PHARMACEUTICAL ENGINEERING®

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March-April 2021 | Volume 41, Number 2

PHARMA 4.0™

PILLARS FOR SUCCESS

All About the Pharma 4.0™ Special Interest Group and Its Working Groups

Holistic Control Strategy: From ICH Quality Guidelines to Pharma 4.0™

Validation: The History and the Promise of Pharma 4.0™

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ON THE COVER The pillars in the graphic represent the various pillars that are part of Pharma 4.0™

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By Joanne R. Barrick, RPh


Joanne R. Barrick, RPh

Better Days Ahead

The last 12 months have felt like the slowest and fastest of times. The days drone on, yet the months fly by. I have now been working from home for a year—5% of my time at Lilly. I feel sadness for so many families who have lost loved ones and/or spent the holidays alone. Dogs and cats appearing in virtual meetings are no longer a huge distraction but a welcome glimpse of social connection.

Just at a time when the number of COVID-19 cases was skyrocketing, gathering size restrictions were being reimposed, schools were returning to virtual only, and hospitals were pushing their limits, antibody treatments and vaccines were approved. I am so proud of and inspired by my ISPE and other industry colleagues who have accomplished years of development work in a matter of months. Thank you for long hours, nights, and weekends you have devoted. Thank you for the unprecedented level of collaboration between companies, regulators, and distributors, and the sharing of manufacturing capacity, all with the common goal of conquering and overcoming this pandemic.

IMPROVED COLLABORATION AND MORE

I think we have all heard "necessity is the mother of invention." While none of us would have chosen to go through this pandemic, we have been forced to work differently and, in many cases, much better. In addition to the improved collaboration, I am amazed by the increased productivity and creativity of many working from home. The need to work differently and much better in the pharma industry was realized several years ago, consistent with the Fourth Industrial Revolution and it has been accelerated by the pandemic.

A collaborative pharmaceutical industry version of this revolution, Pharma 4.0™ (trademarked by ISPE in the EU and trademark registration pending in the US) was started in 2016 by the ISPE Germany, Austria, and Switzerland (D/A/CH) Affiliate and quickly spread into the surrounding regions. Implementation of technologies together with the operating model developed by the ISPE Pharma 4.0™ Special Interest Group are key enablers to improving manufacturing process understanding and monitoring, and facilitate modern manufacturing techniques.

This effort provides valuable, compliant guidance for accelerated process development, improved control strategies for manufacturing consistency and reliability, and real-time utilization of process data. Pharma 4.0™ principles and models facilitate having the right information at the right time, enabling better decisions at all levels of the organization. The Pharma 4.0™ mission is to accelerate transformation, innovation, and full utilization of digitalization for the benefit of patients, and this is exactly the right time to spotlight this effort in this issue of *Pharmaceutical Engineering®*.

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ASEPTIC CONFERENCE TURNS 30

I want to offer my heartfelt appreciation to the Aseptic Conference program committee for their work to present the 30th anniversary event that continues this year as a virtual event. The focus on unraveling the mysteries of Annex 1 and guiding technical modifications needed for compliance is central to this conference. It is still going strong as perhaps the industry's finest conference on sterile manufacturing, filling, and inspection processes, with many attendees participating year after year. Congratulations to Jörg Zimmermann, Dave Doleski, and the entire program committee for their continued outstanding leadership.

MOVING FORWARD

Early in the pandemic, I found comfort in "Better Days," the OneRepublic song. The chorus reiterates "there'll be better days," which keeps echoing in my head. I believe there are truly much better days, not only ahead but in the very near future. However, I will go forward with a much better appreciation of things I previously would have taken for granted, like time with family, friends, and colleagues, and travel.

The "new normal," has never become normal, and as much as we have become very effective at working remotely, there are aspects of seeing all of you face to face that cannot be replaced. I look forward to seeing many of you at our upcoming face-to-face meetings in Dublin, North Bethesda, and Boston.

I believe there are truly much better days, not only ahead but in the very near future.

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

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 By John Clarke


John Clarke

PHARMA 4.0™: The Pillars for Success

Understanding and utilization of Pharma 4.0™ technologies will be critical for students and Emerging Leaders (ELs) as they develop in their careers in the pharmaceutical and life sciences industries. To learn more, I spoke with Edoardo Schiraldi, an Emerging Leader based in Florence, Italy, who works as a Corporate R&D Business Solutions Specialist with Menarini Group, about the "pillars" of Pharma 4.0™ that ELs and others need for success with this important initiative.

Tell me about your role and how it relates to Pharma 4.0™.

I coordinate the resources working on R&D IT implementation projects, providing coaching and supervision and serving as a contact for key business stakeholders. I also manage a R&D corporate project portfolio collecting business needs and supporting the corporate directors in defining and updating the five-year plan for R&D functions. My role requires me to stay at the forefront of emerging Pharma 4.0™ technologies to incorporate and utilize them to their full potential. I also work to define the strategy of Menarini Group robotic process automation and coordinate RPA process discovery activities and project implementation.

What is your involvement with the ISPE Pharma 4.0™ Special Interest Group?

I've been involved with the SIG for the past two years, participating in monthly meetings to define the Pharma 4.0™ communications strategy for upper management. This includes the Pharma 4.0™ LinkedIn group and publishing articles in *Pharmaceutical Engineering*®. I have met many industry experts in this field and now have a network of people to reach out to for information or advice on technical challenges I encounter in my work.

What challenges do you see for companies with implementing Pharma 4.0™?

Attention and interest in the Industry 4.0 concept have greatly increased in the last decade, but there is still not enough awareness about it. Many companies in different industries have started 4.0 pilots and project implementation, but few have defined a clear long-term 4.0 strategy due to the huge initial investment required. In the pharmaceutical industry, specifics such as GxP regulations, validation processes, and patient safety have played a role in delaying exploring and implementing Pharma 4.0™ initiatives.


Edoardo Schiraldi

How can the industry overcome these challenges?

A common mistake is to consider a Pharma 4.0™ project just "IT oriented." While the IT/operational technology (OT) enabling technologies should be considered, other fundamental pillars of Pharma 4.0™ include processes, resources, organization, culture, and change management.

Investing in the right technologies requires a preliminary digital maturity assessment. Considering the IT/OT enabling technologies in relation to the current digital maturity level of the company ensures time and money will be invested in the right implementation projects. Wrong choices can waste resources and have a negative impact on the "4.0 confidence" needed to define a long-term strategy.

Understanding the main features of Pharma 4.0™ and how it can be applied to the pharmaceutical industry is essential. Then processes need to be considered and thoroughly analyzed so they can be reshaped to prepare the general framework for Pharma 4.0™ adoption. These areas are key: introduce workforce cross training and qualification in 4.0 technologies; address culture issues; adopt data integrity by design; and share information about Pharma 4.0™ and its achievements.

Many thanks to Edoardo for sharing his experience and insight into Pharma 4.0. For more information, visit the Pharma 4.0™ web page at ISPE.org/initiatives/pharma-4.0

If you are looking to get involved with your local ISPE Emerging Leaders Chapter or Affiliate, or want to start one, contact me at John.Clarke2@Pfizer.com or visit ISPE.org/membership/emerging-leader

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

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Tanya Sharma

WOMEN IN PHARMA®
and Entrepreneurship

The ISPE Women in Pharma® (WIP) theme for the month of March is entrepreneurship. This word can mean different things to different people, but WIP defines it as the creation of value. Communications, events, and activities during March will focus on supporting small businesses and encouraging leaders around the world to have the confidence, capacity, and willingness to develop and manage a business venture despite the risks that may arise with growth and profitability.

WIP events in March will show support for small businesses through interactive networking sessions that focus on women entrepreneurs. The events will include book clubs, mentor circles, and webinars and will feature industry leaders and entrepreneurs sharing their insights and stories of their experiences, accomplishments, challenges, and successes. Also, life sciences companies will share how they support start-ups and small businesses in the pharmaceutical industry. *The Bridge*, ISPE's WIP newsletter, is highlighting entrepreneurial women and men who are active in ISPE and WIP who will share lessons learned when starting their businesses.

A PERSONAL PERSPECTIVE

As a small business owner, I can share some initial thoughts about starting a business. No road that we take is easy. We must overcome fears, be bold, and be courageous. It is okay to make mistakes; these provide opportunities to learn and grow. It is okay to go slowly; premature moves can present unnecessary challenges.

Do not compare your success and scalability to other small businesses. Maintain accountability and make your colleagues accountability partners. Share your vision for your business with your communities, and recognize and give thanks to all those who support and help promote your company.

Speak often and speak up! Rather than having conversations only with your staff, it is important to reach out to obtain feedback and learn lessons from others in the industry. You do not have to have a plan for everything; sometimes, opportunities will present themselves, and you must be flexible and ready to try these new chances that arise. An idea you have may not work, but that does not mean that all ideas will fail. Keep trying and be creative. There is nothing too small or too large for a business that is starting out—all it takes is confidence and the belief that things happen to those who try.

No road that we take is easy. We must overcome fears, be bold, and be courageous.

Ginny Rometty, former CEO of IBM, said, "I learned to always take on things I'd never done before. Growth and comfort do not co-exist." For us to reach our destination, we must keep our momentum focused and not allow challenges to affect our passion and determination. We must consult with experts for thoughtful advice and acknowledge there is more than one way to accomplish goals.

Respect the opinions and suggestions of others: these can make major differences in your plans and priorities. While you may disagree, it is important to find creative ways to work with others and be open to their innovative ideas. Recognize that starting a business requires substantial time, effort, and energy, but if you are passionate about what you are trying to build, it won't feel like work. It will be fun, exciting, and highly rewarding.

Reach out to me at tanyasharma0304@gmail.com if you have questions about WIP, starting a small business, or supporting entrepreneurs just starting their journey. And if you are beginning to create your own business, good luck!

Tanya Sharma is a Partner at Assurea Consulting, LLC, and the International Mentor Circle Leader for ISPE Women in Pharma®. She has been an ISPE member since 2019.

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ISPE PHARMA 4.0™ SIG AND ITS WORKING GROUPS

By Christian Wölbeling and the ISPE Pharma 4.0™ Special Interest Group Working Group Leads

The ISPE Pharma 4.0™ Special Interest Group (SIG) launched in 2015 to provide a road map for new challenges of digitalization, Industry 4.0, and the smart factory. The SIG addresses how pharmaceutical industry stakeholders, including regulatory authorities, can achieve benefits from Pharma 4.0™ initiatives.

The Pharma 4.0™ SIG has established cross-functional working groups to collaborate in a matrix across all stakeholders in development, quality, manufacturing, engineering, and IT, as well as contractors, technical solution providers, consultants, and operators. The goal is to work on specific topics while engaging all stakeholders and breaking down industry silos.

The lack of cross-cultural thinking, working and acting in silos, and the lack of standardized and harmonized integration were identified as the biggest hurdles to establishing digitalization, which is the systematic digitization of the organization's business processes by applying a digital transformation process. Overcoming these hurdles through the coordinated efforts of the SIG and its working groups enables data-driven and transparent decision-making as the key benefit for the organizations that implement Pharma 4.0™. The transparency needed to accomplish this can be uncomfortable for some stakeholders and involves shifting areas of responsibilities, so the SIG and its working groups take an interdisciplinary and cross-functional approach to create awareness, understanding, and respect. The goals are to engage the overall ISPE community and to contribute to ISPE projects with participation from all Communities of Practice (CoPs). Figure 1 shows the SIG's mission statement.

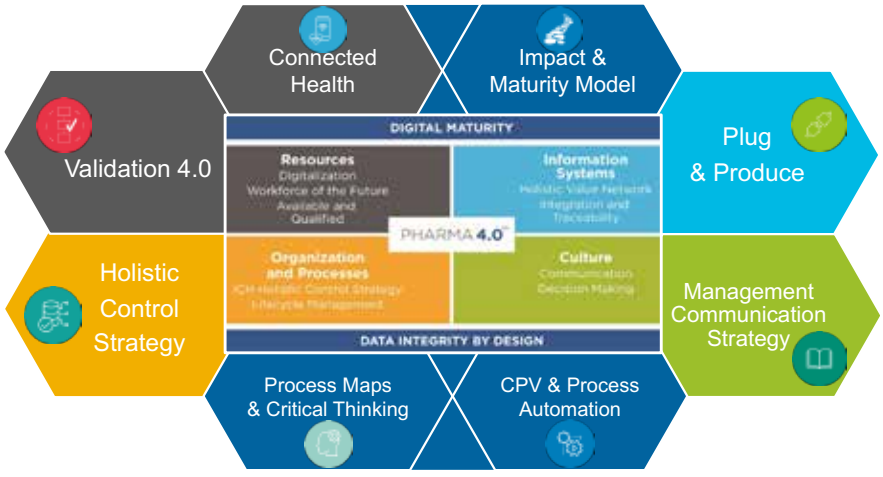
PHARMA 4.0™ HISTORY

The idea of the Pharma 4.0™ SIG was born with ideas written on a napkin in a small restaurant in Basel, Switzerland, in 2015, as Christian Wölbeling and fellow ISPE D/A/CH Affiliate Board Member Marcel Staudt were discussing fundamental problems of automation, integration, and validation in commercial manufacturing. They identified harmonized integration of the shop floor equipment interfaces as one of the obvious and largest benefits of holistic digitalization, but they also understood that all stakeholders—the pharma industry, equipment suppliers, and software partners—needed to collaborate to create an efficient and effective integration scenario to successfully apply Industry 4.0 concepts being used by other industries.

It was also clear that the control strategy defined by ICH Q10 [1] needs a holistic approach and holistic data-driven strategy along the ICH product life cycle. This holistic view derives from material sourcing and development via tech transfer up to commercial manufacturing. The perspective is patient-centric and spans the complete product life cycle, from the development supply chain to the production supply chain, the distribution supply chain, and, ultimately, the patient or customer. These three supply chains need a sound product and life-cycle data concept based on a clear data integrity by design–based approach as defined by the *GAMP® RDI Good Practice Guide: Data Integrity by Design* [2].

Figure 1: ISPE Pharma 4.0™ North Star (mission statement).

Figure 2: The Pharma 4.0™ SIG working groups.



WORKING GROUPS

The following sections introduce the working groups within the Pharma 4.0™ SIG. Figure 2 lists all of the working groups.

Plug & Produce

Wolfgang Dedden, Klaus Sauermann, and Christian Wölbeling started the first Pharma 4.0™ working group, Plug & Produce, in 2017. Early on, SIG members identified harmonized integration of equipment interfaces from the shop floor up to the enterprise resource planning system and across the whole organization as one of the largest benefits to digitalization for pharma and biopharma companies.

In March 2020, leadership for Plug & Produce transitioned to Josef Trapl and Wolfgang Winter. Since then, the working group has restructured, refined its vision and mission (Figure 3), and recruited new participants.

