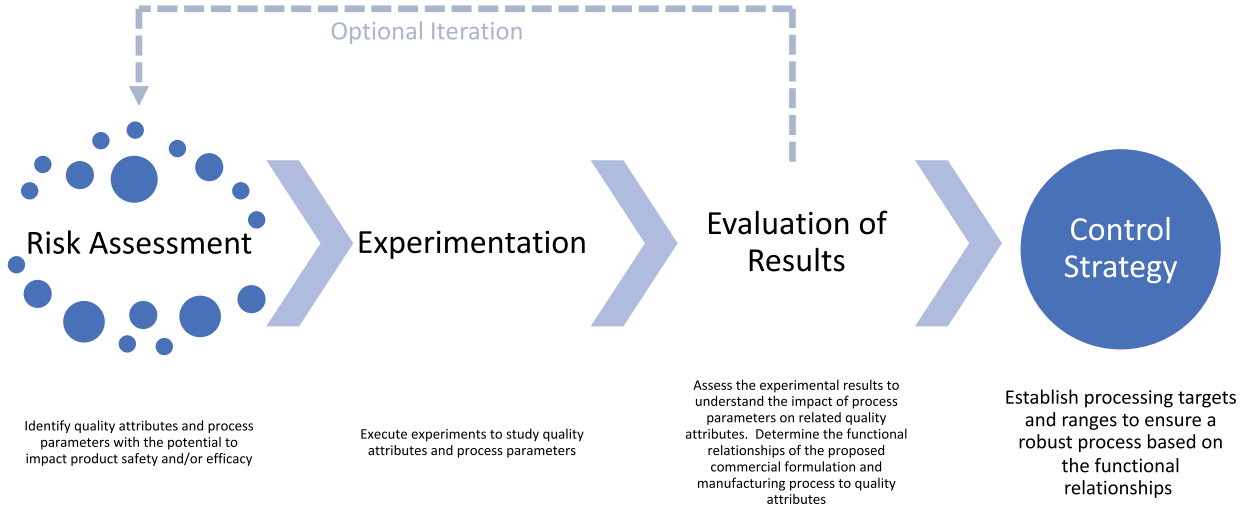
PHARMACEUTICAL DEVELOPMENT

The important aspects of the pharmaceutical development illustrated in Figure 2 will be summarized in the narrative of the comprehensive QOS. According to ICH Harmonised Tripartite

Table 1: Linkage among patient consideration, product design, target attributes, and CQAs.

Patient Considerations	Product Design Considerations	Target Attribute	CQA	Label
Treatment of patients with breast cancer with ability to titrate dose	Three strengths of tablets differentiated by size and debossing	5, 10, and 15 mg film-coated tablets	Appearance	CQA_1
			Identity	CQA_2
Confidence in quality of medicine	Consistent quality with each dose	Meet pharmacopoeia requirements for potency and content uniformity	Assay	CQA_3
			Content Uniformity	CQA_4
Oral once per day dosing	Immediate release oral dosage form	Rapid in-vitro drug release	Dissolution Rate	CQA_5
Easy to open and adequate shelf life	Easy to open with minimum 36 months at 30°C/75%RH	Packaging that protects product over intended shelf life, including HDPE bottle with desiccant	Degradation Products	CQA_6
			Water Content	CQA_7

Figure 2: Development process flow diagram.



Guideline Q8 (R2): Pharmaceutical Development, "Potential drug product critical CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase" [12].

The CQAs are used as a basis for an initial risk assessment to determine areas that may warrant investigation through an experimental plan to determine safety and efficacy risks to

Table 2: Example of a final risk assessment summary table.

Step	Blend							Lubrication			Compression				Film Coat	Pack
DP Attributes	API	Excipient	Pre-blend	Blend screen	Blend revs	Blend time	Blend rpm	Lube revs	Blend time	Blend rpm	Press speed	Tablet hardness	Tablet weight	Pre-compression force	Weight gain	Packaging
Appearance	Y	G	G	G	G	G	G	G	G	G	G	Y	G	G	Y	G
Identity	Y	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G
Assay	Y	G	G	G	G	G	G	G	G	G	G	G	Y	G	G	G
Uniformity of Dose	Y	Y	G	Y	Y	G	G	Y	G	G	G	G	G	G	G	G
Dissolution	Y	G	G	G	G	G	G	Y	G	G	G	G	G	G	G	G
Degradation Products	Y	G	G	G	G	G	G	G	G	G	G	G	G	G	G	R
Water Content	Y	Y	G	G	G	G	G	G	G	G	G	G	G	G	G	R

Key:

- Green: Parameters or material attributes have no relationship to a CQA. Non-critical controls are in place.
- Yellow: Parameters or material attributes have a relationship to a CQA. Critical controls (ECs) are in place.
- Red: Parameters or material attributes have a relationship to a CQA and an edge of failure has been identified. Critical controls (ECs) are in place.

patients. The initial risk assessment is based on information on the target compound as well as prior knowledge and experience from other products with similar characteristics. The results of the risk assessment are used to define experiments.

This assessment is performed for each CQA in turn, identifying parameters or variables that have the potential to affect those attributes. The results of the risk assessment are used to define and prioritize experiments. Results from experiments may confirm or modify preliminary risk assessments. Table 2 shows an example of a finalized risk assessment after experimentation, where items highlighted in yellow and red are described in the regulatory binding elements of the control strategy. Standardizing risk assessment summaries reported in applications will increase transparency and facilitate agreement between global regulatory authorities and industry on appropriate and acceptable control strategies.

The iterative cycle of risk assessment and experimentation can be considered complete when the relationships between parameters and CQAs are understood and take into consideration the broader context of the clinical significance of CQAs and the ability to control them during processing [13]. Transparent communication of the relationship between CQAs, risks, and mitigation strategies will benefit the regulator assessing the application as well as the MAH assessing potential postapproval changes.

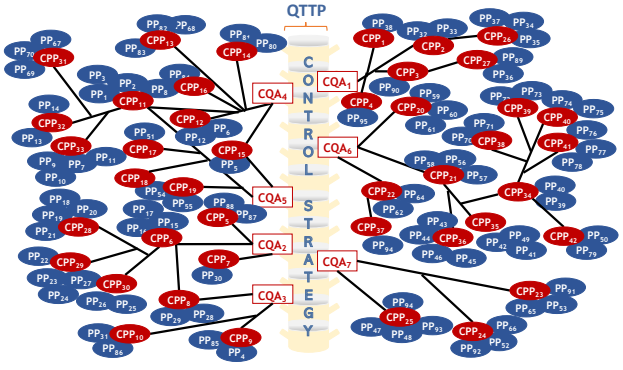
A summary of pharmaceutical development that presents the knowledge gained through the application of scientific approaches and quality risk management during the development of a product and its manufacturing process [12] provides substantiation for the regulatory binding information that define a product control strategy. Provisions for additional detail may be established by hyperlinks to Module 3 within the CTD.

Presenting the Control Strategy

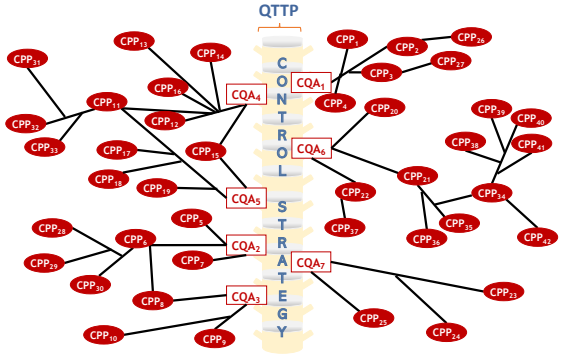
A control strategy consists of "a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control" [12]. Elements of a control strategy may be parametrically based or may be primarily focused on control of process outputs (e.g., attributes, measurements, and responses) [3]. Control of a CPP and/or CMA is achieved by understanding the relationship between input and output variables in a manufacturing process, including material attributes, in-process controls and process conditions, and

Figure 3: The overall control strategy is the "backbone" of a robust product.

Panel A: Functional relationships among CQAs and various process parameters, material attributes, IPCs, tests, and GMP Controls. The details underpinning this would be described in Module 3.



Panel B: Functional relationships among critical elements of the control strategy. The elements of the overall control strategy shown below would be described in Module 2.



operating parameters. Every CPP (CMA and CQA) represents regulatory binding information.

While CMA has not been endorsed as an ICH term, it is being widely used to distinguish the variability associated with conditions in a process, known as process parameters vs. variability inherent in materials used in the process, known as material attributes. Regulatory binding information may also include non-CPPs and non-CMAs in addition to CQAs and CPPs. The distinction between critical and non-critical attributes and parameters will be necessary to ensure regulatory oversight of postapproval management is appropriately differentiated.

Specific controls can be established within the manufacturing process where the boundaries are defined by the inter-relationship between process parameters. Specification criteria are often established to control CMAs. Analytical methods are developed and adopted to evaluate specific materials—i.e., raw materials, intermediates, DS, formulation, and packaging components, DP—against predefined specification criteria to confirm control. While all controls are intended to assure quality product, finished product testing, by itself, does not constitute a control strategy.

The comprehensive control strategy can be visualized in the pictorial diagram shown in Figure 3. The backbone of the control strategy is made up of the CQAs shown as red boxes. Process parameters, material attributes, in-process tests, release tests, and GMP controls, which are critical, are represented by red ovals, whereas those that are non-critical are represented by blue ovals. The diagram shows that some elements of the control strategy have primary functional relationship to the CQAs, whereas others

Table 3: Tabulated critical elements of the comprehensive control strategy summarized in the comprehensive QOS.

Product Attribute	CQA	Functional Relationship	Controls		
Route of Administration/ Dosage Form	Appearance CQA_1	$CQA_1 = f(CPP_1, CPP_2, CPP_3, CPP_4)$ $CPP_2 = f(CPP_{26})$ $CPP_3 = f(CPP_{27})$	CPP_1	CMA	DS appearance (S.4.1)
			CPP_{26}	GMP	Compression tooling (PQS)
			CPP_2	IPC	Tablet hardness (P.3.4)
			CPP_3	IPC	Film coat weight gain (P.3.4)
			CPP_{27}	GMP	Film coat dispensing (PQS)
			CPP_4	Test	Appearance (P.5.1)
Potency	Identity CQA_2	$CQA_2 = f(CPP_5, CPP_6, CPP_7)$ $CPP_6 = f(CPP_{28}, CPP_{29}, CPP_{30})$	CPP_{28}	CMA	DS starting material identity (S.2.3)
			CPP_{29}	CMA	DS reagent identity (S.2.3)
			CPP_{30}	CPP	DS synthetic route (S.2.2)
			CPP_5	Test	DS identity (S.4.1)
			CPP_6	GMP	GMP dispensing (PQS)
			CPP_7	Test	DP identity (P.5.1)
	Assay CQA_3	$CQA_3 = f(CPP_8, CPP_9, CPP_{10})$ $CPP_8 = f(CPP_6, CPP_{28}, CPP_{29}, CPP_{30})$	CPP_{28}	CMA	DS starting material identity (S.2.3)
			CPP_{29}	CMA	DS reagent identity (S.2.3)
			CPP_{30}	CPP	DS synthetic route (S.2.2)
			CPP_6	GMP	GMP dispensing (PQS)
			CPP_8	Test	DS assay criteria (S.4.1)
			CPP_9	IPC	Tablet weight (P.3.4)
			CPP_{10}	Test	DP assay criteria (P.5.1)
Uniformity of Dose	Content Uniformity CQA_4	$CQA_4 = f(CPP_{11}, CPP_{12}, CPP_{13}, CPP_{14}, CPP_{15}, CPP_{16})$ $CPP_{11} = f(CPP_{31}, CPP_{32}, CPP_{33})$	CPP_{31}	CPP	DS milling operation (S.2.2)
			CPP_{32}	IPC	DS end of milling particle size (S.2.4)
			CPP_{33}	CPP	DS step 3R drying temperature (S.2.2)
			CPP_{11}	Test	DS particle size criteria (S.4.1)
			CPP_{12}	CMA	Excipient grade (P.1)
			CPP_{13}	CPP	Screen aperture (P.3.3)
			CPP_{14}	CPP	Blend revolutions (P.3.4)
			CPP_{15}	CPP	Lubrication number of rotations (P.3.4)
			CPP_{16}	Test	Content uniformity criteria (P.5.1)
In vitro Drug Release	Dissolution CQA_5	$CQA_5 = f(CPP_{11}, CPP_{15}, CPP_{17}, CPP_{18}, CPP_{19})$ $CPP_{11} = f(CPP_{31}, CPP_{32}, CPP_{33})$	CPP_{31}	CPP	DS milling operation (S.2.2)
			CPP_{32}	IPC	DS end of milling particle size (S.2.4)
			CPP_{33}	CPP	DS step 3R drying temperature (S.2.2)
			CPP_{11}	Test	DS particle size criteria (S.4.1)
			CPP_{17}	CPP	DP formulation (P.1)
			CPP_{18}	GMP	Dispensing (PQS)
			CPP_{15}	CPP	Lubrication – number of rotations (P.3.4)
			CPP_{19}	Test	Dissolution criteria (P.5.1)
Degradants and Impurities/ Shelf Life	Degradation Products CQA_6	$CQA_6 = f(CPP_{20}, CPP_{21}, CPP_{22})$ $CPP_{21} = f(CPP_{34}, CPP_{35}, CPP_{36})$ $CPP_{34} = f(CPP_{38}, CPP_{39}, CPP_{40}, CPP_{41}, CPP_{42})$ $CPP_{22} = f(CPP_{37})$	CPP_{34}	IPC	Intermediate IPC (S.2.4)
			CPP_{37}	CMA	DS reagent, solvent, and material specifications (S.2.3)
			CPP_{38}	CMA	DS starting material identity and specification (S.2.3)
			CPP_{39}	CPP	DS step 1 reaction completion IPC (S.2.4)
			CPP_{40}	CPP	DS step 2 Stoichiometry (S.2.2)
			CPP_{41}	CPP	DS step 2 reaction temperature (S.2.2)
			CPP_{42}	IPC	DS step 2 reaction completion IPC (S.2.4)
			CPP_{35}	CPP	DS step 3 reaction temperature (S.2.2)
			CPP_{36}	CPP	DS step 3 isolation temperature (S.2.2)
			CPP_{20}	Test	DS impurity limits (S.4.1)
			CPP_{21}	Test	DS residual solvents limit (S.4.1)
			CPP_{22}	Test	DP degradation limits (P.5.1)
	Water Content CQA_7	$CQA_7 = f(CPP_{23}, CPP_{24}, CPP_{25})$	CPP_{23}	Test	DS water content limit (S.4.1)
			CPP_{24}	CMA	Excipient grade (P.1)
			CPP_{25}	Test	DP water content limit (P.5.1)