The working group's vision is to achieve a global Plug & Produce standard that enables end-to-end integration through vendor-agnostic connectivity, interoperability, and big data analytics. The mission is to define, in collaboration with other organizations, the user- and data-centered methodology for vendor-agnostic system integration, building on best practices, frameworks, and existing and emerging standards for interoperability. The key contributions and focus of the Plug & Produce

Figure 3: Pharma 4.0™ Plug & Produce working group vision and mission.

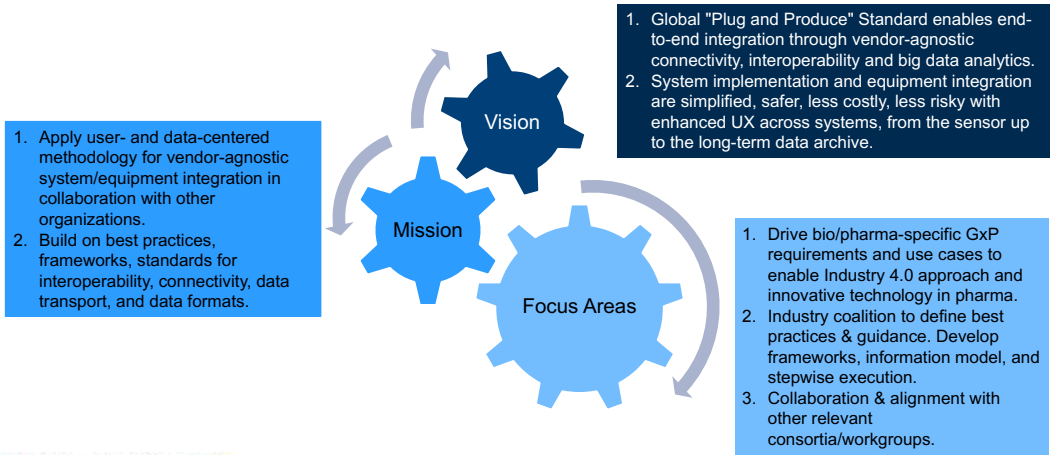
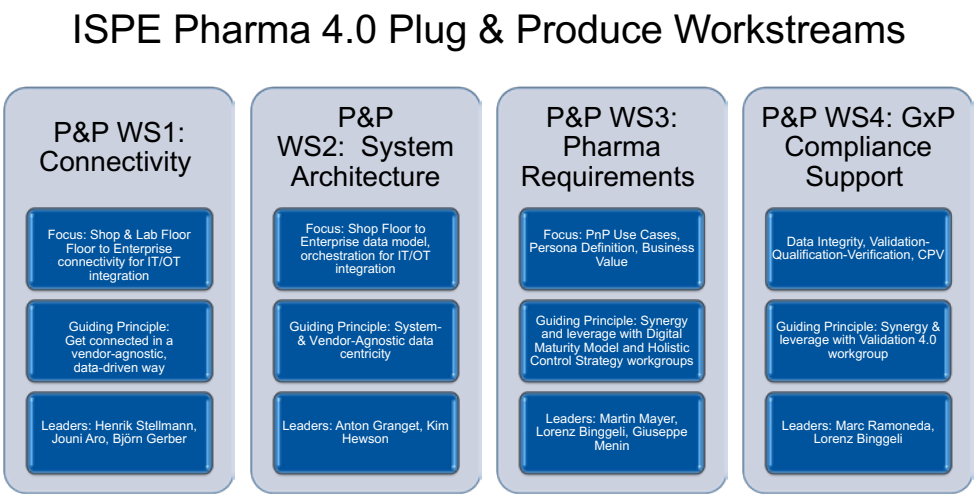


Figure 4: Pharma 4.0™ Plug & Produce working group workstreams as of December 2020.



working group are (a) the pharma-specific requirements that will make Industry 4.0 applicable across pharma and biopharma companies, and (b) being the guiding industry coalition to define Pharma 4.0™ best practices in close collaboration and alignment with other relevant consortia.

As of December 2020, the Plug & Produce working group had about 40 active members from pharma/biopharma, academia, consulting, and suppliers of automation and engineering, package machines, software, and analytical lab systems. The working group reorganized into four interactive, interdisciplinary agile workstreams (Figure 3).

Each Plug & Produce workstream drives a specific proof-of-concept (PoC) project for a specific equipment class to demonstrate the viability of the plug and produce approach. The PoC projects are chosen to enable higher-level use cases, including, but not limited to, drop-in (plug-in) deployment of prequalified equipment, system-wide audit trail review, and predictive prevention of quality-relevant incidents.

For further information, contact the working group leaders: Josef Trapl: Josef.Trapl@Takeda.com and Wolfgang Winter: wolfgang.winter@agilent.com

Management Communication

The Management Communication working group launched during the 2018 ISPE Europe Conference in Rome to help key decision makers in middle and top management better understand how

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Pharma 4.0™ can create the appropriate conditions to achieve successful 4.0 projects. The group's aim as defined in the working group charter is to "define, structure, and execute a compelling, lean, and management-focused communication strategy to promote Pharma 4.0™ initiatives" so that technical information is more understandable at the manager level.

The working group's goals are to orchestrate communication among the SIG's working groups; be available and open to non-ISPE members to showcase Pharma 4.0™ benefits; promote the adoption of innovative technologies and foster Pharma 4.0™ awareness; provide relevant business value and key performance indicators using communications suitable to the target audience; and share industry best practices and real-life use cases.

The working group uses LinkedIn to provide a larger professional audience with news, updates, and opinions. The ISPE Pharma 4.0™ LinkedIn group currently has more than 300 members.

The group also writes articles and creates presentations to highlight management-relevant aspects of Pharma 4.0™ and explain 4.0-enabling technologies to nontechnical audiences. It issues awards to promote excellence in 4.0 projects, and it conducts periodic surveys to monitor the status of Pharma 4.0™ perceptions, challenges, and projects. The most recent survey had 10 questions, and collected over 400 responses from around the world. Findings from the most recent survey were presented during the virtual ISPE Pharma 4.0™ Conference in 2020.

Ten volunteers are now active in this working group. For further information, contact the working group leaders: Davide Smaldone: dsmaldone@menarini.it and Teresa Minero: t.minero@lifebee.it

Holistic Control Strategy

The Holistic Control Strategy working group supports a wider scope of traditional control strategies with the goal to have real-time information and allow data-based decisions. This objective is central to digitalization of data and Pharma 4.0™.

The working group first worked on a definition for holistic control strategy and described how it extended the scope of the traditional product quality control strategy defined in ICH Q8 [3]. The wider scope encompasses the full value network of pharmaceutical operations, covering the upstream as well as the downstream supply chain. It goes beyond the processes for which GMP rules are defined by also covering relevant safety topics, such as impurities from starting materials to the source of origin, and the market environment of a pharmaceutical product, such as its performance in the market (effectiveness of the product and market acceptance). The Holistic Control Strategy working group will also focus on issues related to market availability of drugs, such as installing early warning indicators for drug shortages and helping with anti-counterfeiting initiatives. As an essential tool, quality risk management according to ICH Q9 [4] is recommended.

As a next step, the working group will focus on how to monitor holistic control strategies, including structural questions and principles to address before discussing the technical feasibility of implementation. For instance, who will need which information, when will they need it, and, most importantly, why? Another question concerns the appropriate roles of humans and machines/computers in the data-based decision-making process.

Further questions deal with regulatory oversight: What types of interfaces can be used between manufacturer and regulators, and can they be used for remote inspections? How can computers play a role in organizing quality oversight? How should a quality system operate when a holistic control strategy is implemented? Which level of "digital maturity" is needed to implement a holistic control strategy? Can a holistic control strategy be implemented through a staggered approach or used as a tool to fix weaknesses in an organization or product? Or must it be the starting point?

For further information, contact the working group leaders: Nuha Al-Hafez: nuha.al-hafez@merckgroup.com and Lothar Hartmann: Lothar.Hartmann@phact.ch

Validation 4.0

Launched in 2019, the Validation 4.0 working group works with GAMP® SIGs, other ISPE groups, including CoPs, and the industry at large to develop and publish validation guidance for the pharma and biotech industry to maximize digital innovation while maintaining acceptable control and compliance.

The ultimate goal is to define a holistic validation approach to enable the pharmaceutical and other life sciences industries to realize the Pharma 4.0™ vision and support ongoing adoption of digital innovations in a controlled way. The goal is being achieved by describing and illustrating an approach that incorporates all aspects of validation in an integrated way and shifting the validation focus toward control strategies focused on process and data risk mitigation. Control of data risks means the process and products produced can be controlled.

The working group is seeking to use process and data flow knowledge from the full product life cycle, starting with data from product discovery and product and process development through postmarket activities. Using continuous flow data from all inputs can help verify in real time that control strategies are in place and effective, as required by ICH Q12 [5]. This approach is based on many quality by design (ICH Q8) principles for product and process knowledge, using a risk management (ICH Q9) framework for risk assessment and risk control through three stages of validation [3, 4].

The working group is also seeking outlets such as instructional, educational, and collaborative forums for engaging with the industry. The working group aims to bring together the various aspects of validation in a holistic view and help focus validation where value is continuously added, rather than in traditional and mostly serial approaches.

For further information, contact the working group leaders: Michelle Vuolo: michelle@michellevuolo.com and Tony Margetts: tma@factory-talk.com

Impact & Maturity Model

The Impact & Maturity working group is focused on how to identify barriers to Pharma 4.0™. As noted earlier, on the journey toward Pharma 4.0™, several barriers can significantly slow or even disrupt the progress of implementation. They exist in each element and maturity level of the Pharma 4.0™ model, and in each organizational level. Identifying these barriers as early as possible helps organizations build strategies to avoid or to address them.

For example, in the pharma industry, the huge amount of data collected by manufacturing and quality control equipment and within quality systems is underutilized. Analyzing all existing data and predicting potential risks will allow the industry to bring new products to the market faster and improve stability of the supply chain for marketed products.

For further information, contact the working group leaders: Manuela Gottschall: manuela.gottschall@roche.com, Jens Solsbacher: Jens.Solsbacher@sanofi.com, and Thomas Lee Johnson: tj@agileimmersive.com

Connected Health

The Connected Health working group advocates using the socio-technical model developed at the Tavistock Institute, London, for optimization of healthcare management and delivery of drug products, combination products, in vitro diagnostics, and medical devices, among other products. The socio-technical model marries people and technology to produce better outcomes. It focuses on how technology can advance healthcare services and collect feedback from patients throughout the product life cycle.

With the increase in technology and the greater accessibility of data to the general public and industry/healthcare systems and payors alike, bringing together these aspects of a product life cycle can help provide better patient outcomes.

This working group was formed to consolidate elements across the GxPs and incorporate aspects of real-world evidence and data to provide insights to facilitate improving patient experiences and outcomes. Although in its infancy, the Connected Health working group aims to provide guidance for digitalized healthcare management across the value network.

Colleagues joining the group will bring additional expertise across the GxP landscape to "connect the dots." The Connected Health team looks forward to strengthening their team and providing first points for discussion in the coming year.

For further information, contact the working group leaders: Rebecca Stanbrook: rebecca.stanbrook@novartis.com and Nuha Al-Hafez: nuha.al-hafez@merckgroup.com

Process Maps and Critical Thinking

The Process (Data) Maps and Critical Thinking working group is defining guidance for using critical thinking to create process and data maps. The objective is to harmonize and optimize information flows supporting attributable, legible, contemporaneous, original, and accurate (ALCOA) data, the data life cycle, and other principles that fit the integrated environments of the Pharma 4.0™ world.

Pharma companies are struggling with data exchange because of a lack of harmonized and consistent information flow supporting regulatory needs. Different standards and data formats require large amounts of resources (time, money) to provision, clean, and use the data in a fully useful way. This hinders the full realization of digital maturity and Pharma 4.0™ implementation.

The working group seeks to enable quality and data integrity by design by applying known standards (such as ICH Q8–Q10 and Q12) [1, 3–5], starting with current state processes and data. The group will define standardized ways of applying critical thinking with the target output to redesign and optimize the future state of process flows, data flows, and interfaces to harmonize data formats, reduce the amount of data, focus on relevant data, avoid media breaks, improve data availability, and implement ALCOA and findability, accessibility, interoperability, and reuse (FAIR) principles. The Reference Architectural Model Industrie 4.0 (RAMI 4.0) model is taken into consideration in critical thinking, with the intent to standardize what type of data is used and where it is visible.

For further information, contact the working group leaders: Emmie Heeren: Emmie.Heeren@propharmagroup.com and Michelle Vuolo: michelle@michellevuolo.com

CPV & Process Automation

The working group dedicated to continued process verification (CPV) and process automation was set up in 2020. Its 17 active members from pharmaceutical companies and technology providers offer multidisciplinary insights and experiences from engineering, IT, and automation, quality, and regulation perspectives. With this multidisciplinary approach, three working lines have been defined, each one assigned to a specific team.

CPV Subgroup

With 10 active members, this subgroup works on the application of the Pharma 4.0™ concept to ongoing/continued process verification, or continuous verification of the process. Specifically, the team will explore possibilities of integrating all the necessary data sources to have real-time process information, as well as standardizing the automated statistical treatment of data to simplify generation of CPV reports and evidence that processes are in a state of control. The group worked on a survey on current CPV practices, and the results will be published by ISPE in 2021.

Artificial Intelligence (AI) Use Case 1

Three active members are working on a real use case at mABxience (Leon, Spain). The use case involves applying machine learning to assess whether data generated by a water for injection plant can be effectively used for prescriptive maintenance. Specifically, the aim is to know in advance when the plant needs to be maintained based on the model-predictive indications (condition-based maintenance). A PoC was completed in 2020. Further model-building and qualification of the results has been scheduled for 2021.

AI Use Case 2

Four active members are working on a real use case at Almirall (Barcelona, Spain). In this use case, machine learning is being applied to data generated by a drying process, with the aim of optimizing energy efficiency and cycle times, among other goals, keeping a high quality level. A PoC was completed in 2020, and industrialization and extension of the model to similar equipment has been scheduled for 2021.