may have secondary, tertiary, or beyond. Further, it is shown that some CPPs may impact more than one CQA. For example, CPP_{15}, which is the number of rotations used during lubrication blending, impacts CQA_4 (content uniformity) and CQA_5 (dissolution). Other such examples are apparent in the diagram. It is envisioned that critical elements of the overall control strategy mapped in Panel B would be described in Module 2.

This control strategy diagram illustrated in Figure 3 can be translated into a tabular summary of the product control strategy showing the functional relationship between DP CQAs and CPPs (Table 3).

By clearly defining the product control strategy, the MAH demonstrates assurance of manufacturing process control and product quality and substantiates how a science- and risk-based approach delivers appropriate product quality. When the MAH combines this with a robust PQS, they (a) can guarantee "delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities and other internal and external customers, (b) develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes and (c) identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently" [2].

Regulatory Binding Elements/ECs

In the proposed comprehensive QOS, a summary of pharmaceutical development information, along with a table that conveys the control strategy, is provided. This provides substantiation for the regulatory binding elements such as process descriptions, specifications, and test methods for the DP, DS, raw materials, excipients, packaging materials, and components.

If the MAH chooses to use the tools in ICH Q12, then the regulatory binding information will include both ECs and their associated proposed reporting categories. All parameters that have been identified as having a functional relationship with a CQA are categorized as ECs. Process parameters that have been identified as having no functional relationship with a CQA are assigned as non-critical and categorized as supporting information. ECs describe how a company intends to manufacture and control product quality. Risk-based reporting categories for

Table 4: Proposed content of the comprehensive QOS.

Section within CTD Module 2	Purpose	Suggested CTD Sections to Summarize	
		DS	DP
Target Product Profile (TPP)	Defines the nature of the product, indications (and contraindications) and usage, dosage and administration, dosage form and strengths, targeted patient population, and packaging and storage requirements.	N/A	P.2
Quality Target Product Profile (QTPP)	Describes the elements of the intended DP related to quality, safety, and efficacy and links the CQAs of the DP back through the TPP to the needs of the intended patient population.	S.1	P.2
Pharmaceutical Development: Risk Assessment and Development of Control Strategy	Identifies quality attributes and process parameters with the potential to impact CQAs and presents resulting risk assessment verified by experiments conducted.	S.2.5, S.2.6, S.3, S.4.3, S.4.4, S.4.5, S.7.1, S.7.3	P.1, P.2, P.3.5, P.4.3, P.4.4, P.4.5, P.4.6, P.5.3, P.5.4, P.5.5, P.5.6, P.8.1, P.8.2, P.8.3, A.1, A.3
Summary of Comprehensive Control Strategy	Provides proposed controls to ensure the acceptance criteria for each DS and DP CQA are met.	S.2.1, S.2.2, S.2.3, S.2.4, S.4.1, S.4.2, S.5, S.6, S.7.2	P.3.1, P.3.2, P.3.3, P.3.4, P.4.1, P.4.2, P.5.1, P.5.2, P.6, P.7, P.8.1, P.8.2, A.2
Summary of Regulatory Commitments / ECs and the PLCM (if applicable) Also include any PACMPs (if applicable)	The ECs delineate "which elements in the application are considered necessary to assure product quality and therefore would require a regulatory submission if changed post-approval." [3] The corresponding PLCM document serves as a central repository for ECs and the associated reporting categories (based on potential risk to quality, i.e., prior approval, notification, not reported) for changes made to ECs. Post Approval Change Management Plan(s) (PACMPs) [3], if relevant, provides the requirements and studies needed to implement a future change.	S.1, S.2.1, S.2.2, S.2.3, S.2.4, S.4.1, S.4.2, S.5, S.6, S.7.1, S.7.2	P.1, P.3.1, P.3.2, P.3.3, P.3.4, P.3.5, P.4.1, P.4.2, P.5.1, P.5.2, P.6, P.7, P.8.1, P.8.2, A.2

changes may be proposed considering the control strategy. A PLCM [3] document provides a listing of ECs and reporting categories as well as other commitments such as stability, change management, and postapproval change management protocols.

DISCUSSION

Pfizer submitted a comprehensive QOS along with an original new drug application (NDA) to the US FDA in early 2018. The summary included the concepts outlined in this article and aimed to clearly convey the product control strategy. Following approval of the NDA, a postapproval feedback meeting was held with the FDA to solicit feedback and discuss the comprehensive QOS as a viable and useful review aid for the assessment the NDA.

The reviewers affirmed that the single summary document was easy to use and provided an overall picture of the product. While the document was quite lengthy, and hyperlinking to the data in Module 3 would have been more efficient than repeating tables of information, the comprehensive QOS was beneficial, especially for communication among the multiple regulatory disciplines that contribute to review of CMC content. During the NDA review, relatively few queries for CMC information were received and the reduction was likely (at least partially) because reviewers from other disciplines were able to quickly look at the comprehensive QOS for broader context without issuing an information request.

Based on learnings from this pilot, an optimized proposal for the content of the comprehensive QOS would include key information with linkage to, rather than repeating information contained within, Module 3. Table 4 shows a proposed outline of the information that should be included in the comprehensive QOS.

By summarizing the ECs in the comprehensive QOS, the MAH establishes a clear standard for subsequent postapproval change management.

CONCLUSION

The comprehensive QOS intends to provide a consistent format that could facilitate a better and faster product understanding for both internal and external stakeholders (e.g., inspectors and other multidisciplinary regulatory and industry stakeholders). By clearly integrating and explaining the content of Module 3, the effectiveness of regulatory submissions and reviews (i.e., reduced assessment time and/or queries) could be improved. The comprehensive QOS provides a direct link between the patient and the quality attributes of the product with the safety and efficacy for the patient. It introduces an appropriate science- and risk-based

framework to demonstrate how enhanced process knowledge and product understanding effectively manage risks to product quality by establishing a robust control strategy that is maintained through the life cycle of the product.

The ICH M4Q EWG is currently considering options for the structure and format of the Module 2 that provide easy access to data, analysis, and knowledge management. By structuring Module 2 with a format as described in Table 8, the need for customized summary documents could be addressed and the customized documents eliminated. Furthermore, the comprehensive QOS could serve as the starting point for the CMC assessment. This should foster alignment between inspections and assessments by providing the inspector with a clear concise overview of the product, increase consistency in regulatory reviews among different regions globally, and enable mutual reliance and recognition, particularly for unmet medical needs, to expedite patient access of innovative medicines.

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SPuMoNI: Enhancing Pharma Data Quality Through Smart Technologies

By Mariola Mier, David Cerrai, Juan Miguel García-Gómez, Adriana E. Chis, and Horacio González-Vélez

Funded by the European Commission from 2019, the Smart Pharmaceutical Manufacturing Project (SPuMoNI) [1] harnesses the potential of state-of-the-art technologies for the pharmaceutical industry. This article discusses the main SPuMoNI accomplishments.

The Falsified Medicines Directive "introduces harmonised European measures to fight medicine falsifications and ensure that medicines are safe and that the trade in medicines is rigorously controlled" [2]. Such obligatory safety features, legal framework, and record-keeping requirements have arguably imposed stricter controls for manufacturing of medicaments.

Although the pharmaceutical industry has consistently improved manufacturing processes [3] in compliance with good manufacturing practices [4], there are documented deviations from good practices [5] including the continued falsification of medicines [6]. (Note: The terms "pharmaceutical" and "pharma" interchangeably employ throughout this article.) Disclosure risk assessment techniques in pharma manufacturing typically depend on background knowledge, the behavior of intruders, and the specific value of the data. Often, only heuristic arguments are used, without numerical assessment [7].

The SPuMoNI consortium comprises two pharma industrial partners—PQE Group and FAREVA's Instituto De Angeli—and three academic institutions: the Universitat Politècnica de València (Spain), the University of Thessaly (Greece), and the National College of Ireland (Ireland). SPuMoNI utilizes state-of-the-art technologies to support a smarter industry. These technologies include blockchain for end-to-end verification of manufacturing data, quality assurance methods for data integrity compliance, and modern artificial intelligence (AI) and data analytics to smartly extract, transform, and control heterogeneous data sources within the manufacturing processes to better improve big-data quality and process modeling for a smarter industry [8].

SPuMoNI leverages blockchain technologies to better ascribe and ensure the manufacturing traceability of medicaments. SPuMoNI is particularly timely because blockchain has been proposed to become "a new digital service infrastructure" for Europe [9]. Although blockchain is well-established in the cryptocurrency domain, the systematic application of smart contracts in the pharma industry remains an open problem [10, 11]. Moreover, traceability in manufacturing [12] has traditionally been studied in the food industry, but rarely in pharmaceutical manufacturing, consequently attracting some industry attention [13].

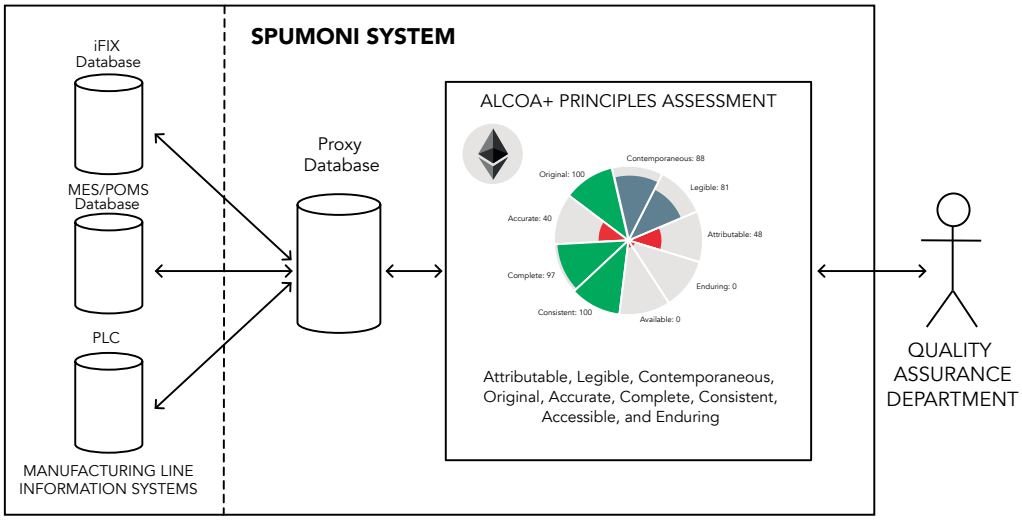
In this respect, ensuring data integrity in compliance with the current Good Manufacturing Practice (CGMP) regulations by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) means ensuring quality assessment of batch reports, audit trails, and system registries in terms of the ALCOA+ principles: attributable, legible, contemporaneous, original, accurate, complete, consistent, accessible, and enduring.

SPuMoNI has produced an innovative scientific approach to systematically establish and ensure constant proof of the authenticity of pharmaceutical manufacturing data and to develop a user-friendly software tool for pharmaceutical officers, following the ISPE GAMP© validation standards, during both the IT development and the use of a qualified IT infrastructure.

End-to-End Verification

Blockchains and smart contracts implement peer-to-peer networks formed by "blocks," creating a distributed ledger where data from one block can only be altered by modifying all subsequent blocks. In the SPuMoNI system, data are stored within a blockchain as tamper-proof data transactions, ensuring that SPuMoNI datasets remain unaltered with a measurable quality of service [8]. Following General Data Protection Regulation (GDPR) and pharmaceutical industry regulations, SPuMoNI uses its own

Figure 1: SPuMoNI system overview.



private Ethereum blockchain network, hosted at National College of Ireland's OpenStack private cloud, to store data descriptors that should remain confidential with a guaranteed data integrity.