For further information on the working group, contact its leaders: Alicia Tebar: atebar@qualitybydesign.es and Miquel Romero Obón: miquel.romero@almirall.com

FOR MORE INFORMATION

The Pharma 4.0™ SIG working groups are always looking for new volunteers. The only prerequisites are ISPE membership and technical and/or managerial expertise to support the goals of the SIG. Contact the working group leads identified above and visit the Pharma 4.0™ page on the ISPE website for more information: ISPE.org/initiatives/pharma-4.0

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ISPE Pharma 4.0™ Working Group Leads

Nuha Al-Hafez, Manuela Gottschall, Lothar Hartmann, Emmie Heeren, Thomas Lee (TJ) Johnson, Anthony Margetts, Teresa Minero, Miquel Romero Obón, Davide Smaldone, Jens Solsbacher, Rebecca Stanbrook, Alicia Tebar, Josef Trapl, Michelle Vuolo, Wolfgang Winter, Christian Wölbeling, and Thomas Zimmer

About the author

Christian Wölbeling is Executive Industry Advisor & Senior Strategic Account Manager at Körber Pharma Software, Lüneburg, Germany, which supplies manufacturing execution systems (MES) and manufacturing IT solutions for the pharmaceutical and biopharmaceutical industries. He holds a master's degree in mechanical engineering. After more than 28 years working in life sciences manufacturing IT, Christian has extensive experience in all GMP-related processes. He has been active in ISPE as founder and Chair of the Pharma 4.0™ Special Interest Group, ISPE GAMP® MES Special Interest Group Co-Chair, ISPE GAMP Member at Large of the European Steering Committee, PAT & Lifecycle Control Strategy CoP Steering Group Member, and ISPE D/A/CH Affiliate Board Member. He was named a Pharma Industry Leader by *Pharmaceutical Engineering*® in 2020. Christian has been an ISPE member since 1998.

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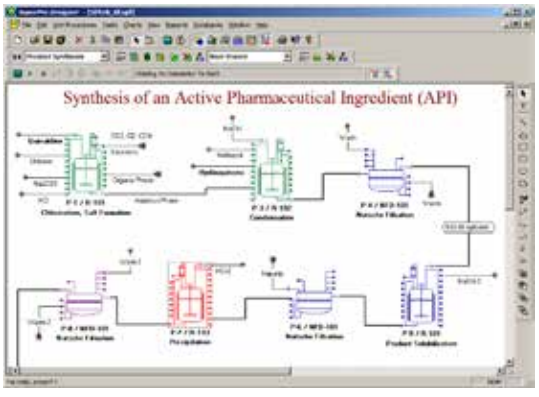

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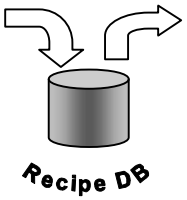

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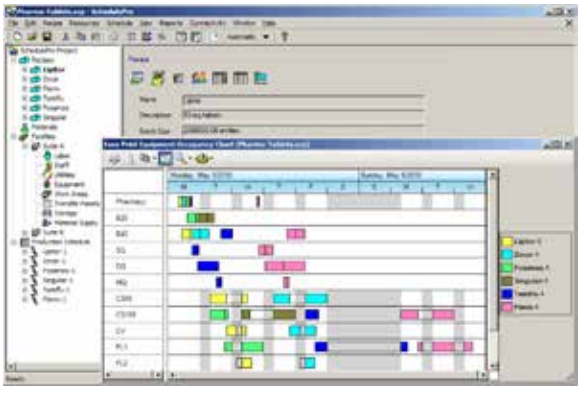

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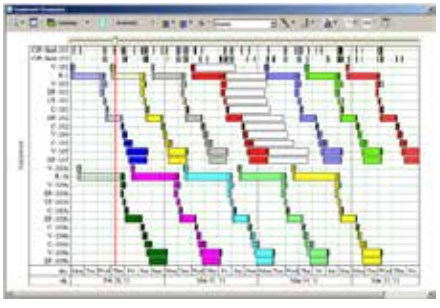

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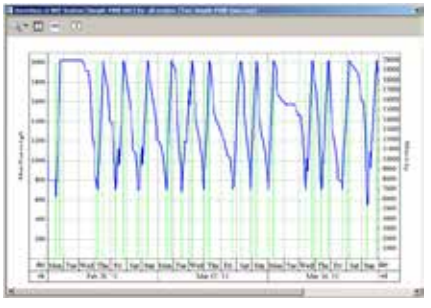

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HOLISTIC CONTROL STRATEGY:
From ICH Quality Guidelines to Pharma 4.0™

By Nuha Al-Hafez, Theresa Allyn, Yvonne Duckworth, PE, Robert W. Landertinger Forero, Lothar Hartmann, PhD, Line Lundsberg-Nielsen, Daniel J. Roberts, Joost Van Den Broeck, and Thomas Zimmer, PhD

The fourth Industrial Revolution (also known as Industry 4.0) is the era of smart machines, storage systems, and production plants that can autonomously exchange information, trigger actions, and control operations free of any human intervention. To ensure future success in the delivery of therapeutic medicines to patients, it is imperative that the pharmaceutical industry move deeper into the fourth Industrial Revolution and embrace increasingly advanced levels of digital maturity through Pharma 4.0™. This article discusses how holistic control strategy can be a bridge from established industry guidelines (ICH Q8–Q12) to the Pharma 4.0™ operating model.

Pharma 4.0™ responds specifically to the question, "How does the pharmaceutical industry embrace and apply Industry 4.0?" The objective is to improve quality and efficiency and make compliance an automatic and seamless part of the quality system. Holistic control strategy is a key to achieving this goal because the holistic approach uses digitization (converting information into a computer-readable format) to enable real-time evaluation of the entire value network and optimize management decisions.

WHAT IS HOLISTIC CONTROL STRATEGY?

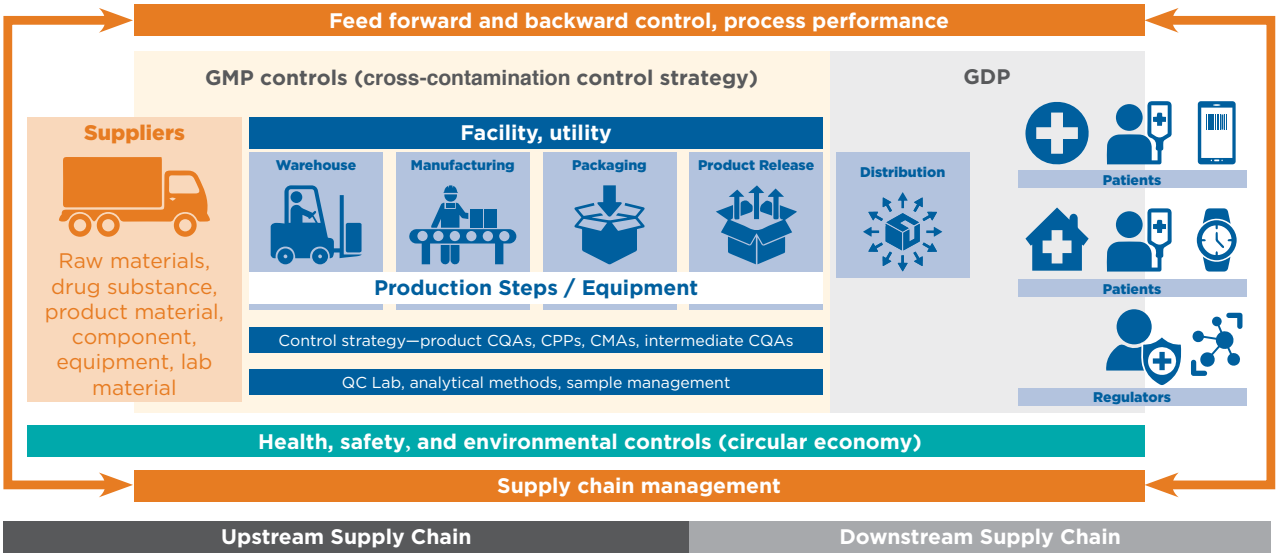
Holistic control strategy [1] has a wider focus than the manufacturing control strategy described in ICH Q8, Q10, and Q11 [2–4] or the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme's "Good Practices for Computerised Systems in Regulated 'GxP' Environments" [5]. ICH Q10 [3] defines "control strategy" as a strategy to ensure that the final product will meet the acceptance criteria of the approved product for patient safety, product efficacy, and quality. The product control strategy controls what is critical to ensure product quality, such as critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs) [2, 4]. However, to maximize the advantages of connectivity, digitization, monitoring, control, and real-time data-driven decisions across the entire value network—including pharmaceutical operations, planning, sourcing, patient feedback, regulator feedback, and market feedback—organizations must move from product control strategy to holistic oversight of product quality and performance.

"Holistic" means the complete view of something, including all influences and all possible contexts. Holism in science is an approach to research that emphasizes the study of complex systems. Systems are approached as coherent wholes, whose component parts are best understood in context and in relation to one another and to the whole.

Thus, holistic control strategy incorporates GMP and Good Distribution Practices (GDP) and defines the controls from a holistic perspective that will ensure product quality and clinical performance, product availability, and product improvement. These controls include material supply controls beginning with the original sources, safety and environmental controls, product distribution controls, and patient and regulatory feedback necessary to respond to quality, supply demands, and life-cycle management.

Such a holistic overview of the control strategy can only be established if the supply network or chain is well understood and digitized so relevant data can be exchanged among the different parts of the supply network. Therefore, holistic control strategy is a systematic and controlled approach for generating, monitoring, controlling, and managing data throughout the life-cycle

Figure 1: The holistic supply chain.



management of a product. It involves the identification of factors critical to the success of the Pharma 4.0™ operating model, such as organizational structure, resources, culture and information systems, understanding of company internal processes (e.g., development, manufacturing, and business), and awareness of in-house knowledge needed to perform the business.

Holistic control strategy enables data-based (electronic) decisions on all aspects of the pharmaceutical product life cycle while maintaining product quality and efficacy for the patient. Furthermore, holistic control strategy includes performance control of product life-cycle management regarding regulatory, operations, and distribution. Its scope covers supply chain and market surveillance issues, including drug demand, drug shortages, and clinically relevant activities of change management.

An organization can achieve a holistic control strategy when the appropriate, desired digital maturity level is achieved across the organization. In a holistic approach driven by digitization, a pharmaceutical quality system (PQS) becomes more effective and more efficient by creating and using real-time information for data-based decision-making.

HOLISTIC SUPPLY CHAIN

As noted, the holistic control strategy includes managing the entire supply chain, which encompasses both the upstream and downstream supply chains (Figure 1).

Upstream Supply Chain

The upstream supply chain links suppliers, their suppliers, raw materials, and manufacturing of the finished product. Drug safety, impurities in starting materials up to the original source of material, detection of unknown impurities, and medical devices and their constituents are some matters to consider when mapping the upstream supply chain for a holistic control strategy. Therefore, the suppliers of all materials used for manufacturing the product, including drug substances, excipients, single-use equipment, filters, chemicals for analytical methods, packaging material, storage containers, and so on, as well as the suppliers of the suppliers, must be covered by the control strategy for the upstream supply chain.

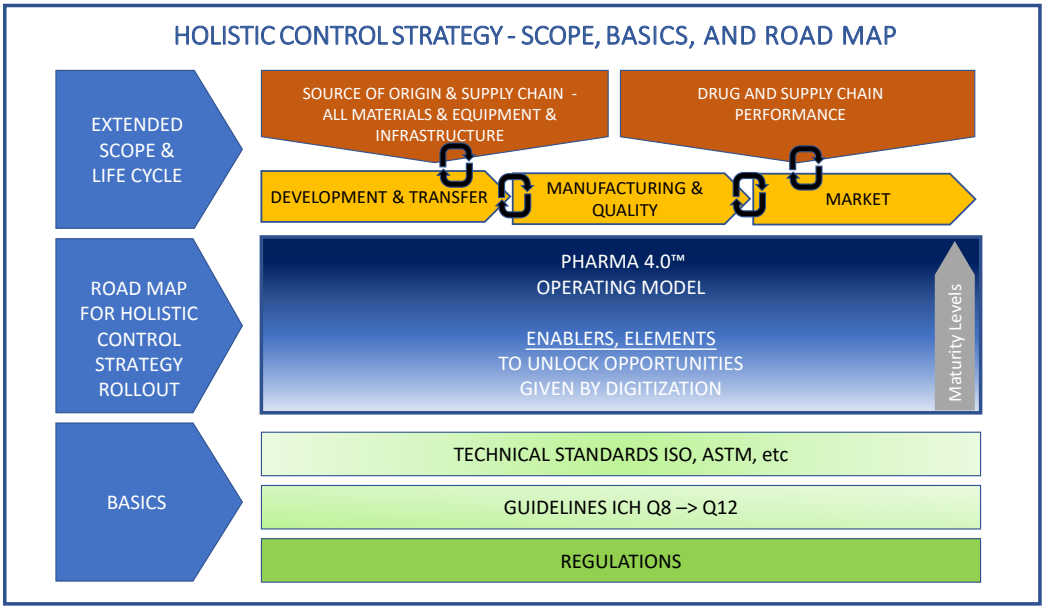
An example of why the upstream supply chain is relevant to the control strategy is the manufacture of a raw or starting material. Although the term "raw material" might imply otherwise, the material must be produced, and in some cases, production occurs in a non-GMP environment [6]. Pharmaceutical manufacturers must therefore strategically anticipate how a change in the raw material manufacturing process might impact the raw materials they buy. Many drug shortage issues have been caused when the supplier, or the supplier's supplier, changes the production process in a way that affects raw material properties, without informing customers in the pharmaceutical industry about this change.

Supply interruptions for long-lead materials, such as resins, and the safety implications of raw materials in relation to manufactured materials are other examples of high-risk concerns in the upstream supply chain. Also, the outsourcing of many pharmaceutical processes or subprocesses in the upstream supply chain to contract manufacturing organizations (CMOs) makes the supply network very complex. If the holistic control strategy accounts for this complex upstream supply chain, the impact of a change in any of the involved steps on the manufacture of the final product can be evaluated and managed in real time.

Downstream Supply Chain

The holistic control strategy's objective for the downstream supply chain is to link manufactured products, distribution, and end users (patients) in a safe manner to ensure product availability,

Figure 2: Holistic control strategy triggers.



minimize the risk of product mix-up, avoid interruption of the supply chain by falsified medicines, and control distribution to the end of the product life cycle, including environmentally safe destruction of excess products and their delivery systems.

The downstream supply chain incorporates storage and distribution, including product protection and traceability to wholesale outlets, health service providers, regulatory authorities, and, in some cases, patients directly. If the product is a connected health product, the downstream supply chain will also cover connectivity of patient data with treatment response and decisions for healthcare management. This connected health focus is wider than GDP and contributes to product life-cycle management, such as next-generation formulation based on data from the entire value network.

The holistic control strategy links the complex downstream supply chain back to manufacturing, so feedback from patients, regulators (e.g., quality issues, inspections, assessments), healthcare providers, patient associations, and payers can be used by the manufacturer to continually improve the process and control strategy, plan supplies based on real-time demand, and enable proper product life-cycle management activities in line with ICH Q12 [7]. For example, in personalized medicine, information about patient responses can be used for product and process improvement, or even for defining the treatment and product demand.