Data Quality Assurance

Data quality assurance targets ALCOA+ compliance, including single- and multiple-batch evaluation analysis by data quality metrics. The single-batch evaluation checks each ALCOA+ principle of the corresponding batch, and the multiple-batch evaluation includes a temporal and multisource variability characterization of both the ALCOA+ principles and specific variables of manufacturing sensors.

SPuMoNI TODAY

Currently running in its latest stages and with a proof of concept already available upon request for demonstration, the SPuMoNI system delivers an ALCOA+ assessment to ensure continuous data integrity of pharma manufacturing reports (see Figure 1) [14].

Furthermore, SPuMoNI has achieved the following significant results in the past three years:

- Collected anonymized datasets with discrete and specific attributes related to environmental conditions of different pharma systems, which are useful for the development of software that already structures data in this fashion
- Issued data integrity guidelines to set the rules on how AI should process data and identify patterns that may lead to compliance issues
- Developed the base AI architecture and further developed additional AI applications for other manufacturing processes related to the pharmaceutical industry to assess data integrity compliance before validation/deployment
- Enhanced multi-node private blockchain networks to ensure data provenance and compliance in a tamper-proof manner
- Released SPuMoNI guidelines as a template of integrated software/network infrastructure for pharma manufacturing
- Deployed a prototype in an industrially relevant environment

As stated, SPuMoNI has produced an innovative scientific approach to systematically establish and ensure constant proof of the authenticity of pharmaceutical manufacturing data. Supported by an ALCOA+ assessment, the SPuMoNI system helps deliver enhanced data quality for the pharma industry.

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David Cerrai, PhD, graduated in computer science at PISA university with a doctoral graduation thesis on VLSI hardware modeling developed in Olivetti R&D. Since 1989 he has worked for large multinational companies and in IT and computerized system validation and management. He is currently the Director of information systems and supply chain/logistics at the Italian pharma companies of FAREVA, based on Istituto De Angeli in Florence.

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Horacio González-Vélez, PhD, has over 20 years of experience in the technology industry and academia. Horacio joined the National College of Ireland to start the Cloud Competency Centre in 2012. He is currently an associate professor and directs the NCI's cloud and data analytics infrastructure, postgraduate programs, and research and innovation initiatives. He is an academic representative to the Steering Group of Technology Ireland Innovation Forum/ICT Skillnet Ireland, a government agency that supports over 15,000 companies nationwide. Horacio started his career as a true dot-commer working in HPC systems engineering and product marketing for Silicon Graphics and Sun Microsystems. He later earned a PhD and a postdoc in computer science at the University of Edinburgh. His research has focused on efficiently employing data-intensive HPC infrastructures to help in the solution of challenging problems in physical and life sciences.

CoP LEADER PROFILES

TERRY JACOBS

Terry Jacobs is Chair of the Oral Solid Dosage (OSD) Community of Practice (CoP) Steering Committee. He is a recognized expert in the design of pharmaceutical, biotechnology, and corporate facilities and has completed projects for clients in the US, China, Mexico, and Saudi Arabia. He has lectured extensively on the planning and programming of laboratories and manufacturing and other industrial facilities.

An ISPE member since 1982, Terry has also served on the ISPE International Board of Directors and helped plan ISPE annual meetings. He is the co-author of *Good Design Practices for GMP Pharmaceutical Facilities* and co-wrote chapters on architecture for the *ISPE Good Practice Guide: Quality Laboratory Facilities* and the *ISPE Baseline® Guide: Oral Solid Dosage Forms (Third Edition)*.

Terry says that recent discussions in the OSD CoP Steering Committee meetings have focused on "net zero facilities and how companies can get there. We hope to be able to present something about it at ISPE's next annual meeting. The collaboration and interaction of ideas that we have at our meetings is fantastic. We have people from different aspects of the industry—owners, manufacturers: all the people involved have different outlooks on what is going on and the resources you need. ISPE has been a great organization to continue my education and develop great friendships. With ISPE, you can work together on something bigger than what you could do by yourself."

When Terry and his business partner founded JacobsWyper Architects more than 40 years ago, they incorporated sustainability principles into projects wherever feasible. "We have been focused on sustainable design from the very beginning and it has become an integral part of our practice. More recently, pharmaceutical companies have begun leading the way on sustainability. We have heard from many who want to be carbon neutral by 2040. I think it is important to integrate sustainable design into every project. We have a responsibility to clients and the planet and in the long run, reducing energy cost is good for everyone."

"The most rewarding part of being an architect is to design buildings and projects for clients that help their employees to be successful at work, ones that go beyond compliance, are sustainable, on budget, on schedule, and are a truly great place to work. The workplace is constantly changing. Twenty years ago, office size was determined by rank in the company; now work is a place to collaborate.

"We are always looking for ways to create a place where people can work together. For example, we designed a new dining hall for one of AstraZeneca's manufacturing facilities. They had a functional cafeteria, but we convinced them to build a more elaborate building with lots of natural light and a new layout and design. Afterwards they told us that the building changed the culture of the site for everyone and made it better."

—Marcy Sanford, ISPE Publications Coordinator

ROUJIAN "RJ" ZHANG

Roujian "RJ" Zhang is Chair of ISPE's new Quality Control (QC)/Analytical Community of Practice (CoP) Steering Committee. He is also Chief Quality Officer at Evive Biotech, responsible for all aspects of quality for the company, ensuring safety and efficacy, making critical quality decisions, and keeping the company up to date with new regulations.

RJ became interested in the pharmaceutical industry early in his life. "My grandfather died of pneumonia in the 1950s. Because he lived in China, he did not have access to penicillin, even though it was invented and being used to treat infections. My cousin, who now works for the FDA, has been studying malaria treatments for decades. Growing up I heard stories about both, and my goal became to not only join the pharmaceutical industry, but to work to make innovative medicine accessible to everyone, and to lower the cost of the medicine as much as we can from the manufacturing perspective."

After earning his degree in biochemistry from Fudan University in Shanghai, RJ moved to the US to work on advanced degrees at the University of Maryland and Purdue University.

"After I obtained my PhD in analytical chemistry from Purdue, I joined Amgen's Process Development department as an analytical chemist supporting multiple blockbuster products. I was fortunate to be groomed by many biotech industry pioneers. I was also able to provide quite a few creative and effective solutions to challenging problems to avoid stockouts."

From Amgen, RJ went to Eli Lilly and Company and then AstraZeneca, where one of the challenges he faced involved developing a QC network across labs at 30 manufacturing sites. "Our executive vice president at the time visited all the sites and said that while they looked great, it was like visiting 30 different companies; there was no standardization at all. AZ's Head of Quality came up with the 4S strategy—Standardize, Simplify, Share, Sustain—and I successfully started a network to apply this strategy that led to the adoption of advanced electronic systems, new technologies, and efficiency gains across the company. The pharmaceutical industry is highly regulated, and it would be great if we could have this type of harmonization across companies."

The ISPE QC/Analytical CoP was established in 2022 to provide a forum for knowledge sharing on a range of topics including out of specification (OOS) investigations, method validation, compendial harmonization, analytical methods lifecycle management, and implementing innovations, such as real-time release.

"One of the first projects the QC CoP is working on is to define best practices for the handling of OOS results. We have assembled a group of subject matter experts across representative companies, and then we also have people from institutes, who bring a fresh perspective. There is so much knowledge that the group possesses. And a lot of CoP members share the same goal as me—to make medication accessible and affordable."

—Marcy Sanford, ISPE Publications Coordinator

Sanat Chattopadhyay


SANAT CHATTOPADHYAY

As Head of Merck's Global Manufacturing Operations and one of the most senior operations leaders in Merck, Sanat is responsible for Merck's worldwide manufacturing operations and product supply, supporting global sales revenue of over $55 billion.

Sanat's organization oversees a complex and large network of manufacturing, commercialization, and distribution operations across four different platforms of pharmaceuticals, vaccines, biologics, and animal health with over 20,000 employees in over 22 countries. Merck supplies over 150 billion doses of life-enhancing medicines and vaccines (human and animal health) to over 140 countries.

Sanat has served on Merck's Executive Committee since 2016. He spearheaded the transformation of manufacturing and supply chain to grow and globalize its vaccine business and played a key part in successfully leading the company's launch of the immuno-oncology product KEYTRUDA in record time by mobilizing a cross-divisional effort to overcome commercialization and supply constraints. Under Sanat's leadership, Merck has been executing significant expansion of its biologics and vaccines manufacturing capacity to reach more patients around the globe.

Before joining Merck in 2009, Sanat served as Senior Vice President, Technical Operations & Product Supply, for Wyeth Pharmaceuticals, with responsibility for product supply, process development, and operational excellence. Previously, he worked at Aventis and its predecessor companies as Senior Vice President, Industrial Operations, and in many other positions of increasing responsibilities for global supply chain, technology, and manufacturing sites across North America, Europe, and Asia Pacific.

Outside of Merck, Sanat is the Chair of the Board of Directors of Hilleman Laboratories, an equal joint-venture partnership formed between Merck and Wellcome Trust, a global charitable foundation dedicated to human and animal health. Sanat holds a master's degree in industrial engineering and management science from NITIE, Mumbai, and a bachelor's degree in chemical engineering from Jadavpur University, Kolkata, India.

Tell us about your journey and the challenges you faced as you got to your current position.

I started my journey in the biopharmaceutical industry after I completed my graduate degree in chemical engineering. I had studied both engineering and management and was not sure where to go when I was contacted by a company called Hoechst AG, a German chemicals and life sciences company where three Nobel Laureates had worked. I thought that a company that had produced three Nobel Laureates could convert me into something great. Eventually I became the head of supply chain and logistics.

At 29 years old, I got the opportunity to become a CEO of a small company. I was afraid to attend the first company board meeting because I thought they might fire me. I received assurance that I would not be fired at the first meeting but was told that would not necessarily hold true for the second. The company was in a lot of trouble, had a lot of debt, and it was a huge battle each day, but I learned that the art and science of running a small business was very different from running a large one.

It was about agility, constant innovation, and resiliency. That truly taught me how to do business during difficult times. Every time I talk to students both inside and outside of Merck who ask me how I built my career, I tell them that that was the best learning I ever had in my career and that sometimes in life it's OK to try to reach for the moon as even if you miss, you will land among the stars.

What do you see for the future of manufacturing?

As a company, Merck has always been driven by innovation. The current healthcare landscape is influenced by a lot of micro and

macro trends, such as shorter innovation cycles, price reform, access expansion, and patient engagement. And the whole system is going to evolve such that there will be a consolidation of providers and payers and nontraditional players.

Cybersecurity threats, the global pandemic, and the Russia-Ukraine conflict have shown us that supply chain disruptions are bound to happen and that we need to increase efficiency, flexibility, and resiliency. Finally, there'll be talent scarcity across our industry derived from high levels of competition in specialized skills, assets, and different ways of working.

At Merck, the first thing we focus on is how to generate a best-in-class, compliant supply. Because if you're not best-in-class in compliance, reliability, and supply, then it's almost impossible to create value for the patients. We need to look at emerging technologies in the context of where the new platforms are taking us. Emerging technologies and platforms are not only about compliant supply, but also products, processes, and supply chains. The whole manufacturing footprint will look different.

The question is how to accomplish this. Technology can be the answer. The rise of new innovations, analytics, and big data can be converted into usable knowledge—knowledge we can harness to transform our models and build that ambitious patient-centric future. At Merck, we are convinced that the future is going to be dominated by the need to garner benefits from investments in emerging science and emerging technology.

Where will technology lead us?

The pandemic has already influenced the future of manufacturing. It emphasized the need for agility and speed in every aspect of our work as well as for a very strong partnership with regulators. It reinforced the importance of access and the need to create products that can reach the most vulnerable patients. We can create a transformative, patient-centric future where all patients, no matter who they are, where they live, or what time of day it is, can receive lifesaving medicines safely, swiftly, reliably, and affordably. To this end, there need to be improvements in the selection of technologies, establishing supply chains closer to the patient, and flexible manufacturing facilities.

Flexible facilities can be constructed at a fraction of today's costs. We will see technologies borne out of rapid clinical development that can allow commercialization from scale-out through intensified processes that can result in better capacity utilization, and they can be supported by digital platforms that enable real-time feedback and active control strategies.

We can also envision making our manufacturing transportable in a way that it can be readily deployed closer to the patient base. Manufacturing facility design will all converge to achieve true plug-and-play paradigms that allow rapid reconfiguration of production spaces and seamless implementation of new innovations.

We will also see the impact of machine learning. For example, in our filling lines, machine learning will constantly teach our cameras so that we falsely reject fewer and fewer drug product units. The use of advanced data analytics will fundamentally increase both in-line and at-line data monitoring and control, and when that is coupled with advanced, multivariate analytics, it will enable in-process quality optimization.

These are just some examples of how the future can get transformed. Whether Merck and the biopharmaceutical industry will be able to achieve this vision in the next few decades is still unknown, but we do know that the advances being made today will undoubtedly move us further along this journey. Manufacturers are going to play a very important role because the potential of science will remain as only potential without manufacturers helping transform the world of biomanufacturing.