DESIGNING A HOLISTIC CONTROL STRATEGY

The design of a holistic control strategy (see Figure 2) requires a monitoring, control, and decision-making system to address key questions such as:

- Who needs what information, when, and why?
- How can regulators be enabled to make effective and efficient oversight of such a complex system?
- How can decision makers be supported? For example, in the future, what types of decision-making can we delegate to computers, and where will human accountability for decisions start? Will regulators ever authorize computers to make decisions without human interference?

The ICH quality guidelines serve as a starting point and the Pharma 4.0™ operating model (Figure 3) is a framework for designing the holistic control strategy.

ICH Quality Guidelines

The ICH quality guidelines define science- and risk-based principles. Of particular note, ICH Q8 [2] and Q11 [4] focus on pharmaceutical drug product and drug substance development, ICH Q10 [3] addresses the PQS, and ICH Q12 [7] covers product life-cycle management. Together, these guidelines can be the foundation for a new, digitization-enabled industrial control strategy with a wider scope. Additionally, when establishing a holistic control strategy, ICH Q9 [8] remains a helpful method for evaluating the associated risks, determining the level of formality and documentation commensurate with the level of risk, and supporting risk-based decisions. The overall goal is to come closer to real-time and data-based decisions.

The holistic control strategy helps implement the science- and risk-based principles effectively by using digitized data in a transparent environment. Digitization allows organizations to better apply the approaches of the ICH guidelines mentioned here.

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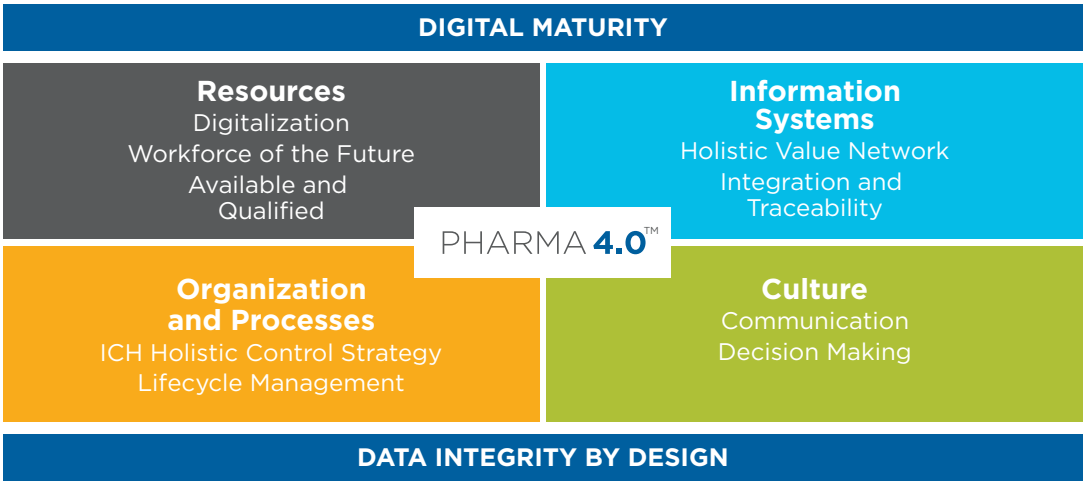
Figure 3: Pharma 4.0™ operating model.



Pharma 4.0™ Operating Model

The "how to" steps of holistic control strategy are embedded in the Pharma 4.0™ operating model (Figure 3). In the following sections of the article, the individual elements of this model—resources, information systems, organization and processes, and culture—and related success factors are discussed.

Creating an overall picture of trigger points for a holistic control strategy helps strategists visualize connection points and synergies, thereby creating transparency for all stakeholders involved. This enterprise view may lead to "blueprints for technology" or dosage form–specific holistic control strategy templates that help build a common understanding and provide insight about why the organization is doing what it is doing in the area of product development. Ultimately, these efforts will aid the organization in achieving an integrated-network mindset that may further advance organization-wide digital maturity.

Resources

When applying the Pharma 4.0™ operating model to holistic control strategy, cross-functional, multiskilled teams considering the entire scope of the product life cycle are essential. In a digitized environment, the human element remains a key success factor.

For product development, qualified cross-functional teams should be defined and made available from the beginning of the life cycle. The optimal makeup of such teams will include experts in the following areas: development, manufacturing, quality, engineering, regulatory, supply chain, digital technology, connected health, statistics, market feedback, and sales. Experts in other areas should be added to the team as appropriate.

The primary task of this cross-functional team is to holistically define the scope and trigger points for performance control of a pharmaceutical product, as shown in Figure 2. A major benefit of having a cross-functional team is team members can provide different perspectives and thoughts on possible risks involved with a process. It is important to assemble this team and identify the roles and responsibilities of team members early in the risk management process.

The commercial manufacturing process needs to have performance attributes during the commercial life cycle, including feedback loops. Those attributes should be considered as early as possible. The needs of patients and customers should be transparently integrated into the performance attributes.

Knowledge management and systems should be designed to ensure employees have information digitally available at the right time, at the right quality, and as completely as required by the purpose, in the right system for decision-making processes.

It might be useful to identify product sponsors who have a holistic view of product development and the technology landscape, leadership experience, and communication skills to negotiate with key stakeholders during development and life-cycle progression.

The provision and distribution of resources within a company is ensured through management commitment. For the PQS, it is extremely important to distribute available resources across functions to ensure all necessary tasks can be performed in compliance with regulations. Highly qualified personnel are needed in all areas, and the following must also be provided:

- Sufficient human resources
- Enough money to fund performance of the assigned tasks
- Necessary infrastructure
- Sufficient time to accomplish the work
- Priorities aligned with quality risk management (ICH Q9) principles [8] and knowledge management

As noted earlier, in a digitized environment, some aspects of the PQS will be taken over by computerized systems, making the interface between machines and people crucial. To carry out activities and decisions in the desired way, the computerized

systems must be fed the right information by humans. Therefore, a holistic control strategy should carefully consider how this will work.

For product life-cycle management, providing a framework to facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner should result in a win-win situation for both industry and regulatory authorities. For example, as a part of the holistic control strategy, different approaches can be used alone, or in combination, to identify established conditions (ECs) for manufacturing processes, as defined by ICH Q12 [7]. The performance-based approach to identify ECs is only be possible after the organization invests in resources to develop data-based models, preferably during R&D for new products and in commercial operations for legacy products.

Organization and Processes

Integrated end-to-end processes across the organization, without silos, are needed to enable the creation of transparent and effective workflows. Business processes are subject to the holistic control strategy, and they need owners with clearly defined holistic roles and responsibilities to ensure that all parties involved collaborate and are aligned with common goals and targets.

Integrated (computerized) systems are connected to these business processes. Therefore, the business owner's responsibility should be flexible and allow easy and reliable change management to accelerate development and time to market, in accordance with quality risk management principles, such as the ultimate priority of patient health.

Because systems are subject to the holistic control strategy, it is important to have proper input from the end users and stakeholders of the systems within the strategy's scope. The first step is to determine the needs of the end users throughout the organization early in the development stage of the process. Additionally, the organization should implement a "sandbox" platform where cross-functional users of the system can provide input into both the design and relevant outputs from the system to ensure appropriate data-based decision-making at all levels of the organization.

For example, the business processes and integrated computerized systems should facilitate proper knowledge transfer between development and commercial operations because holistic control strategy starts with having the appropriate information available at all steps across the value network. To institute a lean digitalized environment, the documentation and approval requirements should be standardized and minimized as much as possible based on the related risk for systems and/or equipment of similar types.

Access to high-quality data is a key success factor in product development, and robust and well-run data management is required to consistently deliver high-quality products throughout the product life cycle. It is essential for the organization to have optimal systems to collect, store, clean, and sort data. Wherever possible, the data management should be automated to avoid the risk of variance or errors related to human interventions.

The organization should also eliminate "automation islands" (automated systems that can't communicate with other systems) wherever possible. When automation islands are absolutely needed, strategists will need to determine how to manage their operations within the integrated digitized environment. If a process requires human intervention, the strategy should clearly establish clear and standardized data creation principles so that information may be leveraged easily, via automation wherever possible, throughout a product's life cycle.

For all these organization and process measures, an integrated and automated self-inspection process can be supportive. Additionally, it may be prudent to define a business process for establishing a product's holistic control strategy itself. A critical element of this business process is collecting, consolidating, and making available incoming information and then driving data-based decision-making at all levels of the organization.

Overall, the holistic control strategy will include the product view, the process view, and the systems view. All work is reflected in data.

As an organization advances its digitized operations, most of the data used during a management review of products, processes, and systems will become compiled by computerized systems. Data can be prepared and made available very quickly, which will allow senior management to react in a timely manner and make data-based decisions in a transparent, logical, and real-time way.

All these activities are guided by the application of best practices in quality risk management and knowledge management. These techniques are necessary to assess the robustness of the created data that become the basis for taking further decisions, made today by managers and in the future by machines. These aspects will also be part of a holistic control strategy.

In product life-cycle management, the details of ECs and the associated reporting category will depend on the extent to which the company can apply knowledge from product and process understanding (i.e., development and experience accumulated throughout the product life cycle) to manage risks to product quality. To enable a holistic control strategy, the organization should transition from a parameter-based approach to a performance-based approach for identifying ECs.

Many postapproval CMC changes could effectively be managed by the company's PQS, reducing the need for extensive regulatory oversight prior to implementation. However, this requires a mature PQS to accommodate such changes. Organizations can benefit from using an automated and standardized risk-based process to determine which changes could be managed through PQS and which changes would require regulatory submissions.

Information Systems

Similar to the organization and business processes, the requirements for information systems, as part of the organization's computerized systems, should be designed prospectively and aligned with process and digitization requirements to enable an optimal digitalized environment. In this environment, information

systems will capture experimental, study, and analytical data in addition to process information, and sophisticated information systems will be responsible for automating most PQS maintenance. Also, timelines will be adhered to as programmed; documents can be automatically updated according to the available data of the entire computerized system; manual documentation will be reduced to a minimum; and information systems can be programmed by humans to make some decisions on their own. All of this will lead to a higher degree of compliance with regulations and accelerate processes.

Additionally, a new concept of connected databases and computerized systems will address questions regarding who needs what data, when, and why. This connectedness is needed to structure the big data management capabilities of computerized systems used in quality systems of the future.

During the early stages of information system development, IT stakeholders should help evaluate how data will be stored, reviewed, backed up, and retrieved throughout the life cycle of the system. A risk evaluation early in the process should be used to identify and understand the critical data points to capture and review to make product quality–based decisions. Subsequently, the critical data should be readily available and accessible to all appropriate stakeholders in the organization; this demonstrates an appropriate level of digital maturity.

Furthermore, technical processes should be designed to have the capability of a "digital twin" as early as possible, reflecting the product and process control strategy. Input, output, and controls, as defined by the control strategy, should be digitized through a qualified interface embedded in a valid (technical) process. All of the organization's standard operating procedures (SOPs) should be digitized and available online at all times. Also, a system architecture connecting all functions relevant for the product in development, including a master data management architecture, should be available.

In an organization that has optimally advanced along the digital maturity spectrum, the collective (product and process) data platform should be readily available and accessible to all appropriate experts. From the technology perspective, a major strategic task is determining, in a holistic way, what types of systems, platforms, and interfaces are required to connect all engaged functions and to collect, store, clean, and prepare the process and product data. This will be a hallmark of a state-of-the-art holistic control strategy. A common set of user requirements and enterprise functionality, including interface standards, might convince industry stakeholders of the value of developing such systems.

Among the systems typically included in a manufacturing facility are the overall process control system, site data historian, manufacturing execution system, laboratory information management system, enterprise resource planning system, and computerized maintenance management systems. These systems typically require some level of integration. Building information management systems (e.g., systems using environmental monitoring data, room classification systems), electronic laboratory notebooks, and digitized SOPs are additional systems that can be included the integration strategy. Integration among all systems is very important for achieving the desired level of digital maturity.

Effective integration among systems has multiple benefits. It allows operators and users to have access in an organized manner to data from various systems, and it permits regulators to access data as required for review, with remote access a possible option. Such external engagement would be defined by established protocols based on defined criteria or content readily available to regulators through routine means (electronic common technical documents, PQS and annual product quality review documents, etc.). In these ways, system integration may also help accelerate the submission approval process by providing transparent access to application data during a regulatory preapproval inspection.

Culture

Though digitization creates new opportunities for implementing a holistic control strategy, an organization cannot achieve its holistic control strategy goals if the cultural environment is inadequate. Specifically, creating a culture of transparency and trust within an organization is a key aspect of implementing a holistic control strategy.

In general, cultural changes are driven from the top down. Breaking down organizational silos is a critical part of the cultural change needed to support a holistic control strategy, and this is best accomplished with support and endorsement from senior-level leadership.

When operations and systems are digitized, a company no longer needs classical multi-level departments. Instead, it needs trained and multi-skilled employees who can function as experts and decision makers in a process-oriented lean organization. For example, in the future, the quality unit will no longer need staff to review batch records because this work will be done electronically. However, the quality unit will need workers with high levels of statistical competency to evaluate and assess the robustness and reliability of available data. Furthermore, these employees will need to understand the process and take ownership of it.

Another cultural change required for a holistic control strategy implementation is greater transparency between organizations and regulators. Supported by big data technological applications that help facilitate mutual transparency, a culture of openness, trust, and confidence between regulators and industry could encourage regulators to reduce the frequency for inspections or shorten the time required for the submission approval process.

Trust-building factors include the establishment of clear rules for information sharing between companies and regulatory agencies, with a clear, shared understanding of why information is shared. This culture may be built intentionally through iterative demonstrations of mutual trust between marketing authorization holders and regulators. A natural starting point might be for the organization to grant health authorities limited access to the PQS to enhance transparency and speed of approvals; then, as the

expectations of this exchange are normalized, the parties could consider expanding information sharing for other purposes.

When implementing a holistic control strategy as a risk-based system, it is important for leadership to communicate that this effort is embedded in a company-wide continuous improvement initiative to ensure quality, improve efficiency, streamline operations to make the daily work easier for employees, and make more real-time, data-based quality decisions.

LOOKING FORWARD

This article has outlined the rationale for adopting a holistic control strategy that covers the entire product life cycle and explained in broad terms what is required to achieve this goal. An important next step on this journey will be exploring use cases that detail how digitization and knowledge management affect the monitoring of holistic systems, as well as how to create the right management oversight. Additionally, we envision providing use cases about regulatory considerations.

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Lothar Hartmann, PhD, obtained his diploma and PhD in technical chemistry from the Technical University of Berlin and worked more than 28 years for Hoffmann-La Roche and Johnson & Johnson in various functions in global and local quality. Today, he works with PhACT as Managing Director. He has served in leadership roles for numerous organizations, such as Vice Chair of APIC/CEFIC, Chair of European Biopharmaceutical Enterprises, and Chair of BioManufacturing Working Group, and was a member of the ICH Q7 Expert Working Group. Lothar has been an ISPE member since 1996.