How will this benefit patients?

Access and cost will be the key areas where we can create a huge amount of value for the patient. Patients should benefit from having more accessibility to more affordable drugs. It is possible for us to make the presentation of the product very different in the future and the whole concept of access is going to look different for patients if we can revolutionize the patient experience.

Imagine technologies that do not require skilled administration, where we will have significantly advanced intradermal, subcutaneous, mucosal, and oral routes of administration; devices such as patches and on-body injectors that will revolutionize the patient experience; and physician administration that will be transformed into at-home administration without loss of efficacy.

From an affordability point of view, we can use technological advances to reduce the unit cost of the product. If it is small molecules, which involve synthetic chemistry, we can apply biocatalysts and many other steps to be able to reduce the cost. We can create global transportation solutions to reduce the transportation cost.

What role does ISPE play in all of this?

I think trade associations like ISPE play a very important role in promoting best practices: they inform public policies and regulations and develop industry standards.

ISPE connects industry leaders and brings together pharmaceutical knowledge that helps manufacturing and supply chain innovation. It helps us think about how to innovate in operational excellence and how to bring new regulatory insights to enhance efforts in the industry. ISPE is a great example of how companies can come together, not as competitors, but as collaborators to help patients.

Future Leaders' Days 2022

By Melisa Arslantepe and Natalie Schützler

The event, organized by and for recent graduates and students by the ISPE Emerging Leaders Community of Practice (CoP), offered high-quality presentations and interactive workshops where participants could immediately apply the newly acquired knowledge.

"What is ISPE?" "Why are you a member?" "What do you do there?" We've been asked these and many more questions multiple times since joining ISPE. After the ISPE Emerging Leaders Future Leaders' Days 2022, we wish we had taken everyone who had ever asked us a question about ISPE with us.

The ISPE Emerging Leaders CoP has regional subgroups spread across the globe. It aims to provide students and people new to the pharmaceutical industry with the opportunity to take their first steps in a new environment and to equip them with a broad pharmaceutical knowledge and skillset. Future Leaders' Days events take place once a year and are completely organized and planned by Emerging Leaders. This year's event was hosted by Sanofi and PwC in Frankfurt. We highly appreciated the hospitality and supporting program and want to express our deepest gratitude.

This year's event was also my first time to attend Future Leaders' Days and I am so glad that I was a part of the organization committee consisting of ISPE Emerging Leaders: Dr. Natalie Schützler, Dr. Melanie Austrup, Svenja Meyer, Kieu-Trang Tran, Dany Shami, Christoph Bierer, Rebecca Roscher, Silvana Schramek, and Tom McDermott. Believe me when I tell you that the outcome of our planning has even exceeded our expectations.

The event started with a guided tour through the Industriepark Höchst. A bus drove us around the park for about an hour, and we were accompanied by an expert who showed and explained the individual Sanofi facilities.

The first day ended with an amazing networking dinner in the Sky Lobby of the PwC Tower. Being located on the 48th floor of the tower offered an incredible view of the Frankfurt skyline. To engage everyone in discussion, PwC organized an interesting panel discussion on the topic of environmental social governance. The panel included three experts from the focus area and led to an engaging discussion with the entire audience.

On the second day, participants reconvened at the Sanofi site for a program of talks and interactive workshops. The program was structured into two topical streams: Career & Leadership and Digitalization & AI. The two streams ran simultaneously, and participants could freely switch between the two. From the exciting talks and stimulated discussions, you could clearly feel the motivation and enthusiasm of all the participants during the event.

The organizing committee was amazed by the efforts of all speakers to deliver high-quality presentations and interactive workshops where the participants could immediately apply the newly acquired knowledge in playful exercises. Again, we would like to express our deepest gratitude to all speakers.

Our speakers in the Career & Leadership stream were Chris Williams, Jasmin Raschendorfer, Erwin Seelhorst, Anne Reuschenbach, Tristan Tait, and Laura Brieden. They covered topics like inspirational leadership, career development, value of mentorship programs, agility of working groups, and many more.

The Digitalization & AI stream was represented by Robin Schiemer, Gregor Schug, Jan Derfoth, Roland Wölfle, Ángel Gil Nolskog, Christian Müller, and Tobias Hahn. The talks covered topics such as smart factory, in-silico accelerated CMC, value of data for business operations, and many more.

In both streams, an interactive session followed a block of two talks, led by the two respective speakers, engaging all participants in collaboration, reflection, and teamwork.

The organizing team Lead and Co-Chair of the ISPE D/A/CH Emerging Leaders & Students, Natalie Schützler, summed up the Future Leaders' Days 2022 perfectly: "ISPE Future Leaders' Days is networking, networking, networking."

It is difficult to summarize two incredibly successful days in one article. We recommend that you simply be a part of the ISPE Emerging Leader Future Leaders' Days 2023 and take this experience with you. And who knows, maybe you also want to be part of the next organizing team.

Melisa Arslantepe is a QA Specialist at Bachem AG. She joined ISPE in 2022.

Natalie Schützler is a Change Leader at Sanofi. She joined ISPE in 2021.

New Guide Explores Best Practices in Pharmaceutical Containment

"Over the past 20 years, there have been an increasing number of highly potent materials handled within the pharma industry, to the point where most modern products require some degree of containment or other exposure control to maintain safety," said guide team member Peter Marshall, AstraZeneca (retired).

The *ISPE Good Practice Guide: Containment for Potent Compounds* covers all aspects of pharmaceutical containment, including background to safe working levels, mechanisms of exposure, and how exposure can be controlled. There are chapters on typically applied approaches used in containing exposure for commonly applied process systems across all elements of pharmaceutical development and manufacturing.

"In most countries, there is a hierarchy of measures to avoid risks: from elimination of the material to finally PPE. Containment (engineering controls) are amongst the preferable measure to be taken. PPE is the last barrier of defense," said guide co-lead Dr. Rainer Nicolai, Product Owner Engineering Consulting, F. Hoffmann-La Roche Ltd.

Developed by a multinational team of experts consisting of engineers, toxicologists, hygienists, and analysts from major pharmaceutical companies and suppliers, the guide aims to consolidate this widely dispersed knowledge base into one document. It describes and discusses the containment methodologies, processes, and technologies commonly used in the pharmaceutical industry when handling potent compounds.

The guide contains numerous photos on the wide range of technologies presented, such as isolators, process interfaces, transfer ports, air locks, filtration systems, containment performance assessments, and cleaning/waste treatment. Additional topics include GMP aspects, containment systems' life cycle, unplanned emission/spillage recovery procedures, and the development of a containment strategy.

To learn more about this and other ISPE Guides, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Publications Coordinator

Meet the ISPE STAFF

Heather Patterson

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Heather Patterson, Human Resources Manager.

Tell us about your role at ISPE: What do you do each day?
I am responsible for compensation management and payroll, benefits administration, employee relations, talent acquisition, and regulatory and compliance management.

What do you love about your job?
I love helping people and I get to do that in so many different ways in this role. Talent acquisition is one of my favorite parts of my job. I love meeting new people and sharing information about ISPE with them. ISPE is always looking for new talent. Our latest career opportunities are posted at ispe.org/about/careers

What do you like to do when you are not at work?
I was born and raised in southeast Texas and I enjoy spending time with my family. We love to go hunting, saltwater fishing, and traveling to the mountains. One of my hobbies is photography, so I enjoy taking landscape and wildlife photos when we travel. When I'm at home, I love to cook for my family and friends.

ENHANCED INTERVENTION DETECTION in Aseptic Fill Using AI/ML

By Michelle Vuolo, Christoph Koeth, and Robert Wherry

We will show how continuous, real-time capturing of data with immediate data analysis by an ML algorithm can improve control over a critical quality attribute. The ML-analyzed data provides the evidence for validation of the change by demonstrating more control over the process along with a decrease in process risks.

Implementing and validating a new process, or maintaining the validation status during process changes, is a requirement of the pharmaceutical industry. From a process life cycle perspective, validating and maintaining the state of validation is the "maintenance of the process in a state of control during routine commercial production" [1]. To that end, the basic premise of Validation 4.0 is that validating a process is demonstrating that the control strategy is in place and effective using quality by design (QbD), knowledge management (KM), and risk management (RM) principles. These principles identify the critical parameters and attributes that need to be controlled and demonstrate how these parameters and attributes are maintained by the control strategy.

The Validation 4.0 approach offers a more sound and scientific approach than merely "revalidating the process" and should enable faster adoption of new technologies and innovation in a regulated environment. The Validation 4.0 approach shows how the control strategy mitigates risks to product quality to ensure patient safety.

This case study demonstrates the implementation of an enhanced control strategy for aseptic technique in an isolator or a restricted access barrier system (RABS). The innovative control strategy involves the use of a ML vision system for monitoring potential intrusions during human interventions into the Grade "A" environment (i.e., the aseptic critical zone) on the RABS filling line.

THE CURRENT PARADIGM

The current control approach for aseptically filled sterile products is the use of media fills. Media fills are a process simulation because sterility testing all product vials is not feasible. Typically, production lines are initially qualified using three media fill runs (aseptic process simulations) followed by a single media fill run performed semiannually to show continued control. Modifications to the process usually require requalification (including in some cases another media fill). For a media fill to be considered successful, there should be no growth detected, and the number of "contaminated" vials must meet the warning limit and action limit criteria established by the most recent regulatory agencies' and industry standards [2].

The aseptic process simulations serve to evaluate the overall production environment as established through aseptic controls such as cleaning and sterilization of the room and process equipment, air filtration (monitoring air flow rate and pressure differentials), continuous microbial monitoring (via sedimentation plates), and nonviable particulate (particulate counters) monitoring of the environment.

These media fill process simulations also serve to evaluate the aseptic technique used during operator interventions. Interventions during these simulations must meet certain requirements, as outlined by the US FDA [3]:

- At least three consecutive separate successful runs be performed during initial line qualification
- Routine semiannual qualifications are conducted for each processing line
- Representative activities and interventions of each shift and shift changeover should be incorporated into the design of the semiannual qualification program
- All personnel authorized to enter the aseptic processing room during manufacturing, including technicians and maintenance personnel, should participate in a media fill at least once a year

Interventions are required and inevitable, but human interventions have the greatest potential variability and subjectivity and therefore pose the biggest risk to product sterility. Currently, the effect of these manual interventions cannot be monitored directly. More specifically, there is no objective determination as to whether an operator intruded into the critical zone of an aseptic filling area during the intervention. Operators and secondary monitors may detect some obvious cases of intrusion into a critical zone, but not every instance may be discovered. Also, determining whether an intrusion occurred and documenting that intrusion adds to the challenges of performing aseptic technique properly (and perhaps adds to the subjectivity of the current control strategies).

The current control strategies used to mitigate the inherent risks of manual interventions are:

- Extensive operator training and operator adherence to procedures
- Preventive rejection of potentially contaminated objects (i.e., the culling of containers)
- Frequent verification by performing media fills at certain intervals

As an additional control strategy, some companies use a second person to monitor and document interventions. Using this second person mitigates the risks associated with the additional distraction of manually documenting the interventions. These control strategies, however, still depend on a subjective determination as to whether an operator intruded into a critical zone during the intervention.

Also, consider the detection of a "contaminated" vial from a media fill run from a risk perspective. Media fills may have an inherently low probability of detection because the following sequential events must occur for a media fill vial to exhibit a positive-growth result:

1. A microbe is on the operator glove.
2. The operator enters the critical zone.
3. The microbe is transferred from the operator glove to the critical zone.
4. The microbe enters a container.
5. The microbe grows in the container during incubation.

The preceding sequence of events and their probability are an aseptic technique "black box" and are generally considered as a single event. A low probability of detection implies that media fills are best for detecting gross microbial issues. However, if an operator entering the critical zone can always be definitively determined, then probability of detection becomes very high, and the control strategy is improved, with a large degree of subjectivity removed.

As an enhanced control strategy, this case study looks at an ML vision system that objectively determines when an operator has intruded into a critical zone. This case study focuses on the process validation aspects and does not explore the validation of the ML algorithm and predictive model software. Currently, no definitive method for ML software validation has been established by either regulators or industry. The ML software validation approach used for this case study is explained elsewhere [5].

CASE STUDY: AN ENHANCED CONTROL STRATEGY

This case study focuses on the critical quality attribute of sterility and is therefore focused on the contamination control strategy. It explains a new approach for controlling the sterile attribute achieved using an ML vision system to monitor interventions into the aseptic critical zone on the RABS filling line. The objective of this case study analysis is to use QbD, KM, and RM principles to demonstrate that this new control strategy is more effective than the existing control strategy for aseptic technique human interventions. This improvement in the control strategy is characterized by better detection of intrusions into the critical zone during human interventions.

As an enhanced control strategy, this case study looks at an ML vision system that objectively determines when an operator has intruded into a critical zone.