Line Lundsberg-Nielsen runs her own consultancy business and works as a consultant for NNE supporting clients in developing and implementing manufacturing processes for pharmaceutical products. She has spent more than 20 years in the pharmaceutical Industry. Line holds a PhD in PAT. Her work focuses on science- and risk-based approaches in QbD, PAT, control strategy, process validation, qualification, technology transfer, and Pharma 4.0™. Line has been a member of ISPE for more than 15 years and has served in many roles. She is currently the Chair of the global PAT & LCS CoP steering committee, serves on the Pharma 4.0™ SIG advisory board, and is a member of the SIG's holistic control strategy and validation 4.0 working groups.

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2020 ISPE Pharma 4.0™

VIRTUAL CONFERENCE HIGHLIGHTS

By Thomas Zimmer, PhD, Christian Wölbeling, Chloe Lang, and Teresa Minero

Through this difficult time of the COVID-19 pandemic, ISPE has remained active. At the 2020 ISPE Pharma 4.0™ Virtual Conference, 17–18 November, 174 attendees gathered online to discuss and learn about the progress of the pharma-specific industry 4.0 approach, Pharma 4.0™ (now a registered trademark in the European Union).

This article covers some highlights of the conference. Videos featuring presentations from the conference are available at ISPE.org/conferences/2020-ispe-pharma-40-virtual-conference#

AMIT NASTIK, NOVARTIS

Amit Nastik, Global Head Strategy & Operations and Local Markets Manufacturing, Novartis, opened the conference with the first presentation on his vision of Pharma 4.0™ operations. He categorized the opportunities to embrace data and digital across the pharma value chain in three areas.

- Innovation:
  - Bring clinical trials to the patients.
  - Combine medicines with cutting-edge technology.
  - Mine clinical trial data for new insights.
- Operations:
  - Streamline scheduling and shop floor control using integrated manufacturing execution systems and enterprise resource planning.
  - Automate and replace manual operations through robotics.
  - Use artificial intelligence (AI) to enable demand forecasting and integrate sales and operations.
- Engagement:
  - Transform pharma commercial models.
  - Launch excellence along the patient funnel (i.e., the customer's path from brand awareness to brand loyalty and advocacy).
  - Provide innovative digital solutions for customers.

Although there are these opportunities, Nastik noted that the pharma industry tends to be cautious about embracing new technologies for a variety of reasons: Pharma is a highly regulated industry where every change in manufacturing needs to be registered and documented. Pharma is historically a very strong, high-margin business with the focus more on developing new products than on process improvements. Additionally, top-line growth, quality, and product availability are main priorities. Hence, pharma manufacturing is much less advanced than manufacturing in other industries with regard to continuous process flow, extensive automation, supplier integration, and continuous in-process control and monitoring.

Nastik explained that applying Pharma 4.0™ levers will lead to efficiency gains across various dimensions. Advanced analytics and machine learning (ML) will support cognitive processes and require decision-making based on data and analysis. Robotic process automation will be applied to processes with a large share of manual and repetitive tasks, and physical robots will perform processes to move physical goods. All of these uses of technology will result in better buying decisions and improved flow of materials, integrated and digitalized business planning, connected sites making medicines efficiently, streamlined and faster batch release, end-to-end product traceability, and an uninterrupted supply of high-quality medicines to patients.

TERESA RODO, MERCK HEALTHCARE KGaA

Teresa Rodo, Executive Vice President Global Healthcare, Merck Healthcare KGaA, spoke on the theme "boost and sustain performance" and emphasized that the principle of "from purpose to people through performance" can help the industry successfully realize the power of digitalization.

To illustrate the "power of purpose," she recalled John F. Kennedy and his mission to bring a man to the moon in the 1960s.

Even the cleaning service personnel at NASA's Cape Canaveral facilities understood their work as a part of this mission.

At Merck, the purpose is dedication to human progress—this is the leading idea guiding the healthcare strategy for the company's products.

Rodo said that being a global innovator starts with shop floor employees, who are now working with real-time performance-indicator dashboards (no more paper).

She also noted the role of operations in providing a competitive advantage for Merck. Two of the main drivers in operations are cost and cash competitiveness and supply flexibility. Merck defines their operational levers, midterm goals, and yearly objectives with great visibility and transparency—which is only possible when operations are supported by digitalization.

Rodo said that the engagement of people is of equal importance in operational success; this is the emotional aspect of the business, with a focus on mindsets and behaviors. Diversity and inclusion are essential, and they are being achieved through communities of volunteers, training, the ISPE Women in Pharma® program, objectives for senior leaders, and other initiatives. Another driver of engagement is sustainability. For example, "green" teams are prioritizing efforts to lessen the use of plastic materials to protect the environment.

As a final point, Rodo said that using all forms of modern media not only engages people and generates momentum but also helps organize interactions among all stakeholders in the organization. It is important to reward success and recognize people's performance and resilience in this complex new world of digitalization.

JAMES THOMAS, BAYER AG

James Thomas, Head of Digital Strategy, Bayer AG Pharmaceutical Division, gave a talk titled "Driving Digitalization for Pharma Manufacturing."

He identified several opportunities associated with using digitalization to connect key equipment and lines across the manufacturing network: getting real-time operational data, deploying advanced analytics, data sharing to enhance product launches and predictions, and avoiding machine downtime and equipment failure. As challenges, he noted a historically heterogeneous equipment landscape, the current management of data/buffering, the data integration blueprint, and the focus on brownfield and greenfield sites.

Regarding digitalization of the end-to-end supply chain, Thomas envisions the achievement of autonomous planning and identified as opportunities a new level of transparency that allows companies to do simulations; the integration of suppliers, raw materials, and contractor's activities; and the better identification of downstream costs and opportunities. As challenges, he identified multiple internal and external data sources; the so-called last mile for data (i.e., the telecommunications networks that deliver data to end users), which often has limitations or is costly to manage; the limited willingness of many to share data; and the need to take a leap of faith in change management.

It is important to reward success and recognize people's performance and resilience in this complex new world of digitalization.

In practical terms, Bayer combines data in a data and analytics platform to implement use cases, drive collaboration, and create new business models in lighthouse projects. Another key success factor is developing skills and a "digital mindset" across the organization.

DAVE S. STERNASTY, ELI LILLY AND COMPANY

Dave S. Sternasty, Vice President, Corporate Engineering and Global Health, Safety, and Environment, Eli Lilly and Company, shared his perspective on future operations in an era of technology and digitalization.

He said the three integrated priorities of manufacturing are supply, launch, and productivity. The digital plant agenda is built on a strong foundation with the steps being:

1. Pre-digital plant
2. Digital silos
3. Connected manufacturing (the situation today)
4. Predictive plant (the company's goal for 2023)
5. Adaptive plant

The elements to achieve a predictive plant are in six areas: data and analytics, supply chain, laboratories and quality, manufacturing execution and automation, manufacturing support, and facilities and security/integration.

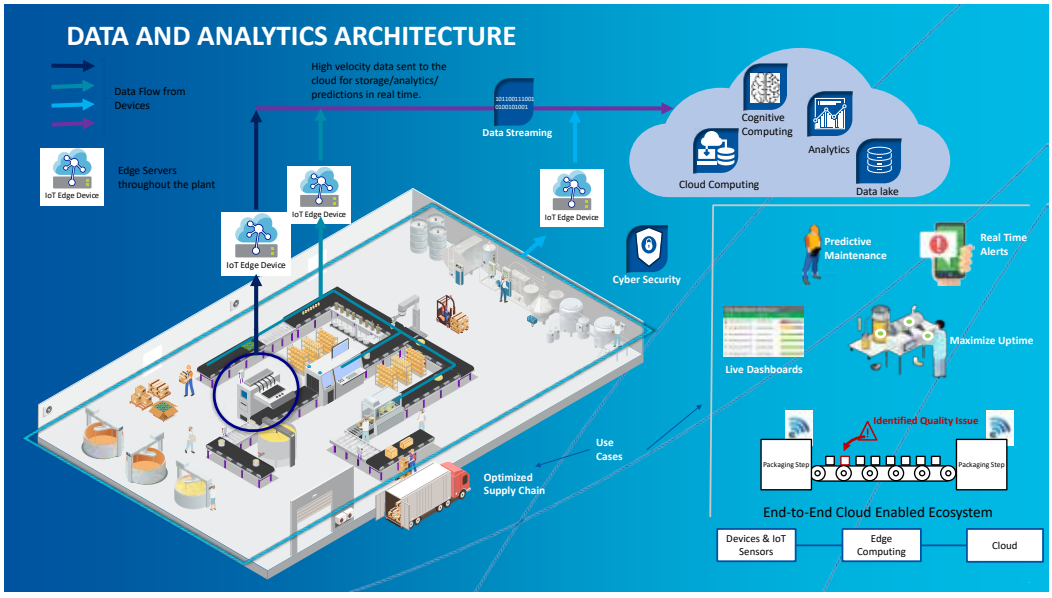
Sternasty used a parenteral filling line as a real-time predictive analytics example. A decontamination process with a four- to six-hour cycle time and a certain variability in performance could be managed to predict the expected outcome within four minutes and with 87% accuracy. This would help increase line availability and productivity, and would improve process knowledge.

Figure 1 represents Eli Lilly's data and analytics architecture, which starts with internet of things (IoT) devices that collect data from the shop floor and ends with information stored in the cloud. It is an end-to-end connected system that gives information about real-time events, issues, and production progress to decision makers. Even the predictive maintenance program is integrated.

GIUSEPPE RECCHIA, DAVINCI DIGITAL THERAPEUTICS

Giuseppe Recchia, Cofounder and CEO of DaVinci Digital Therapeutics, Milan, Italy, presented on digital health approaches.

Figure 1: Data and analytics architecture at Eli Lilly and Company (used with permission from D. Sternasty, Eli Lilly and Company).



He noted that digital health tools have a range of purposes and uses, from promoting well-being by allowing consumers to track their diets, sleep, and activity to helping patients and providers manage serious diseases and providing data for research (Figure 2).

Digital therapeutics is a subgroup of digital health with well-defined purposes: to treat and manage specific diseases or conditions. Because they are designed to modify disease states, digital therapeutics require regulatory agency approval and a physician prescription, and the cost may be covered by health insurance. As examples of successful digital therapeutics applications, Recchia noted those used in the surveillance of oncology therapy and for treatment of insomnia.

He explained that the "active ingredient" in digital therapeutics is an algorithm. Digital "excipients" include reminders, appointment managers, scheduling tools, automated assistants, tools to alert or contact physicians, patient education, data integration, gamification, media libraries, progress tracking tools, rewards to reinforce patient behaviors, feedback, and social media applications to provide peer support and comparisons.

Like drugs, digital therapeutics are developed in a preclinical phase and a clinical phase. Digital therapeutics development is a structured process with research, software devlopment, pilot clinical development, and full clinical development including randomized controlled trials. After that, there is a submission-approval process followed by a postmarketing surveillance.

Recchia also noted some issues with digital therapeutics. These include creating a level of evidence to demonstrate clinically relevant results, reimbursement challenges, and questions about the design of clinical trials, such as how to test digital therapeutics in an "analogical" trials environment.

Rechhia emphasized that in chronic desease management, digital therapeutics normally will not substitute for a drug therapy; instead, they work as additive therapies, which can improve patient outcomes, increase the therapeutic value of a drug, optimize a drug life cycle, create access to real-time data, personalize a drug therapy, and thus round out the therapeutic offering.

BARRY O'SULLIVAN, UNIVERSITY COLLEGE, CORK, IRELAND

Barry O'Sullivan, Professor, School of Computer Science and IT, University College Cork, Ireland, gave a presentation titled "Artificial Intelligence for Connected Health Post COVID: Technical and Ethical Challenges."

Noting that the term "artificial intelligence" (AI) was invented in 1955, when people still thought that computers could "think," O'Sullivan explained that it took a long time to develop the first AI technologies (e.g., game computers, self-driving cars, and robots). Now AI has advanced to the point that retail companies can use data analytics to predict customer behaviors.

The use of AI has ethical implications; for example, AI might be used to influence outcomes of democratic elections. O'Sullivan emphasized that AI methods themselves are not the problem—it is the way we use them.

How are AI and ML helping to fight COVID-19? As an example of an established AI application, O'Sullivan noted the use of computed tomography images to diagnose COVID-19. Apps can also organize and provide access to information about the development of infections. A Canadian start-up company has used AI to anticipate outbreaks, mitigate risk, and build resilience. Another startup, Closed Loop, uses AI to prioritze resources for those most

Figure 2: Selected types of apps and devices in the health sector (used with permission of Giusppe Recchia).

vulnerable to COVID-19 complications. Huge volumes of data from public sources are available, and AI gives scientists ML-enabled capabilities to search the COVID-19 data set. Researchers from Harvard University and the Massachusetts Institute of Technology are currently developing a COVID-19 AI diagnosis application using only coughs recorded from phone calls.

Turning to the regulatory framework, O'Sullivan mentioned the European Commission's "Coordinated Plan on Artificial Intelligence" [1], published in 2018. Two of the main outcomes of the related High-Level Expert Group on Artificial Intelligence are the "Ethics Guidelines for Trustworthy AI" [2] and the "Policy and Investment Recommendations for Trustworthy AI" [3].

The following requirements for AI are outlined in the Ethics Guidelines:

- Human autonomy and agency
- Technically robust and safe
- Privacy and data governance
- Transparency
- Diversity, nondiscrimination, and fairness
- Societal and environmental well-being
- Accountability

An assessment list is available to check any system against these requirements. The next step for the expert group is a white paper on risk-based AI regulation. Possible requirements could address training data, data and record keeping, information to be provided, robustness and accuracy, human oversight, and specific requirements for biometric identification.

PANEL DISCUSSION

After their individual presentations, all of the speakers participated in a panel discussion moderated by Chloe Lang, Manager of Data Science EMEA, Sartorius, and ISPE Emerging Leader, and Christian Wölbeling, Executive Industry Advisor, Körber Pharma Software, and founder of the ISPE Pharma 4.0™ Special Interest Group (SIG). The key questions addressed were:

- What is the biggest hurdle for Pharma 4.0™ digitalization?
- Who is driving the change: which department or organization?
- How do universities play a role? What collaborations are happening?

Overall themes that emerged throughout the discussion were embracing new talent and skills, creating an environment for "out of the box" thinking, collaboration, and integration.

The main rationales for moving toward Pharma 4.0™ are a combination of strategy, business cases, and problem solving. Finding problems to solve helps make digital changes tangible and is a way to attract new talents, develop new skills, and accelerate entrepreneurial thinking, which helps companies and the workforce see and embrace potential changes. Collaboration both internally within companies and externally with universities and suppliers is crucial to drive a Pharma 4.0™ vision.

Panelists highlighted that these changes cannot be managed by one function within an organization; there has to be a multifunctional approach. For example, IT can enable the changes, but business and strategic objectives need to be considered. In many cases, companies have established partnerships that have been in place for many years. But understanding how universities are fostering digital aptitude in their graduates is also important for

working with and attracting the younger workforce. Overall, more engagements are starting in areas like smart manufacturing initiatives to move AI and ML to manufacturing environments. As more data become available, more opportunities arise, which also brings the challenge of working out where to start and how to identify what is significant and interesting. With all the focus on AI and ML, it is also important to remember that implementing algorithms is not the only challenge—stakeholders must also consider how to interpret and use the data in a validated environment and how to manage the life cycle efficiently.

Although the concept "digital transformation" may be easy to define, it can be difficult to ensure everyone has the same understanding and expectations. Panelists said that integration remains the biggest hurdle. In addition to data and interface integration challenges, integration will involve breaking down cultural silos and filling the need for a workforce with cross-functional skills. Product integration is important both to ensure patients have the ability to use digital therapeutics products, and to ensure data and information flow automatically and efficiently within organizations.

By creating an environment where not only the data but also people and functions are interconnected, organizations can foster space for innovation, try different approaches, and take radical steps. The integration of industry, suppliers, and contract manufacturers also helps build relationships and understanding, creating more of a community and network. For example, while it is not possible to visit contract manufacturers at the moment, having systems set up to share data and information makes it easy to follow what is happening at production sites without having to visit in person. In digital therapeutics and other areas of digital innovation, the need for rules, guidance, and collaboration across industry and regulatory/government agencies was also highlighted.

One of the closing thoughts was that transformation is a marathon, and it takes time and clear change management to ensure transformations are impactful; if the organization is not engaged, the benefit of digitalization will be low.

HEIKE ROEDER, BAYER GERMANY

Heike Roeder, Lead Digital Tranformation QMS, Bayer Germany, presented on "My Life in Quality 4.0." She explained that a quality manager has a legal responsibility for quality oversight of operations, quality, and compliance. This responsibility will not change in a digitalized world, but the methods to achieve it will. She described the changing decision-making paradigm, which is impacted by the connectivity of data and people. This already requires a cultural change toward openness and transparency, and away from functional silos and organizational chart–defined responsibilities. Data ownership means responsibility for correctness of data and data integrity—it is not about "possession" of data interpretations of sovereignity over the "ownership" of data.

Content-wise, the paradigm change goes from retrospective control to predictive prevention. Also, the paradigm should be patient-centric: i.e., the patient outcome will be more in focus than in the past, when comparisons to defined and approved specifications were the only criteria for quality.

Roeder next presented a practical business case driven by the Pharma 4.0™ approach: the electronic standard operating procedure (SOP). The SOP of the future is digital, user friendly, precise, and intuitively easy to understand. It is mobily accessible from everywhere, provides the right information at the right time and the right place, and is delivered in a customized, attractive format (which might include text, voice, graphics, or video).

ALEXANDRA GREBE DE BARRON, BAYER AG

Alexandra Grebe de Barron, Data Product Owner in Digital Transformation & IT, Bayer AG, presented "FAIR data for Better Patient Outcomes." FAIR data and digital assets are findable, accessible, interoperable, and resuable. This concept clarifies the context, meaning, trustworthiness, and origin of data, and how data can be used, with a clear and accessible data usage license.

Grebe de Barron said data-driven insights are redefining the health services landscape: Patients, payers, and providers are becoming "superconsumers" empowered by data. "Sick care" is turning into healthcare focused on prevention and the affordability of care. Blockbuster drugs will increasingly be replaced by precision medicine that uses data mining to deliver therapies tailored to specific patients. Disconnected healthcare will become connected healthcare as systems integrate healthcare data, human efforts, and machinery to offer better interventions.

Algorithmic medical applications can identify individual patient risk for a defined endpoint, which helps physicians make the right treatment choices. Based on a new and complete data set, algorithms can be developed to predict the future development of a disease on a patient level.

PHILIP M. GAMMELL, ASTELLAS PHARMA, INC.

Philip M. Gammell, Associate Director Engineering, Astellas Pharma, Inc., presented a Pharma 4.0™ business case on the "Connected Worker." The pilot project involved a tech transfer from Astellas to a contract manufacturing organization (CMO) where workers were connected with wearable devices, smart glasses, and mobile devices. The overall approach involved:

- A scope review with the CMO to identify use cases, coordination agreements, and stakeholders
- Infrastructure tests with initial device and platform testing
- Training and live testing before production, with key users, to finalize a testing protocol
- Live testing during production, including creating user credentials, developing procedures, and collecting feedback
- Conducting final use cases at local sites and collecting feedback
- Next steps, such as a road map for implementation with all CMOs

The connnected worker pilot met its goal for replacing paper-based processes with digital processes through an innovative solution using augmented reality, smart glasses, and voice-activated and

hands-free methods. Additionally, real-time data and key performance indicators are available.

MARKUS ZEITZ, NOVARTIS

Markus Zeitz, Quality Innovation Hub Lead, Novartis, presented on Novartis's efforts to achieve scalable, centralized, and system-wide audit trail review and visualization. He began with the US FDA definition of an audit trail [4]—"a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record"—and noted that regulations such as Annex 11 and 21 CFR 211 require review of audit trails for GMP-relevant changes and deletions. Audit trail review, he emphasized, is a key activity to ensure data integrity.

Zeitz said that the vision is to change audit trail review from a human-driven, time-consuming, and paper-based process to a fully data- and computer-driven process covering metrics, logs, and events. The core element in the Novartis case is a big data analytics platform with online reports, web access, and alerts.

The main process steps are investigating, monitoring, and analyzing data. The consolidation of data after sourcing from various sources is done by robotic process automation. A challege is the standardization of data requirement across the existing landscape of data sources.

PANEL DISCUSSION

A Q&A session with Roeder, Grebe de Barron, Gammell, and Zeitz provided an opportunity for audience members to pose their questions. The main directions of questions may be summarized as follows:

- Challenges to overcome in Pharma 4.0™ implementation, whether detected from the Pharma 4.0™ survey or experienced in projects (including the presented cases)
- Relationships between the Pharma 4.0™ approach and the aims, methods, and practices found in regulations and guidelines (such as the ICH Q series of quality guidelines)
- The role of enabling technologies in designing a Pharma 4.0™ plan of interventions

The holistic approach to Pharma 4.0™ is crucial to overcome the main implementation challenges. Whereas Pharma 4.0™ projects are often seen as technological projects, thinking outside of silos is always key—it is necessary to widen plans, include competencies, involve the organization, and have strong sponsorship. In other words, success depends on approaches and governance that are cross disciplinary. If this cross-disciplinary need is underestimated, the program is at risk for failure.

For regulations and guidelines, the answers shared in the session may be summarized by the initial statement of the Pharma 4.0™ SIG's mission: "Provide practical guidance, embedding regulatory best practices, to accelerate Pharma 4.0™ transformations." The ICH Q series of guidelines, in particular, are integral part of the Pharma 4.0™ view and method. Every contribution from industry, from authorities, and from the academy is totally welcome and expected.

Regarding the role of enabling technologies in the pharma industry, and others, it is widely observed that a certain effort must be devoted to solving the risk of possible ambiguities in defining such technologies to improve mutual comprehension and create an effective business case. This is an area for the work to come from the Pharma 4.0™ SIG.

The Q&A session also raised matters to be considered for the next editions of the Pharma 4.0™ survey. Pharma 4.0™ approaches help improve the GMP situation, but they have an impact beyond GMP on making processes faster, less costly, and more reliable.

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"HOW TO PITCH AND SHAPE A PHARMA 4.0™ PROJECT" WORKSHOP

By Teresa Minero

During the ISPE Pharma 4.0™ Virtual Conference, the Management Communication working group of the ISPE Pharma 4.0™ Special Interest Group (SIG) held a workshop to support ISPE members in pitching, shaping, and presenting a Pharma 4.0™ project/program to company management.

The workshop, which was organized and led by Davide Smaldone, Corporate IT Demand Manager at Menarini Group, Edoardo Schiraldi, Corporate R&D Business Solutions Specialist at Menarini Group, and Teresa Minero, Founder & CEO at LifeBee–Digitalizing Life Sciences, was very interactive, with 30 attendees from many countries and roles.

The presenters introduced the workshop by sharing their "Management Pharma 4.0™" draft presentation. The target of this presentation is senior management, not technical professionals. A new creative graphic design, sponsored by the ISPE Italy Affiliate, was used to communicate the messages. Smaldone asked the workshop participants for their analyses and comments.

Minero next discussed the values of a 4.0 program both in pharma and in other industries. She summarized the results from a Politecnico di Milano (Italy) research project [1] that sought to measure the value of 4.0 in terms of objective parameters. The researchers conducted a survey of more than 4,700 companies from several industry sectors, including 72 companies that were "particularly active" in Industry 4.0 programs from the early 2010s. The analyzed parameters showed that for those companies engaged in 4.0 projects, revenue growth was greater than 8%, gross profit margins increased by more than 37%, and labor-added value increased 60% with an increase of only 31% in labor costs. The research clearly demonstrated the value of the 4.0 mindset and projects for companies on a medium- to long-term scale.

DESIGN THINKING METHODOLOGY

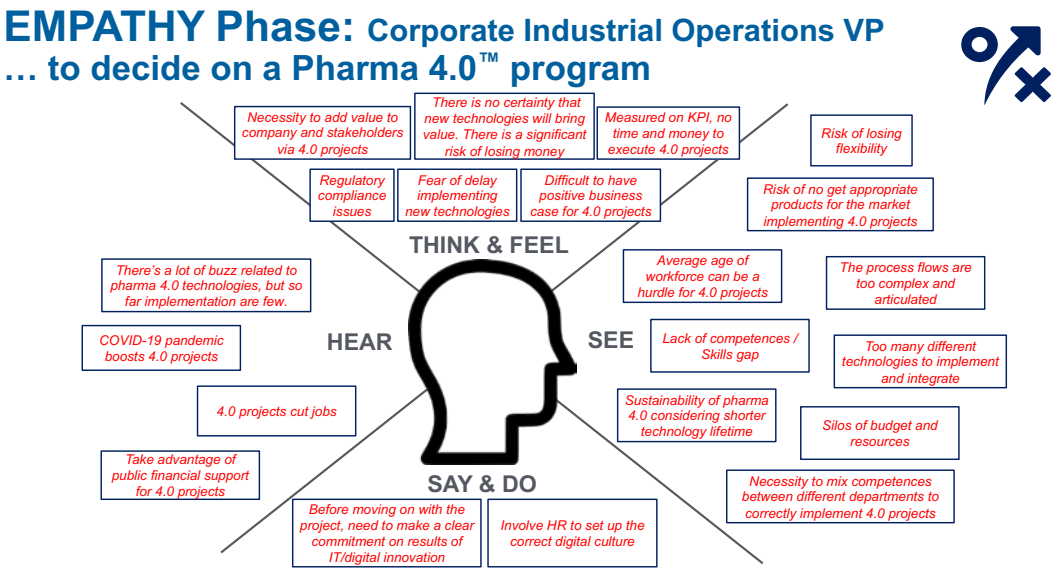
Schiraldi kicked off the interactive part of the workshop by introducing the phases of the "design thinking" approach that would be used during the session.

- Empathy phase: This phase aims to identify the possible objections and obstacles, clearly stated or even only perceived, that may prevent stakeholders at a company management level from deciding to approve a Pharma 4.0™ program. The objective is to see the 4.0 proposal through the eyes of the interlocutor (senior manager), through the four dimensions of:
  - Hearing—what they hear on the subject from peers, the media, advocates, and others
  - Thinking and feeling—what their beliefs, inspirations, and worries are
  - Seeing—what they observe and note from their environment, market, product, and processes
  - Saying and doing—their attitudes in their usual activity and behavior

- Reframing phase: This phase has two parts.
  - Challenges—Reframing begins by focusing on what senior management will identify as the challenges of a Pharma 4.0™ program, as discerned from the empathy phase, and drafting appropriate responses.
  - Solutions—Once challenges are identified, it is possible to focus on practical and methodological measures to enable a Pharma 4.0™ program.

To illustrate these phases, the attendees were asked to imagine being one of their company's senior managers, such as the industrial operations vice president, who has the authority to review and approve a key Pharma 4.0™ program. From this perspective, attendees identified the likely obstacles and doubts that would need remedies and answers before the vice president would let the program proceed, and worked through reframing the challenges to highlight their solutions.

Figure 1: Empathy phase elements identified in the workshop.



EMPATHY PHASE

Figure 1 shows what the workshop attendees imagined during the empathy phase about the vice president's perspective on the Pharma 4.0™ potential project. The "obstacles" to the project were clustered as follows:

- Compliance: Obstacles include the vice president's perception of the company's current position and their concerns about the need to align the new 4.0 approach with regulatory guidance and the expectations of regulatory agencies.
- Economics: The vice president will be concerned about the costs of a 4.0 program relative to the tangible value that such a program can bring to the company. The vice president may only have a general awareness of the costs of 4.0 programs and requires a well-developed, focused business case for the specific project.
- Knowledge: A wide spectrum of information must be shared with management and personnel. They will require a reliable image of the proposed state-of-the-art 4.0 initiative, including its actual effect on the workforce profile, the project's features and objectives, its operational aspects, and its impacts on processes.
- Organization: The company's organization will need to change to benefit from and manage the 4.0 perspective. Success of the 4.0 program will depend on an "all for one and one for all" attitude and willingness to break (or reshape) existing silos.
- Competencies: The vice president will have concerns about workforce 4.0 features and workers' potential resistance to change. It will be important to show how existing or new structured programs of education and training can fit into 4.0 project implementation.
- Strategy: In recent years, many companies have developed 4.0 pilots and projects, but many of these efforts lack a mid- or long-term strategy with a precise definition of business targets and a sound road map to enable the transformation.

Amid these obstacles, workshop attendees also identified factors that may encourage the vice president to support implementation of a 4.0 company strategy:

- The company may be able to take advantage of public financial support for 4.0 projects (several nations are sponsoring the 4.0 transformation in the industry with special taxation or financial benefits).
- The COVID-19 pandemic has demonstrated the need for and value of 4.0 projects (e.g., programs enabling remote work by digitalizing processes and information).

REFRAMING PHASE

Challenges

Challenges in the reframing phase are certain. However, the Pharma 4.0™ SIG's communication framework offers support to overcome them.

Identifying challenges can be a first step toward defining feasible, proactive responses to objections and obstacles arising from the company mindset and organizational structures. Asking "How might we…?" helps define these responses (see Figure 2 for examples).

Workshop participants identified the following main challenges for a Pharma 4.0™ project along with their possible answers:

- Economic challenges: These challenges are resolved mainly through tangible responses to tangible questions.