To implement this new control strategy for monitoring interventions, one main equipment change was required: multiple cameras had to be retrofitted into the existing RABS aseptic core. Cameras were positioned to provide different views and perspectives into the same critical zone filling and handling areas. Adequate coverage was then verified using smoke studies. These cameras supply time-stamped video images for analysis. The analysis is then performed using two distinct ML random forest (RF) classification algorithms for two objectives:

1. To detect glove insertions into the isolator or RABS.
   - Detection capabilities localize and classify the intervention into different actions.
   - This ML detection extends beyond current technology (for example, using light barriers) for a simple detection of "glove port insertion."
2. To differentiate between critical and noncritical interventions.

The ML RF algorithms establish a mathematical model (that is, a correlation) between the video images and whether an operator has intruded into the critical zone. To establish that correlation, the ML algorithm was trained with labeled images, including borderline or edge cases. To properly identify and label the borderline/edge images, smoke studies were used to precisely define the coordinates of the critical zone. Line speeds were established and qualified prior to the smoke studies, and media fills were performed after the smoke studies to capture a significant volume of video images for training the ML RF algorithms. After extensive training, testing, and validation, the ML RF algorithms were verified to provide an accurate analysis of when an operator intruded into the critical zone during an intervention.

These ML RF analyses provide a fully automated, objective verification of operator adherence to aseptic technique (that is, avoiding the critical zone during interventions) while minimizing risk by releasing operators from distracting activities (like documentation). Vials are rejected or discarded when critical zone intrusion is detected during operator interventions. The relevant parts of the time-stamped video are retained as part of the batch record and replayed for operator training/retraining purposes.

This case study shows that the Validation 4.0 approach, applied to a process change, ultimately demonstrates that risk is lowered and that the change provides increased control over patient safety as compared to the current control strategy.

Table 1 lists the key benefits accomplished by the change from human monitoring to monitoring by ML analysis. Also in the table are data integrity upgrades in terms of some ALCOA+ improvements (ALCOA = Attributable, Legible, Contemporaneous, Original, and Accurate; + = Complete, Consistent, Enduring and Available).

Because the ML RF analysis provides 100% real-time, automated monitoring of operator interventions, it may remove the need for media fill assessments of the operator interventions. The aseptic environment control strategies combined with the ML RF analysis of operator interventions may be sufficient for isolator or RABS production suites. Aseptic environment control strategies include:

- Cleaning and sterilization of the room and process equipment
- Air filtration (monitoring air flow rate and pressure differentials)
- Continuous microbial monitoring (via sedimentation plates)
- Nonviable particulate counters monitoring

A failure modes effects analysis (FMEA), or other RM approach, of the aseptic filling operation may be sufficient if it can be clearly demonstrated that the control strategy provides sufficient continuous monitoring, and that all sterility failure risks have been adequately mitigated. Fundamentally, ML-enhanced vision systems—where the images are evaluated for "correct" operator activities—provide an inline/online process analytical technology for achieving continued or continuous process validation. The authors believe that this approach is a significant improvement over the current media fill process simulation control strategy, and may someday remove the need for media fills.

APPLYING VALIDATION 4.0 TO THE CASE STUDY

As stated previously, the Validation 4.0 approach aims to validate a process by demonstrating the control strategy is in place and effective using QbD, KM, and RM principles. These principles may be used in a three-step approach to show the importance of what process aspects need to be controlled. Step 1 takes a QbD approach to provide a high-level process flow showing the relationship of sterile product filling and media fills. Then, the data is identified at each process step, whether they are inputs, outputs, or transacted data. Step 2 uses RM to assess the risk of each data point within the context of the process step and identify the risk control measures for the more critical process steps/data points. For purposes of this case study, these steps are demonstrated by comparing the current paradigm against this change to the ML visions system. Step 3 builds the evidence that the control strategy is in place and effective.

We will show, by comparison, how the change discussed previously will provide equal or better control around mitigating risk to product quality and ultimately patient safety.

Step 1: Process and Data Flow

We start with a QbD approach rooted in product and process understanding. Then we map out the process flow and identify the data created, transacted, and processed at each step. Figure 1 provides process flow steps (QbD) applicable for this case study. It is not a detailed view of all steps necessary to manufacture a sterile filled product. Figure 2 provides the process data elements steps (KM).

Step 2: Risk Assessment (Risk Management)

RM typically looks at three factors to assess risk: severity, frequency of occurrence, and probability of detection [6, 7]. For purposes of this case study, we will not dive deep into risk assessment methodology but will show simple evaluations to demonstrate the approach. For operator interventions, any intrusion into the critical zone could be considered high severity, and this can be linked to QbD thinking due to their ability to potentially impact patient safety. The frequency of occurrence (of the operator interventions that intrude into the critical zone) is variable depending on the type of filling operation, as well as from media fill to production run and from production run to production run.

Regardless, most likely every batch has some interventions that intrude into a critical zone, and therefore the frequency of occurrence may be considered moderate to moderate-high. The risk factor most affected by the change is probability of detection. Visual, human monitoring may be categorized as moderate to moderate-low because the borderline/edge cases may not be consistently detected by the visual observer, whereas video imaging coupled with ML RF analysis provides a high probability of detection.

Also, as discussed previously, a media fill may not detect a poor performance of an aseptic technique because a series of sequential events must occur to detect a poor performance with a positive-growth test result from the media fill.

As illustrated in the risk assessment diagram in Figure 3 (before change) and Figure 4 (after change), the criticality of the data elements from the process does not change. Based on QbD, the criticality of the data remains, as it directly relates to controlling the critical quality attribute: a sterile product. What does change is the detectability of failure of these data elements upon implementing the artificial intelligence (AI; video analysis) and automated recording of critical data elements.

Table 1: Key benefits of moving from human monitoring to monitoring by ML analysis.

Current Control Strategy – Human Monitoring	Enhanced Control Strategy – Monitoring by ML Analysis	Data Integrity Improvements
Subjective human observation to classify interventions, which can result in human visual variability in real time coupled with real-time decision-making.	ML is trained by a human but not under real-time constraints of filling operations. Objective ML analysis then identifies and classifies the interventions limiting real-time fluctuations.	Accurate
Delayed operator recording of activity after completion.	Real-time capture of activity (no distractions/no forgetting).	Contemporaneous Accurate
Media fill assessment of operator interventions.	Continuous 100% monitoring for the assessment of operator interventions.	Consistent

Figure 1: Process flow steps.

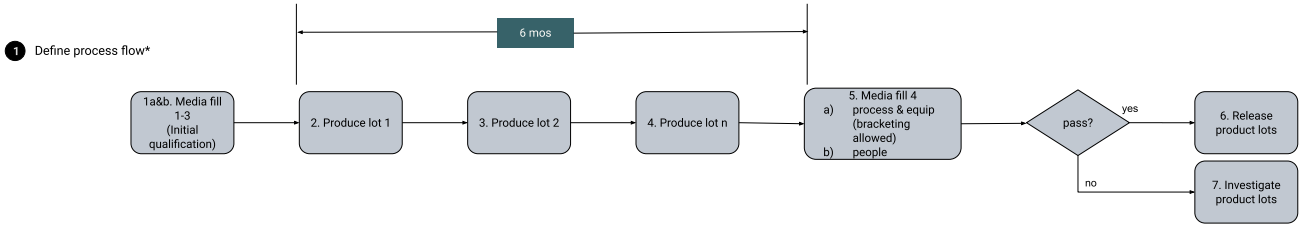
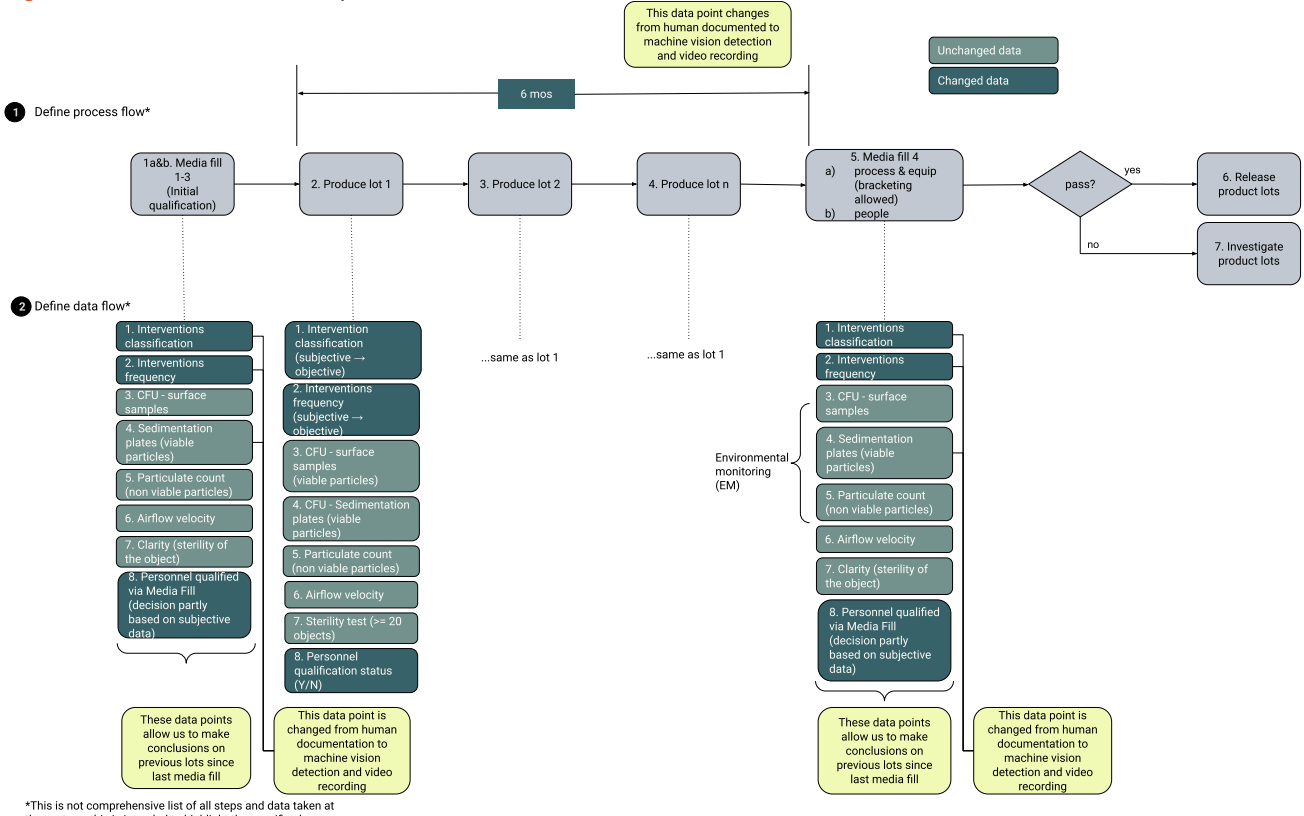


Figure 2: Process and data flow steps.

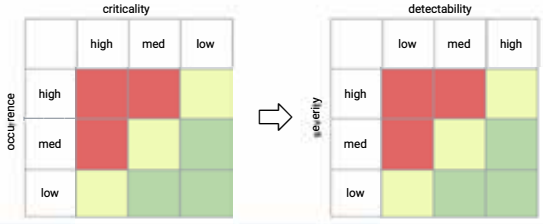


*Light green denotes current process and dark green denotes target process after change.

Figure 3: Risk management before change.

3 Perform risk assessment on the changed data elements and define resulting control strategy focusing on higher risk data.

Definitions Used
- Criticality: how critical is the data point to assuring patient safety or product quality
- Vulnerability: how vulnerable is the data point to assuring data integrity (ALCOA+)
- Detectability: how likely is an error in this data point to be detected, given current controls



BEFORE CHANGE

		Criticality	Occurrence	Detectability	Overall risk	Control strategy	Demonstration of effectiveness (qual/quant)
Media Fills	1.1 (& 5.1) Intervention classification	high	medium	low	high	• Operator Training • 2nd operator/quality verification	• Sterility of the media fill • Quality assessment
	1.2 (& 5.2) Intervention frequency	high	medium	low	high	• Operator Training • 2nd operator/quality verification	• Sterility of the media fill • Quality assessment
	1.3 - 1.6 (& 5.3-5.6) EM	high	medium / low	low	high / medium	• Sterile media (HEPA filters, ...) • Room controls	EM program... • EM plates • People • Air quality
	1.8 (& 5.8) Personnel qualification status (Y/N)	high	medium	low	high	• Operator Training • Plate counts?? • Performed biannually?	• Plate counts? • ...
Product Fills	2.1 Intervention classification	high	medium	low	high	• Operator Training • 2nd operator/quality verification	• Sterility of the end product • Sterility of the past media fill
	2.2 Intervention frequency	high	medium	low	high	• Operator Training • 2nd operator/quality verification • HEPA • Room controls	EM program... • EM plates • People • Air quality
	2.3 - 2.6 (& 5.3-5.6) EM	high	medium / low	low	high / medium	• Sterile media (HEPA filters, ...) • Room controls	EM program... • EM plates • People • Air quality
	2.8 Personnel qualification status (Y/N)	high	medium	low	high	• Operator Training • Plate counts?? • Performed biannually?	• Plate counts? • ...

Step 3: Control Strategy

The process flow step shows that the effectiveness of aseptic technique is only evaluated during the media fills and subjectively monitored during the production runs. The data flow step shows that continuous video-capture and ML analysis provides data that is more accurate, contemporaneous, consistent, and complete compared to human, visual observation during media fills and production runs.