Figure 2: Reframing phase challenges discussed in the workshop.

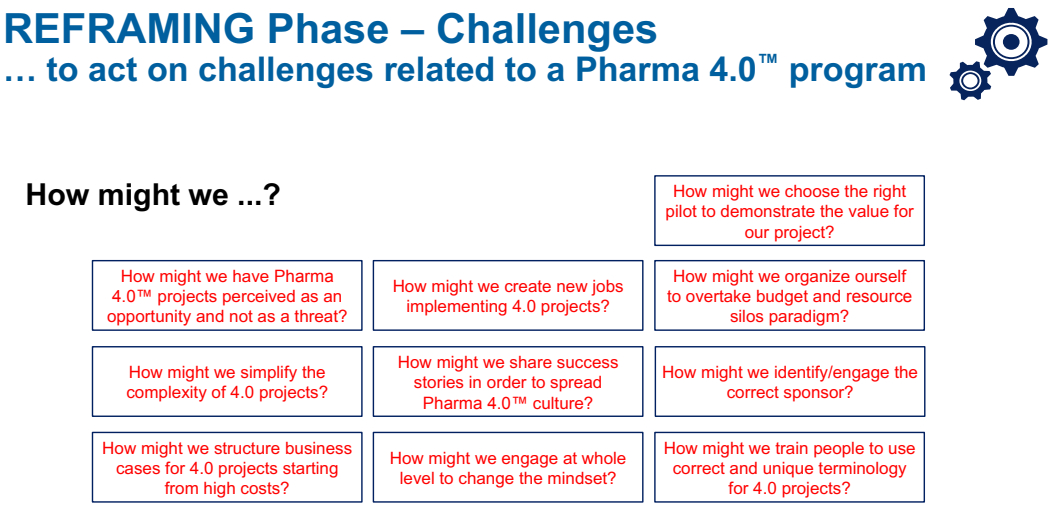
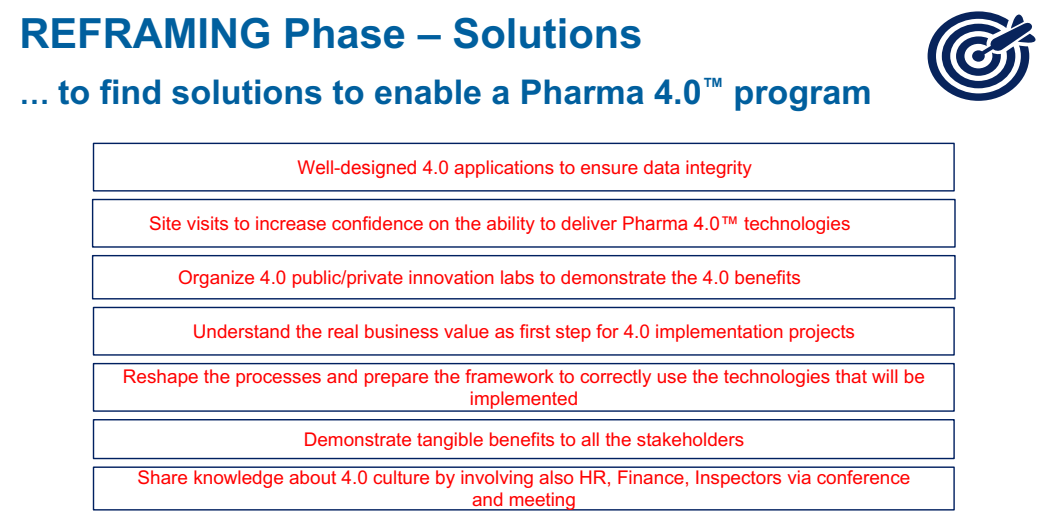


Figure 3: Reframing phase solutions that emerged from the workshop.



- Knowledge-related challenges: These challenges are always best managed with tangible, company-focused answers, which can be derived from the general 4.0 knowledge developed through the ISPE Pharma 4.0™ SIG's work.
- Organizational challenges: These challenges are mainly addressed by focusing on the company's self-awareness, the maturity and experience of the company with regard to 4.0 programs, and the ISPE Pharma 4.0™ SIG's work in this area.

Solutions

In the reframing phase, solutions are intended as a first set of directions to be pursued to successfully create the conditions for a Pharma 4.0™ project. Solutions proposed in the workshop (Figure 3) can be grouped in the following main areas:

- Design: The main way to answer to organizational, knowledge-related, and economic challenges is to ensure that when the 4.0 initiative project is put into practice, program/project setup, design, and implementation are all robust.
- Knowledge: A successful 4.0 effort will include explicit actions to appropriately increase, widen, and/or consolidate the company's culture and mindset.

CONCLUSION

Pharma 4.0™ is a journey the pharmaceutical industry should embrace, and quickly, for the sake of all stakeholders. There's a lot of value to be achieved for companies, but also some challenges to be faced. Here are five key actions that senior management should put in place to enable success:

1. Value the wide range of benefits of Pharma 4.0™ based on the company's specific business goals.
2. Promote the creation of a sound road map, taking into account the digital maturity and the compliance needs.
3. Offer sponsorship to drive innovation and open new factual horizons.
4. Foster the cultural change necessary to explore trails that have never been walked for an effective transformation.
5. Sustain the knowledge sharing among all functions and stakeholders. Professionals need to learn, compare, and debate ideas, successes, and failures with their peers from the whole ecosystem: industry, vendors, academy, and regulators.

During the 90-minute workshop, attendees generated a large volume of challenges and solutions; however, their ideas are not an exhaustive list. If you have identified any touch points that we have missed or have any other questions, suggestions, or ideas, please let us know by contacting the chairs of the working team: Teresa Minero at t.minero@lifebee.it and Davide Smaldone dsmaldone@menarini.it

ISPE and its working groups provide a unique and powerful platform to support management and professionals in their journey to Pharma 4.0™—only together we will create enough fuel for the thrilling future that awaits our industry.

Acknowledgments

Thank you to everyone who participated in the workshop and to the ISPE staff who helped us create this fantastic interactive event, despite the pandemic.

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Teresa Minero has been the Founder and the CEO of LifeBee, a business consulting and digital company dedicated to the life sciences, since 2004. She has more than 30 years of experience managing international consulting and digital innovation projects for production, logistics, quality, regulatory, and research and development, and managing startups and business divisions for international consulting groups. She has spent more than 25 years working in the life sciences. Teresa currently serves on the ISPE International Board of Directors and is a member of the ISPE Pharma 4.0™ Global Special Interest Group Steering Committee. She has been a lecturer and chair at many conferences and is the author of several articles on digitalizing life sciences and 4.0. Teresa has been an ISPE member since 1995.

DATA SCIENCE FOR PHARMA 4.0™, Drug Development, and Production—Part 1

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

Digital transformation and digitalization are on the agenda for all organizations in the biopharmaceutical industry. But what are the main enablers of intelligent manufacturing? We hypothesize that data science–derived manufacturing process and product understanding is the main driver of digitalization in the bioprocessing industry for biologics manufacturing. In this article, the first of a two-part series, we analyze the prerequisites for establishing data science solutions and present key data science tools relevant to the process development stage.

Part 2 will focus on applications of data science tools in product life-cycle management. The goal of the series is to highlight the importance of data science as the necessary adjunct to digitalization for intelligent biomanufacturing. We focus on the potential of data science in industry and present data science tools that might deliver fast results in different subject areas. We want to stimulate the use of data science to transform drug production and achieve major business goals, such as accelerated time to clinic and market and improved process robustness based on continued process verification (CPV).

DIGITALIZATION AND DATA SCIENCE

Industry 4.0 and the industrial internet of things (IIoT), as defined elsewhere [1], have become the innovation drivers and game differentiators of today's industry and all related business areas. They redefine complete value chains encompassing production planning, warehousing and logistics, manufacturing process and material design, plant operations and safety, monitoring and maintenance of facility and equipment, tight integration of suppliers and customers, and marketing and sales.

The term "digitalization" is often used very broadly. In this article, we define it within the pharmaceutical context as the conversion of all data along the product life cycle, from pharmaceutical development and manufacturing onward, into a computer-readable format. However, the availability of data is itself insufficient. We need to learn from the data through data science because human capabilities may be limited due to the complex nature of the data.

Specifically, digitalization and related data science tools for the biopharmaceutical industry mainly act on two dimensions:

- The manufacturing process chain (Figure 1)
- The product life cycle (addressed in Part 2)

These dimensions are, of course, interlinked.

The enhancement of the manufacturing process chain by digitalization affects the supply chain, logistics, and predictive—rather than preventive—maintenance. In addition, the enhancement impacts process robustness, process understanding for

Figure 1: Effect of Indutry 4.0 enablers on the manufacturing process chain. Upper arrow: Conventional approach. Lower arrow: Perceived extended process chain using IIoT enablers. The red elements have a strong feedback loop (e.g., from maintenance data to supply chain management and logistics).

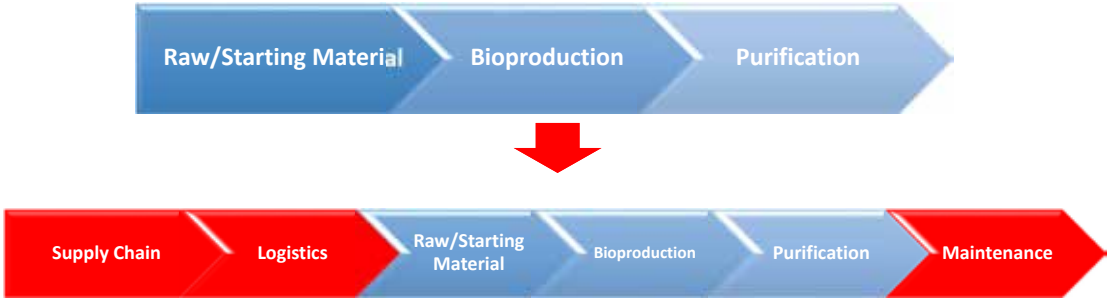


Figure 2: Application of data science tools to advance intelligent manufacturing.

product life-cycle manangement purposes, and deviations management.

Hence, the objectives of the digitalization-enhanced manufacturing process chain are:

- Integrate data from facilities, sites, suppliers, and clients.
- Use quality metrics to increase process and manufacturing transparency.
- Allow feedback loops within the life cycle for continuous improvement.
- Establish multiproduct facilities in response to shorter product life cycles.
- Allow flexible resource management.
- Establish transparent and flexible business process workflows.

Without any doubt, sufficient data are already available to realize these objectives. However, the data must first be managed to achieve a structured format—data management is a key prerequisite for data science. Additionally, there is the strong need for software tools to generate knowledge from data. Current tools include data visualization and data-driven or mechanistic models [2]; these are used to provide ontologies and taxonomies [3].

Data science is used to gather and provide the knowledge needed for the timely and predictive development of new pharmaceutical drugs. Recent advancements in data science pave the way for a second revolution in medical sciences based on a rational understanding of the patient's disorder, science-driven (rather than heuristic) drug development and manufacturing, and knowledge-based and individually tailored therapy.

Data science is the most recent data, information, knowledge, wisdom (DIKW) concept [4]. In the bioprocessing industry, it is used to turn data into information, which can then be transformed into knowledge applicable across the product life cycle. Thus, it permits organizations to follow the ICH Q12 guideline for life-cycle management by providing a data-based set of established conditions (ECs) [5]. Data science also allows intelligent processing in control strategies according to the sequence of primary data collection, followed by the evaluation of information, generation and provision of knowledge, and, finally, a high level of manufacturing intelligence and comprehensive understanding. Figure 2 illustrates how data science tools enable intelligent manufacturing, which, in our view, is the main goal when following Industry 4.0 principles.

DATA SCIENCE PREREQUISITES

Data Alignment, Contextualization, and Integration

According to surveys, data scientists spend the majority of their work time preparing and processing data [6]. Having worked for many years as and with data scientists, our experience upholds this finding. Up to 80% of the data scientist's time is dedicated to data alignment, cleaning, and contextualization, and setting up

The intellectual property of pharmaceutical companies is mainly present in the form of data.

test data sets. Data scientists must repeat these basic work tasks on a daily basis because there is an unlimited amount of possible and different data formats, many of which are unsuitable or nonstandardized. As a result, only about 20% of the highly skilled data scientist's time is available for building training sets, writing algorithms, building and refining models, and delivering knowledge.

This arrangement is not cost effective. Data processing and organization do not deliver any value by themselves, even though they are indispensable prerequisites to advancing drug development and production. Moreover, manual data manipulation bears the risk of introducing human errors into the data set.

There are multiple reasons for this awkward predicament. One is the vast diversity of data and data applications in the pharmaceutical industry—material supply information, data on the history of the used strains, experimental design data, process raw data, analytical data, derived process data, associated metadata, statistical models, mechanistic models, hybrid models, single-unit operation models, holistic models (e.g., integrated process models and digital twins), analysis workflows, validation workflows, and batch records, to name just a few. (A digital twin is a virtual representation of a physical or intangible object existing in the real world. With a twin, we can design experiments, predict process outcomes and even optimize the process in real time [7].) Currently, all these types of data are usually stored as paper records or in nonstandardized relational databases (such as programming scripts) or tabular files. As we have noted, converting such data to knowledge is the primary purpose of data science. However, other essential prerequisites must be implemented before the conversion can succeed.

Standards and Interfaces

Open-source, interoperable, platform-independent, widely accepted and implemented standard formats would help reduce the amount of time currently used for data processing and contextualization. However, given the market economy and the speed of development, the IT industry is affected more than any other industry by proprietary de facto standards, such as using Microsoft products. These standards prevent an efficient reuse of algorithms and data science tools.

Various attempts are currently under discussion for implementation of open-source standard formats. For example, the Allotrope Foundation aims to define and implement a common data format that focuses on the contextualization and linking of analytical data [8]. The lofty goals of the Allotrope project are much appreciated, and the project is well supported by discrete manufacturing industries. A similar project, with focus on the process industry, is Data Exchange in the Process Industry (DEXPI). This initiative aims to set up an ISO standard to enforce a common data storage and exchange approach [9, 10].

To use open-source standards and formats in pharmaceutical manufacturing, regulated companies must adopt proper controls. For example, the US FDA's predicate rules influence which tools and systems are used in computer validation.

Open-source projects are far from general implementation, and it is unclear whether any of these approaches will become a commonly used standard. There is a danger that these efforts will not result in applied tools. Sometimes, the overhead to implement an interface in a standardized format is simply too high relative to the cost of an unstandardized format such as a simple CSV file. To encourage the adoption of open-source standard tools, leading software providers, application developers, and industrial organizations need to commit to making tools and their related interfaces easy to apply and implement.