The risk assessment step shows that the risk of not detecting an intrusion into the critical zone is eliminated (or at least greatly reduced) compared to the human, visual observations of operator interventions. As well, potentially the occurrence of intrusions goes down because the operators are focused on doing the work rather than documenting the work.

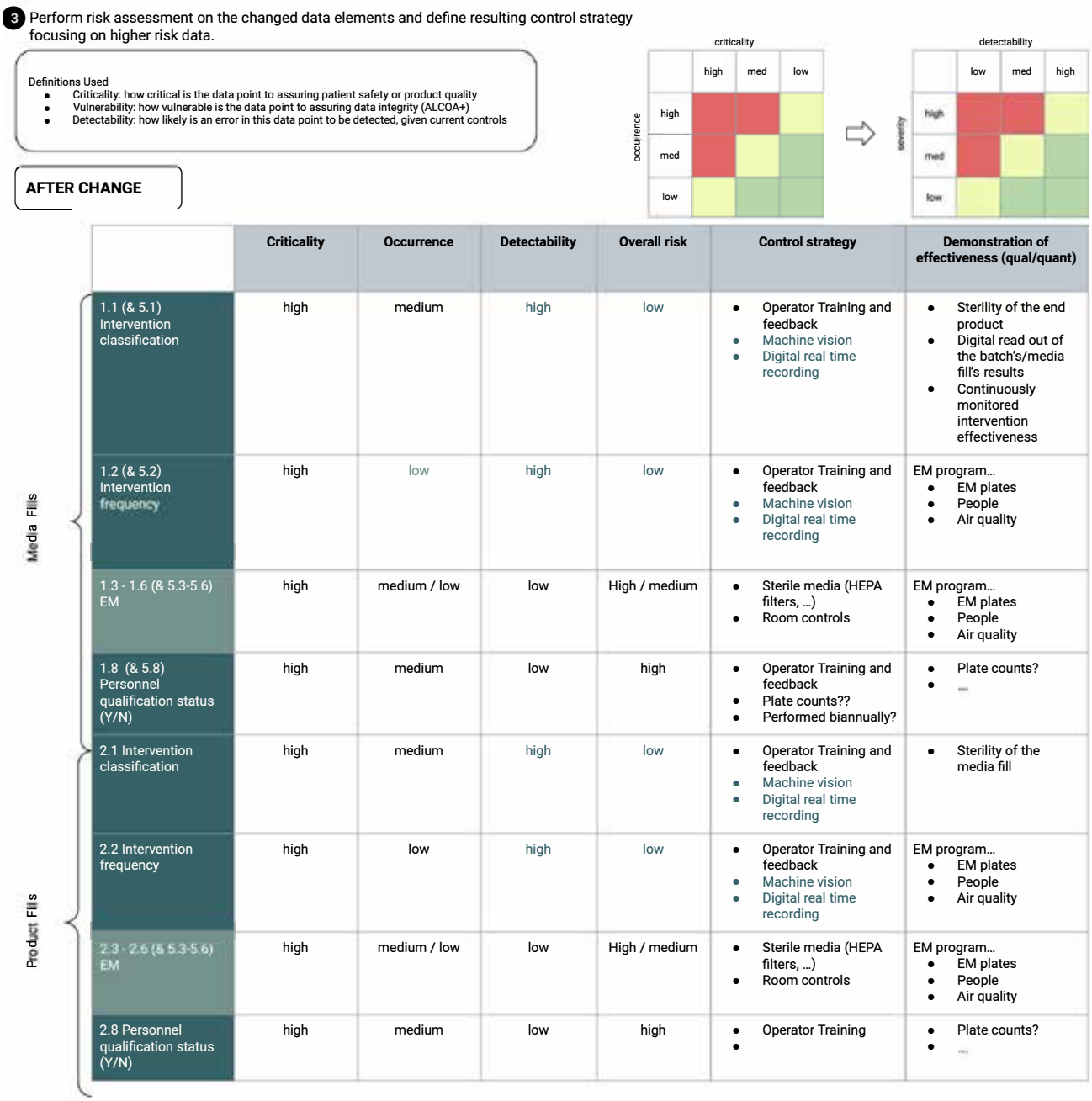
Thus, from the QbD, KM, and RM perspective, the change enables a much more rigorous control of the process and achieves an enhanced control strategy. The control strategy consists of operational and technical controls that are in place to mitigate high-risk data elements as defined by QbD concepts; the data elements that are closer to managing or characterizing our product are most important to control.

SUMMARY OF CONTROL STRATEGY CHANGES

With the preceding evaluation of the critical data elements associated with the aseptic processing of sterile products, we have demonstrated that the ML-enhanced, automated, continuous monitoring provides a better level of control than the traditional media fill approach for documenting sterility assurance.

The evidence provided by the control strategy, the risk assessment, and the rigorous validation of the ML model demonstrate that the proposed change, the ML-enhanced vision system

Figure 4: Risk management after change.



observation of operator interventions, is an improvement over current control methodologies. The evidence shows better control (lower risk) associated with the sterile product than before the change, as summarized in Table 1. Changes from control strategy, quality RM, and validation perspectives are discussed next.

Control Strategy Perspective

Operator interventions and the possible/probable intrusions into critical aseptic zones is the current "weak link" in control strategy for aseptic processing and media fill validation. ML enhances the monitoring of operator interventions by automating the detection of operator intrusions into the critical aseptic zone(s) and monitoring the process continuously. The ML-enhanced, automated, continuous monitoring of operator interventions is objective rather than subjective and is therefore an improved process control over the subjective human observation of operator interventions.

Quality RM Perspective

Media fills represent a high risk. The unknown release of aseptically produced product heavily relies on statistics and decisions

Table 2: Improvements with ML-enhanced vision system observation of operator interventions.

What's Changing	Supporting Evidence
Intended changes • Interventions classification source changes from subjective to objective (human → camera with ML) • Intervention frequency (human → camera with ML, every vial evaluated) • Move from operator training and frequent verification (statistics) → 100% real-time verification	**ML data** • Camera vision coordinates in correlation with smoke study data (to determine critical zones). • Video recording of entire batch. • Design, training, and testing documented [5].
Unintended positive changes • Instant feedback to operators, which provides more effective and continuous training in aseptic technique in real time. • Much more granularity on each individual batch in production, essentially making the intervention a data point. This concept may enable attributing a process risk factor to individual aseptic productions [8]. • Media fill does not always fully and accurately simulate production. ML observation during production always captures what occurred. • Future Goal! Replace the detection of microbial failures in media fills (discrete moments) with ML continuous and real-time video surveillance of the actual product.	In principle, in other training circumstances where the feedback is real time and ongoing, operator improvements are typically seen. However, because of privacy restrictions, this is not currently being measured. Ongoing work is evaluating how to best measure this.

that are derived based on the unknown probability of the occurrence of a microbial contamination during a media fill (versus a production run) and the unknown likelihood of detection (via growth in the limited number of media fill runs). Therefore, outcomes of media fills/aseptic process simulations can only indicate an approximation of actual sterile filling.

The ML-enhanced, automated continuous monitoring of operator interventions represents a lower risk because of the high likelihood of detections (of operator intrusions into a critical zone). The probability of occurrence of any intrusion into a critical zone is assumed to be at least equivalent to what might occur during a media fill. Additionally, any intrusion has the potential to cause a microbial contamination.

Therefore, compared to the unknown likelihood of detection of the media fill approach, the ML-enhanced, automated continuous monitoring approach provides an extremely high likelihood of detection. From a quality RM perspective, the ML-enhanced, automated continuous monitoring, with its high likelihood of detection, results in a much lower risk overall.

Validation Perspective

The ML algorithms have been designed, extensively trained, rigorously tested, and verified by performance metrics to provide an accurate analysis of operator intrusion into the critical aseptic zone during interventions [4]. After development, extensive "process validation" testing was performed to demonstrate that the ML model worked in a "live" aseptic process situation. This extensive testing, both during the development of the ML model and afterward in the actual aseptic process, provides the statistical evidence that the controls are established and effective; the control strategy is effective.

Any changes made to the processes would require normal change control, including change impact assessment and verification that the control strategies remain effective. This would include evaluation of the ML algorithm and its ability to detect any new/changed critical zones due to changed operation. Retraining of the ML algorithm may be necessary to detect any new or changed operation.

CONCLUSION

The use of AI/ML as discussed in this article provides a rapid and automated personnel monitoring method in critical zones for an aseptic filling process within a closed environment. For the acceptance of AI/ML as a rapid and automated personnel monitoring method, the principles and approach used for the acceptance of rapid and automated microbial monitoring methods should be considered. Volume 4, Annex 1 of EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use, Section 9.28 states: "rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods." [2]. This Guideline does not address the use of AI/ML because AI/ML is not listed among the technologies in Section 1 (Scope) [2]. Nonetheless, this same approach could be used for the adoption of AI/ML when used as a rapid and automated personnel monitoring method.

This case study shows that the Validation 4.0 approach, applied to a process change, ultimately demonstrates that risk is lowered and that the change provides increased control over patient safety as compared to the current control strategy. We identified that the monitoring of operator interventions is a process parameter critical for patient safety. Through quality RM techniques, the current controls of media fills and observed interventions during routing production were shown to be of a higher risk than the control achieved by the ML-enhanced monitoring of operator interventions.

Furthermore, we are potentially able to certify operators to a higher level of confidence because they can focus on the filling operation while the ML-enhanced monitoring with video recording can continuously document interventions in real time. The objective evidence demonstrates that a ML-enhanced vision system provides a better level of control for sterile fill processing than with the current aseptic validation methodology. This demonstration of a higher level of control essentially demonstrates that the process is validated after change.

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About the authors

Christoph Köth currently heads the innovation group located at the Fresenius Kabi sterile manufacturing plant of drug products in Graz, Austria. Before joining Fresenius Kabi, Christoph gained more than 20 years of experience in the pharma industry in different roles, ranging from Head of QA and Head of Production and Engineering. Deep involvement in managing central IT systems not only helped him finance his studies in chemical engineering (MSc, University Linz) and business administration (MSc, University Linz and MBA, University of Cincinnati) but also helped him found an IT startup. In his current role, Christoph and his team focus on rethinking current practices and implementing process innovations using new technologies including artificial intelligence. He and his group also develop innovative technology enabling next generation production methods primarily targeted at sterile (and complex) products. He has been an ISPE member since 2019.

Michelle Vuolo currently leads Quality at Tulip Interfaces, Inc, which develops and sells a frontline operations platform where manufacturers of many industries can build digital content to manage their operations. Before joining Tulip, Michelle spent over 24 years in the biopharmaceutical and medical device industries in many different roles, including QC laboratory, engineering technical support, quality assurance management, and computerized systems compliance. Michelle has a strong understanding of the needs of the life sciences industry and is now motivated and driven to evolve stagnant ways of meeting compliance requirements, especially as it relates to the 4.0 world. She has been an ISPE member since 2008.

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METHODOLOGY TO DEFINE a Pharma 4.0™ Roadmap

By Emmie Heeren, Arend Jan Wassink, Venkateshwar Rao Nalluri, and Sebastian Niederhauser

In the context of data integrity, data flows are essential. The FDA, PIC/S, and WHO have all emphasized the importance and benefits of data flows in their guidance on data integrity. The key to data integrity compliance is a well-functioning data governance system [1, 2] in which the data flow path for all business processes and equipment—such as in manufacturing, laboratory, and clinical studies—is fully understood and documented by a detailed process data flow map.

Based on robust data flows, aspects and required controls can be assessed in detail—for example, manual data entry, interfaces between systems, media change, data conversion, data migration, and data archiving. Process and data flow mapping allow us to apply critical thinking [2] to data management and to achieve a holistic approach that not only ensures data integrity, but also offers the most efficient use of data and electronic systems needed for the next step toward digitalization.

This article provides insight into process maps and data flows in the biopharma industry using the Reference Architecture Model Industry 4.0 (RAMI) [3, 4]. RAMI integrates all assets, including physical items, software, administrative shell, documents, and personnel. It supports the analysis of Industry 4.0 systems and interfaces by mapping them to a three-dimensional (3D) representation. When all assets are integrated, RAMI will enable the transition to full digitalization. The RAMI model is primarily used as a tool for designing integrated operations.

ISPE's Pharma 4.0™ Process Maps and Critical Thinking Subcommittee offers a perspective on how process data flow maps could be generated using a four-step model. The Subcommittee's four-step approach starts with mapping existing process. Existing process maps can be used if they are up to date. In this approach, the data life cycle and RAMI are used as tools to map the current state already in the Pharma 4.0™ framework. RAMI is also used later to design the end state. This approach visualizes data and processes from a data-centric perspective, making it easier to identify gaps, inconsistencies, and scope for improvement. By defining an envisioned end state with achievable, intermediate states, an organization will grow and evolve gradually into the new Pharma 4.0™ operating model. It also has a positive impact on maintaining the validated state of the impacted computerized systems and on the planning of budgets and resources. The four-step approach is introduced as a methodology. Each step is explained in the context of the entire process. The concepts introduced here will be topics for future articles.

PHARMA 4.0™

One of the principal tenets of Pharma 4.0™ is digitalization, which "will open new horizons to achieve new levels of connectivity, transparency, agility and productivity through the application of faster and more accurate information for decision-making. [5]. The vision is to design a connected architecture in which data are used as a single source of truth and available at any level at any time. Achieving this vision will require the industry to effectively use all data from and about processes, which can be then actively used for decision-making.

Traditionally the industry used the ISA-95 model for digital systems [6], which put processes at the core. Data were primarily generated at level 1 and 2 systems and then fed through a series of connections up to the business solutions level. However, the process-centric approach of this linear model limited data integrity control capabilities. In an interconnected Pharma 4.0™ world, the hierarchy of systems is moving toward a model where data are connected directly to the data source—the original data—and promote a "single source of truth."

RAMI 4.0

Industry 4.0 concepts, structure, and methods are being adopted worldwide to modernize manufacturing. Industry 4.0 concepts are being applied to process industries to achieve a holistic integration of automation, business information, and manufacturing execution function to improve several aspects of production and commerce across process industry value chains for greater efficiency. RAMI 4.0 [3] was developed by the German Electrical and Electronic Manufacturers' Association (ZVEI) to support Industry 4.0 initiatives.

RAMI 4.0 defines a service-oriented architecture (SOA) where application components provide services to the other components

Figure 1: Process-centric vs. data-centric approach.

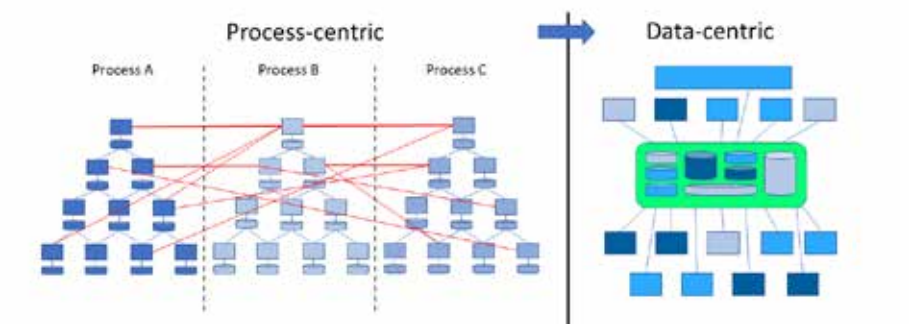
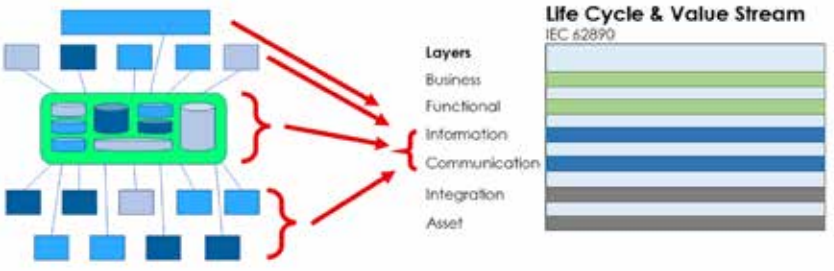


Figure 2: Data-centric approach used in RAMI.



through a communication protocol over a network. The goal is to break down complex processes into easy-to-grasp packages, including data privacy and information technology (IT) security. The characteristics of transition from Industry 3.0 to Industry 4.0 can be observed in various aspects, as presented in Table 1.

Table 1: Characteristics: Industry 3.0 vs. 4.0.

Industry 3.0 Characteristics	Industry 4.0 Characteristics
Hardware-based structure	Flexible systems and machines
Functions bound to hardware	Functions distributed throughout the network
Hierarchy-based communication	Participants interact across hierarchy levels
Isolated product	Communication among all participants
	Product part of the network
	RAMI 4.0 structure

Because current processes are not designed based on the Industry 4.0 architecture, this transition will need to be implemented step-by-step. The approach presented next offers guidance for the start of such a transition. The approach can initially be applied to a subprocess, then extended to linked processes. By repeating the approach, the existing processes can be adapted to Industry 4.0 characteristics, resulting in the digitalization needed for the desired levels of connectivity, transparency, agility, and productivity through the application of faster and more accurate information-enabled decision-making.

THE FOUR-STEP APPROACH

In a traditional Pharma 3.0 environment, automation is implemented from a process-centric perspective. This leads to a top-down or vertical automation stack (refer to the ISA-95 model). Data that are generated, collected, and used remain within the boundaries of the process. Where interactions with other processes are required, this is implemented using dedicated and often proprietary interfaces. Due to the lack of a defined structure, these interfaces become very complex and difficult to understand and maintain.

In a Pharma 4.0™ environment, digitalization shifts the focus from the process to the data to achieve new levels of connectivity, transparency, agility, and productivity through the application. Successful digitization requires a data-centric perspective. Therefore, processes should be reviewed from this perspective. Figure 1 shows this shift in perspective.

To implement Pharma 4.0™ to its full extent, a structure is needed to connect and store data in a transparent way and, in turn, should be made available in real time to the target users. The structure designed for this environment is RAMI [4]. This model (Figure 2) was initially created to focus on a structured description of a distributed Industry 4.0 system to identify standardization gaps. In this approach, RAMI is used as a tool to design the envisioned end state and to identify optimizations.

To reach the organizational and architectural structure, a basic four-step approach is used that can be continuously repeated

Figure 3: The four-step approach.

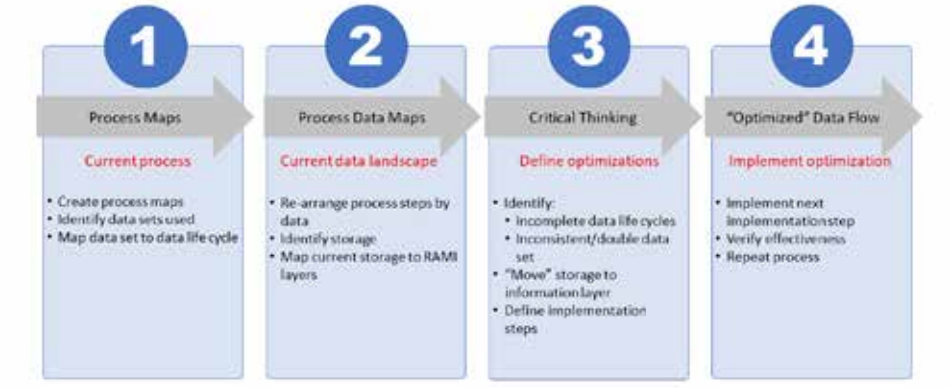
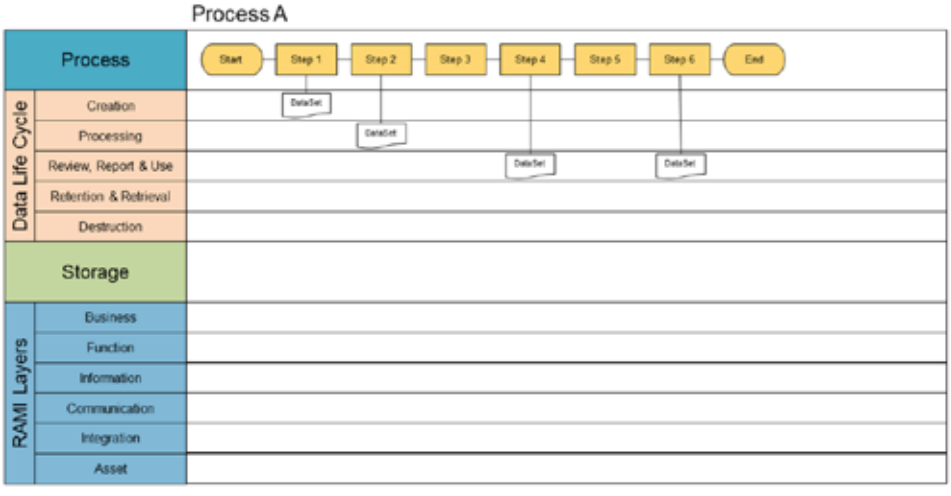


Figure 4: Mapping the process steps and data sets.



to create the level of optimization needed. At its core, the process will document the current state, define the envisioned end state, and construct a path from the current state toward the end state. This path will be split into steps, or work packages, that contain a manageable number of improvements for the organization to take the next step on the path. Figure 3 shows all four steps.

The first two steps (process mapping and process data mapping) are used to document the current state. The third step (critical thinking) is the phase where the envisioned end state is defined and the path to move from current to end state is constructed. In the fourth and last step, the defined work packages are executed. Once a work package is completed, the effectiveness will be assessed where needed.

These four steps are interconnected as the processes provide input for the data mapping. One step leads to the other and the process repeats. Changing the perspective from process-oriented mapping (step 1) to data-oriented mapping (step 2) will provide necessary input for the critical-thinking process (step 3). Process optimization (step 4) is the execution phase and is dependent on the integrated preceding steps. Once process optimization is complete, the effectiveness of the optimization must be assessed, the new current state updated, the envisioned end state verified, and corrective measures, wherever needed, defined. With this, the process becomes iterative toward the envisioned end state and beyond.

In this methodology, the various dimensions of RAMI will be used to analyze the current state (Pharma 3.0 environment) and to determine the desired end state. Analyzing the data life cycle and the RAMI structure regarding the process and data flows gives us insights into the starting point and the interconnectivities.

Process Mapping

The first step toward optimizing production processes is to understand the current state via process mapping. The driver for process mapping in the context of the four-step approach is to lay the foundation for data mapping later. This helps define the origin of the data [7, 8] and helps us understand the interdependencies among the disparate processes and systems. It is important to understand that the mapping in this approach is intended to gain insight in one single process, from beginning to end. Therefore, each process will be mapped separately.

In general, process maps provide insight into a process, bring a high-level understanding of each process step, and help identify inefficiencies such as bottlenecks, repetitions, and delays. The process maps also identify inputs and outputs of individual process steps. Many organizations already have documented process maps. These maps provide a good starting point, assuming they are fully up to date.

The core requirement for process-oriented mapping is to have a complete sequential lineup of process steps within a specific process. Figure 4 shows the basis for creating the map. These process steps are recorded in the process lane of the diagram. In this phase, we are also identifying which data sets are used in each process step. This can either be input or output. Therefore, the next step is to identify the data sets as input or output for a process step. Each identified data set will be placed in its appropriate stage of the data life cycle.

A data set is defined as the sum of the data that travels through the data life cycle. The GAMP® structure of the data life cycle is used as a basis, which consists of different phases, namely creation; processing; review, reporting and use; retention and retrieval; and destruction [2]. A data set in this context is defined as a conceptual view of a data record, independent of its form.

A data set is only complete when the data life cycle has followed each step and is complete. As discussed later in this article, only complete data sets will be able to transfer to the Pharma 4.0™ environment. However, a data set will almost never complete its full data life cycle within a single process. The result of the first step in the four-step approach is process maps for all the processes. Figure 4 is an example of a simple process.

Process Data Mapping

The process data mapping phase is a detailed exercise to identify the interdependencies on a data level. This means focusing on a single data set and connecting it to process steps in every process to look at the processes from a data point of view. Process data maps link the different processes that interact with the data set and show the data flow [2, 9].

To continue process data mapping, a single data set will be mapped. Each process map is reviewed and where the data set is found, the process step is taken and copied into the process data map. Once all process steps are identified and copied, we end up with an overview of all occurrences of the data set. Figure 5 shows all processes of a single data set. Each step that interacts with the data set is copied into the process lane.

Because the data set is only a conceptual representation, we now need to identify where the data set is stored. This can be a reference to a computerized system or a paper document or form. This reference is documented in the storage lane. We will also identify at which level of the RAMI layer a data set currently exists. The following guidance can be used:

- Asset: A data set is not digitized and/or can only be accessed through an asset. Examples include paper forms and documents, files, and databases on a local computer disk not accessible through the network.
- Integration: A data set is digitized, centrally stored, and can be used by multiple processes. However, these processes need to have access to the system managing the data set.
- Communication: Multiple systems can use a data set, usually through dedicated (proprietary) interfaces. Processes can seamlessly use multiple external data sets through a single system.
- Information: Data sets are available to all processes, can be accessed in unified way, and are independent of systems and data formats. This is the targeted layer for Pharma 4.0™ for connectivity, transparency, agility, and productivity.

Note that a data set can go through the various stages of the data life cycle multiple times. Therefore, it may occur multiple times in a data life cycle phase. At this point it is also important to check if a data set touches each life cycle phase, meaning there is a defined process step that creates a data set through a defined process that deletes or destroys the data set. If a step is missing in the life cycle, it should be flagged for further investigation. If a data set is stored at multiple storage points, such as in different databases and/or on paper, it is likely to have redundant data. Data sets should be aligned with regard to data format and metadata to be able to interconnect the data. The data set only completes the data life cycle when the destruction step is reached.

The data set is not yet aligned with the data life cycle phase. Aligning the data set enables us to visualize the current state with regard to storage, duplicates, missing data, or misalignments on data format and metadata. By moving the different process steps to group the data set per life cycle phase, we can visualize where data are created, processed, reviewed, reported, used, retained, retrieved, and, finally, destroyed. Figure 5 demonstrates what an aligned data life cycle for a data set would look like.

Visualizing the process steps through the various data life cycle phases triggers visualization of the disparate data storage and potential redundant data. By following the data life cycle phases in a sequential manner, the potential introduction of any redundant data are visualized and missing data life cycle phases are easily identified. This method of visualization has already inspired us to think about the data architecture and how it interacts with the various processes, which brings us to the next and third step of our methodology—critical thinking.

Critical Thinking

Up this point, the methodology describes the route to visualize the starting situation before beginning the integration to the Pharma 4.0™ architecture. Critical thinking is the core of the approach.

At this stage, the end state will be defined within the architecture of Pharma 4.0™. However, envisioning the end state is not the most challenging aspect. Because the Pharma 4.0™ vision is a paradigm shift from the previous Pharma 3.0, this will not just be a turnkey solution. The most challenging part of the process is uncovering the path to the end state.

A path needs to take the current position into consideration and move in the direction of the end state. Taking an aerial view,

For the Pharma 4.0™ environment, it is envisioned to have one single source of truth entering the RAMI architecture. This will affect how processes will be designed. It is not sufficient to create a process within its own silo.

where both the current state and the end state are within scope, will be needed to define intermediate states. Manageable projects or work packages can be created to realize the intermediate states and allow for reflection on achievements: Was the change effective? Does it bring the end state closer? Is correction required? This process is repeated until the envisioned end state has been achieved.

To be viable in a Pharma 4.0™ architecture, data need a set of minimum conditions:

- The data life cycle must be fully implemented.
- Data sets must be free of duplicates (remove redundancies).
- Data sets must be accessible in a unified way.

Using the current state, the end state can be defined considering these three minimum conditions. (The envisioned end state from a data-oriented perspective is shown in red in Figure 5.) To do this, we need to go back to the concept of critical thinking. *ISPE GAMP® Guide: Records and Data Integrity* defines critical thinking as "a systematic, rational, and disciplined process of evaluating information from a variety of perspectives to yield a balanced and well-reasoned answer" [2]. The four-step approach is the systematic process. We have gathered and evaluated our information by creating the process data maps. Now we can analyze them and identify potential issues and opportunities for optimization.

Figure 5 also shows that the data life cycle has been completed by defining the need for a destruction step. But it is not just a matter of defining solutions for the correction and optimization we have identified. In Pharma 3.0, we may have different types of storage within one data set, whereas in Pharma 4.0™, it is envisioned to have one single source of truth entering the RAMI architecture. This is achieved by moving data sets into the information RAMI layer (red dots). To enable this, all the data sets in the "information" layer must be accessible in a unified manner. This means a process must be able to access a required data set in a technology-agnostic way. In principle, a process can access all available data sets within the "information" layer with the appropriate authorization.

The RAMI architecture is designed to seamlessly integrate all layers into a holistic view of the available data. Data creators, such as the assets in the asset layer and the digitized databases in the integration layer, provide their data to convergence information layer. This will be done without needing to know which process is using the data. In the RAMI architecture, the purpose of data creators is to publish. On the other hand, data users, such as functional or business processes, will use the data set without any required knowledge of the underlying assets and databases.

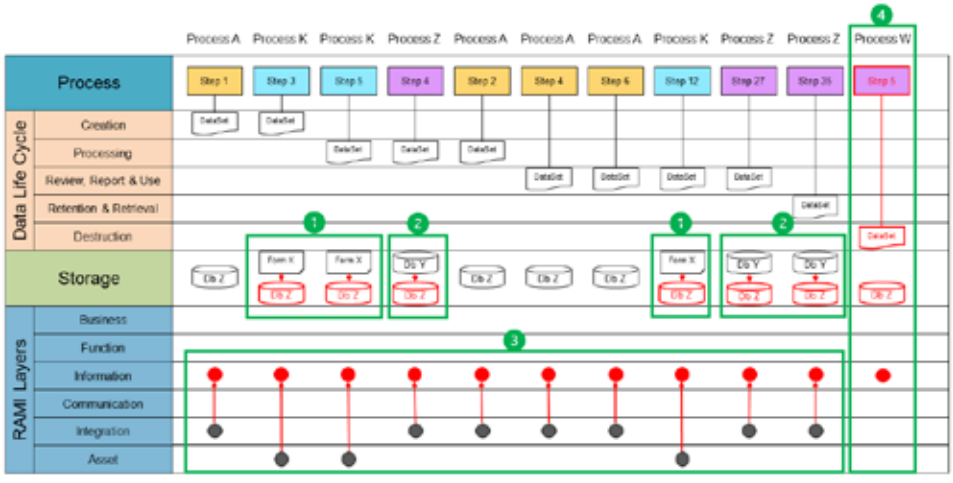
Once the end state is clear, a viable and achievable path must be defined. Because Figure 5 encompasses the entire view for the data set and both the current state and end state are represented, it provides the view we need. A path is created by defining the intermediate stages. An intermediate stage can be defined as the next achievable state that retains the operational state of the organization. A work package or project is a set of activities to realize this intermediate state. Each intermediate result will bring the organization closer to the envisioned end state.

In Figure 5, the identified intermediate states are depicted as green boundaries. Within these boundaries, the change from current state to the new (intermediate) state is shown, with the new state in red. For each state, the activities must be worked out to realize each defined intermediate state. It is to be noted that Figure 5 is merely an example of how the intermediate states can be reached. Because we need to be thinking critically, this approach can change according to the specific needs of a process.

The process lane shows how the different steps, appearing from different processes (Process A, K and Z) are connected in the data set. At this stage we consider the process and the data-oriented mapping to be completed.

1. Optimization starts with digitalization of non-digital systems. The first intermediate state, green block 1, shows the transformation from a paper storage system toward the chosen digital storage for the particular data set. In this case the storage system for the data set is a new storage system, i.e., Db Z.
2. The next intermediate state, green block 2 shows the existing digital storage system (Db Y) will be transformed to the storage system Db Z.
3. Now that the data set is digitalized and transformed into a single storage system, the next step is to integrate this new storage system on the RAMI information layer (green block 3). For example, process step 1 from process A and process step 3 from process K both create data for the data set. Process A creates it in a digitized format at the RAMI integration layer. This data would be available throughout the process. However, process K creates it at the asset layer; in this case on paper. This means that the data are only available within process K if it is executed at the asset itself (the paper). In the previous step, we have already harmonized the data set into a single storage system. By creating the data set in the integration layer, the data set will

Figure 5: Data-oriented mapping with envisioned end state.



Intermediate step	Description
1	Transformation from manual storage system to digital storage system for data set (Db Z)
2	Transformation from digital storage system Db Y to digital storage system Db Z for data set
3	Intermediate actions for integration of the data to be taken for each process step belonging to the data set
4	Destruction of the full data set

become available for all processes. The existing processes must be modified to interact with the harmonized data set.

4. Data sets are incomplete without a plan for destruction of the data set. Therefore, an integrated method must be designed to destruct the data set at the set destruction time (green block 4).

Now we have a road map to the envisioned end state and the defined intermediate states that will enable the organization to move toward the end state. The work to realize these steps can now start.

Optimized Data Flows

In this final step, the execution of the work packages starts and the intermediate states will be implemented, bringing us closer to our envisioned end state. The work packages can be handled like any regular project within an organization. This means that not only must funding and resources be secured, but also that the validated state of systems must be maintained. The usual change control and validation activities will be used to govern the implementation of the work packages.

To manage this process, we can use the principles of continuous improvement. With this, the four-step approach becomes an iterative process. Once an intermediate state has been achieved, the following steps will be completed before we can start executing the next work package:

- The current state must be updated. All processes and process data maps must be updated to reflect the new current state. By doing so, we can acknowledge the achievements and ensure we have an up-to-date current state as a basis for further improvement.

- The effectiveness of the implemented work package must be verified. Did it realize the next step toward the envisioned end state? Are all affected processes still in an operational state? Are affected computerized systems still in a validated state? If the goals of the intermediate state have not been fully realized, this will have an impact on the defined path. Where required, any rework or additional work can either be defined as a new intermediate state or be included in the next intermediate state.
- The next intermediate state and envisioned end state must be reviewed. Is the defined end state still valid and viable? Are there new insights and/or new (emerging) technologies that could impact the envisioned end state? Realizing the end state requires mid- to long-term planning. It is not to be expected that either the organization or technologies remain static.

A review at each intermediate state will help maintain the direction toward the end state, even if this end state changes. These reviews may result in the need for corrective actions or changes in work packages. By using the "critical thinking" principles again, the required actions can be defined and incorporated into the work packages for the next intermediate states. By repeating this process for each of the intermediate states and implementing the required changes in a timely manner, we will ultimately reach our envisioned end state.

We have explained the four-step approach using a simplified single data set. In reality, an organization has many different data sets. Some will be comparable and can be grouped together in work packages and others will require separate work packages. By consistently using the four-step approach, by keeping a holistic view of all business processes and data sets, and by consistently applying the principles of critical thinking, the path to envisioned end state in a Pharma 4.0™ architecture is achievable.

CONCLUSION

Digitalization opens new horizons to achieve new levels of connectivity, transparency, agility, and productivity by applying faster and more accurate information to automated decision-making. The fundamentals of the digitalization process lie in the structure underneath the data being created, used, reported, stored, and destroyed.

Currently, in the Pharma 3.0 environment, the approach for automation is process-centric. However, moving to Pharma 4.0™, centralizing the data life cycle will lead to a data-centric approach. Each data life cycle needs to be completed and aligned to be considered a data set. In current production processes, different data sets are created for each process. Visualizing the data sets among different process steps will automatically trigger missing, misaligned, or duplicate data. Moving to Pharma 4.0™, each data set will need to be assembled at any time in any business layer. Therefore, a system needs to be in place to show the data architecture and how it interacts with various processes.

The RAMI architecture is originally a design tool, used for designing Pharma 4.0™ processes. In this representation we are not designing new processes; in fact, we are making the transformation from a current situation toward a Pharma 4.0™ architecture. Therefore, the bottom-up RAMI architecture approach, moving from the asset layer toward the business layer, is envisioned.

RAMI is used as a basis to create a data-oriented structure. By analyzing the defined data sets with the RAMI layers in combination with the storage conditions, the gaps for the data-centric approach become clear. During critical thinking, these gaps can be identified as potential issues and opportunities for optimization. Defining intermediate end states with the four-step approach is part of the process in the transformation toward Pharma 4.0™ architecture.

For the Pharma 4.0™ environment, it is envisioned to have one single source of truth entering the RAMI architecture. This will affect how processes will be designed. It is not sufficient to create a process within its own silo. In principle, a process will use data sets that are available within the information layer or create new data sets if not yet available. The process of critical thinking is needed to move forward, to envision the holistic view on data processes, and define intermediate and end states. Existing processes will change in how they need to interact with data.

Once all processes are ready for a single source of truth, the business layer can be looked at in a bidirectional view, where in the second perspective, the business layer defines how the other layers of the RAMI must be integrated to achieve the business objectives. A further goal of the RAMI representation is to create an administrative shell that fully communicates with the integrated systems, databases, applications, etc. The administrative shell contains data storage systems that allow interoperable information exchange via the communication layers. The data are stored in the information layer and then used to exchange data between functions, services, and components.

Using the four-step approach is an iterative process that will lead to the envisioned end state of one single source of truth and using the administrative shell. The key is to start the process small and work consistently and systematically through the different intermediate stages. Only when the four-step approach is complete can another level of complexity can be added, and the four-step approach started again.

To complete the definition of the end state moving toward Pharma 4.0™ production plants, the appropriate technologies to realize this end state must be defined as well. The approach described in this article also raises questions about real-time availability of the data, the speed at which data are available, availability of data to the targeted users, and compatibility among disparate systems. How this can be accomplished—and more detail about the process and data-mapping techniques—is beyond the scope of this article and will be covered by future publications.

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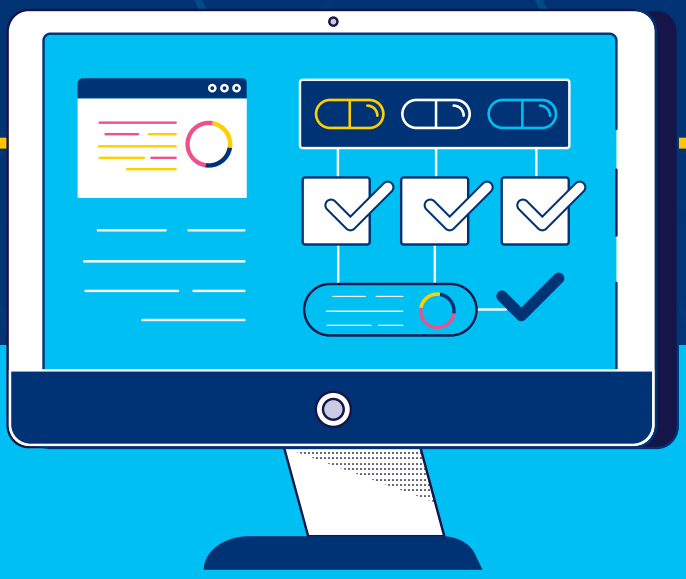

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