The historic evolution of the Open Platform Communications (OPC) standard is a noteworthy model for other internet of things (IoT) applications. An OPC interface is used in the automation industry for communication between different software tools. Previous OPC standards had several technical drawbacks that limited their use for the IoT. One of its biggest issues was that they were based on Microsoft's DCOM specification. Communication in a complex network was usually only possible with workarounds such as additional OPC tunnel tools. During the last decade, collaboration among different parties resulted in a unified architecture standard, OPC-UA, which is a generic, open-source, platform-independent, network- and internet-ready interface standard with built-in advanced security features. OPC-UA is functionally equivalent to the older versions of OPC but is extensible and allows modeling of data as more complex structures. The named features make OPC-UA the preferred standard for IoT applications.

Data Security and Data Integrity

In the pharmaceutical context, data security and following GAMP® guidelines [11] are highly critical. The intellectual property of pharmaceutical companies is mainly present in the form of data. Research and development data, drug manufacturing recipes, process metadata, and batch records all contain massive

amounts of information that can be potentially converted into valuable knowledge. In the past, pharmaceutical companies protected their data using organizational and technical firewalls, resulting in data segmentation. Parts of a company's data infrastructure today are strictly shielded from other parts by using separated networks. Obviously, a high interconnectivity of devices and systems counteracts such security approaches. Pharma 4.0™ demands devices, users, and data scientists to be part of a common network. At the same time, access permissions need to be handled with fine granularity, providing just those access permissions to each element in the network that are actually required. To realize the Pharma 4.0™ vision, companies need to rethink their IT security fundamentals, deriving security systems from the internet of information and implementing them into the IIoT.

Data integrity is a related aspect of data security. Data integrity often refers to the completeness, consistency, and accuracy of data. According to US FDA guidance [12], "Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)." With data being the foundation of work and the basis for decisions, data integrity is crucial to the pharmaceutical industry. Regulatory agencies reacted to the lack of data quality and integrity in the past by publishing guidelines highlighting the importance of data integrity for the industry and for the patient safety [12–14]. To guarantee unequivocal data integrity, centralized IT systems have to be reassessed due to the complexity of validation of good data housekeeping, and alternative solutions need to be discussed. One approach is to separate parts of the data by, for example, storing them in a distributed ledger that is not under the control of a single party and therefore allows better control of data management [15].

Sandboxes and Test Environments

In discussions of data scientists' challenges and efforts, the actual implementation of developed algorithms and tools in production environments along the product life cycle is sometimes overlooked. Often, data scientists can quickly develop an algorithm or set up a model. However, it is not always clear how these results can be brought into production and used in a real-time context.

Current manufacturing environments are quite different from the development environments of data scientists. Data scientists are eager to use the latest tools and state-of-the-art technology. In contrast, automation specialists setting up the production environments are more cautious about the adoption of new technology that might put safety at risk. They usually rely on older, but time-proven, stable tools and software products. Bringing these two worlds together is a challenge, which is rarely addressed early enough in the implementation process.

Similarly, algorithms developed by data scientists in their development environments cannot simply be copied and pasted into the production environment. Often, a finished algorithm is just a prototype that proves feasibility. Too many promising tools never end up in a production facility.

Sandbox mode development and test environments can help overcome these issues. Development of data science tools requires time-consuming exploration involving many feedback cycles, such as agile development strategies. Data scientists need virtual production environments to test their algorithms and software solutions to improve these tools' applicability for commercial GxP-compliant drug manufacturing.

PROCESS DEVELOPMENT TOOLS

Factors such as increased competition and resulting cost pressures in the biopharmaceutical market, new modalities for personalized medicine, and reported threats of drug shortages provide incentives for organizations to develop, in the words of the Janet Woodcock, Director of FDA CDER, a "maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight" [16]. Specific hands-on goals in process development can be summarized as follows:

- Accelerate bioprocess development by avoiding iterations and deploying strategies to reduce the number of experiments.
- Develop universal scale-down models to accelerate process characterization, allow troubleshooting, and avoid unexpected scale-up effects.
- Deploy process analytical technology (PAT) strategies to (a) provide improved real-time operational control and compliance, (b) serve as an objective basis for process adjustments, and (c) provide a comprehensive data set for technology transfer decisions.
- Implement strategies to target integrated bioprocess development rather than optimizing single-unit operations only.
- Capture platform knowledge to achieve synergies with other products and extrapolate to other process modes such as continuous manufacturing.
- Allow life-cycle management aligned with ICH Q12 [5], including holistic knowledge and product life-cycle management. This should include clear feedback loops from manufacturing into process development to establish holistic manufacturing control strategies.

Development-Oriented Tools

Table 1 lists data science tools that can be used in the bioprocessing life cycle. When an organization has a data management system in place that follows ALCOA principles, these tools can address almost all industrial needs.

Statistical tools for business process workflows

Multivariate analysis (MVA) has been used for decades, and several MVA-dedicated software tools are available to improve business process workflows. More advanced methods have recently been developed, and respective good practice guidelines have been established [17]. The goal is to identify correlations between process variables, raw material attributes, product quality attributes, and the metadata from electronic batch records or electronic

Table 1: Mapping data science tools to industrial needs in the bioprocessing life cycle ("X" indicates a main application).

	Tools							
Industrial Needs	Statistics and Data Science Workflows	Digital Twin Generation	Digital Twin Deployment	Integrated Digital Twins	Digital Twin Validation, Evolution, Maintenance	Real-Time Environments	Process Control Strategies	Production Control Strategies
Accelerated process development	X		X	X		X	X	
Scale-down models	X	X		X				
PAT			X	X	X	X	X	
Integrated process development	X			X		X	X	X
Platform knowledge	X	X		X	X			X
Life-cycle management	X			X	X			X

lab notebooks (ELN), and use those correlations as data-driven models to both establish control strategies (e.g., in stage 1 validation tasks) and generate hypotheses for mechanistic investigations and improved process understanding.

Digitalization will furthermore allow seamless interfacing between operational historians, laboratory information management systems, ELN, and so on, and should include automated feature extraction from 2D data (e.g., spectroscopic or chromatographic data) and 3D data (e.g., from flow cytometry or microscopy). Inspired by FDA validation guidelines [18], such tools should be integrated in a business process workflow or in process maps [19]; for example, they might be linked to risk assessments, which in turn are facilitated by data science. This integration will help organizations establish clear traceability of decision-making along the manufacturing process development and manufacturing process characterization steps. For example, power analysis is used to reduce the risk of overlooking a critical effect of potential critical process parameters (CPPs) on critical quality attributes (CQAs), and to justify the proven and acceptable operating ranges [20].

Workflows for model and digital twin generation

Since the publication of the ICH Q11 guideline [21], the use of first-principle models (which can be implemented in digital twins) is encouraged along the product life cycle. These models are also perceived to be a significant enabler for life-cycle management in accordance with ICH Q12 [5, 22]. However, a digital twin should not be the product of a single modeling expert, because the acceptance of the model as well as life-cycle maintenance will fade out when the expert is no longer available. As viable alternatives, concise workflows for model generation have been in place for more than a decade [23]. These workflows are known as good modeling practice and use classical mathematical tools for model calibration—such as sensitivity, practical identifiability analysis, and observability analysis—for deploying the model with a suitable PAT environment [24].

As data are made available in cloud solutions, digitalization will further enable software-as-a-service (SaaS) solutions for the generation of minimum targeted models [25], in which mechanistic links, as assembled and uploaded by the academic community, are tested for suitability to the given data set and modeling goal. Hence, existing data science workflows are facilitated by novel cloud solutions, resulting in an accelerated, sound, and science-based approach to generate digital twins.

Model and digital twin deployment

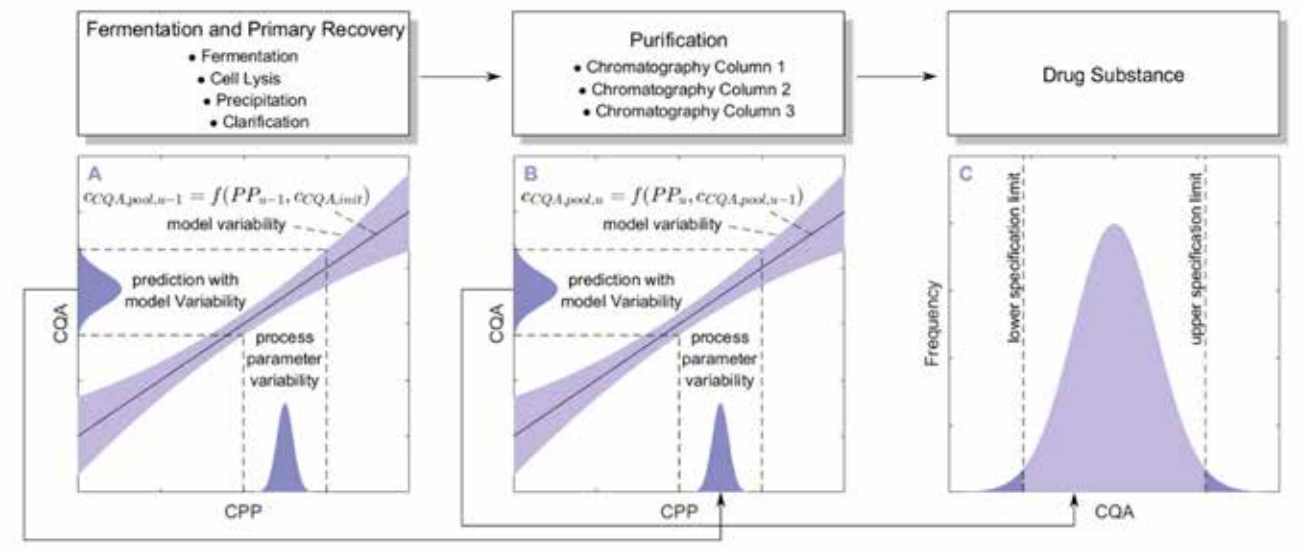
Models capture comprehensive process understanding. Hence, they are perfect tools to provide knowledge for manufacturing intelligence. In technological language, models can be deployed in a multiparametric control strategy in a real-time context. Model-based control or model predictive control (MPC) software sensors are well established in the conventional process industry, but they have hardly been used so far in value-added process industries such as the biopharmaceutical sector. Why not?

One issue is the lack of appropriate knowledge management tools and strategies. Once data are provided to the modeled process in a real-time context, knowledge management tools are needed to check whether the model and the underlying knowledge are still valid. As ICH Q12 emphasizes, the industry needs computational model life-cycle management (CMLCM) strategies [26], which are also an integral part of product life-cycle management, to enable feedback loops and continuous improvement of the process chain and product life cycle.

The execution of the knowledge-based strategy will lead to intelligent manufacturing and the realization of Pharm 4.0™. Digital twins can help enable us to achieve this goal in variety of ways [4].

It is widely recognized that digital twins can be used for experimental design. For example, digital twins help predict optimal feed profiles to a certain target function such as the optimum

Figure 3: Schematic description of an integrated process model using a Monte Carlo approach: 1,000 simulations are performed, each having a different set of process parameters and a different initial specific CQA concentration. Multiple linear regression models describe the relationship between the CQAs of unit operation B and the process parameter (PP) of this unit operation, as well as of the previous unit operation A. Thereby, models from multiple-unit operations (A, B) are connected to predict the CQA distribution in the drug substance (C). For this, Monte Carlo simulations can be used. Reprinted from reference 30: Zahel, T., S. Hauer, E. Mueller, et al. "Integrated Process Modeling—A Process Validation Life Cycle Companion." *Bioengineering (Basel)* 4, no. 4 (2017): 86. doi:10.3390/bioengineering4040086. Copyright ©2017 by the authors.



time-space yield [27]. Recently, digital twins have also been used for automated model-based redesign of experiments; in this context, the digital twin is deployed in real time and informational content is maximized concurrent to the ongoing experiment [28, 29]. These approaches clearly outperform classical design-of-experiment approaches in terms of both the number of experiments and the accurate identification of process parameters critical for optimum process performance.

Digital twins can also be deployed in real time throughout the product life cycle as process control strategies. When digital twins are set in place, they can be used to predict the impact of design decisions, anticipate bottlenecks, and provide efficient up-front training for new operational processes and advanced operator support (e.g., by means of augmented reality).

What is needed for digital twin deployment, and how can digitalization help? Currently, many digital twin implementations use classic proprietary academic tools, such as MATLAB, but the industry currently tends to use open-source environments, such as R and Python, whose functional scope can be extended by built-in editors, such as Jupyter Notebook. From the user's perspective, there is clearly a need to provide harmonized computational environments, thus avoiding manual data transfers or establishing interfaces between individual software packages. These interfaces should also follow the prerequisites of data management described previously.

Integrated process models

Established process models mainly focus on single-unit operations. However, process robustness and demonstrated manufacturing capability can only be reached via a consistently robust process chain. A seamless interplay between the unit operations needs to be elaborated for this purpose (Figure 3) [30]. Integrated process models, similar to those established in other industries (ASPEN, G-Proms), need to be applied to integrated bioprocesses. These models should quantitatively demonstrate the process understanding and include the elaborated proven acceptable ranges (PARs) of individual unit operations [17]. Subsequently, the models should allow the interconnection of the individual unit operations and be able to assess the error propagation within the variation in the PARs using sensitivity studies and, for example, Monte Carlo simulations. As a result, integrated process modeling enables the identification of process parameters that are critical to the entire process chain. It further allows the definition of the necessary control strategies along the entire process and, in turn, reduces the number of experiments needed for comprehensive process validation and for the defined and proven production capability.

Model validation, evolution, and maintenance

To deploy a model, we need to make sure it is valid and remains valid in a GxP environment. Initial model validation is only the first step, as the model will evolve as unforeseen variables are

encountered and planned changes are implemented over the product life cycle. The ongoing validation process is commonly known as CMLCM [26]. For execution of CMLCM, digitalization features computational model environments (CMEs). The engineering environment allows for further development of methods and requires significant input from modeling experts. Workflows contained in the customer tuning environment can be triggered by the customer and run (mostly) automatically. The in-line system contains parts of the model (algorithms) required and frequently called at run time. Data science tools for fault diagnosis need to be further developed and implemented in this environment to deploy this CME concept.

Real-time environments

Real-time environments in the Pharma 4.0™ context are currently specified in ongoing work by the ISPE Pharma 4.0™ Special Interest Group's Plug & Produce working group. The main requirements for digital twin and knowledge deployment solutions with respect to data science are to:

- Allow real-time data management and feature extraction from different data sources as input vector to digital twins (actually the outputs of the real process).
- Use modular design for flexible production [31], enabling quick product changeovers and continuous biomanufacturing, with all its requirements for standardization of data interfaces.
- Provide the ability to integrate and run complex digital twins for timely control of product quality, including multiple-input and multiple-output (MIMO) and MPC algorithms, just as they have been in place in other market segments, such as the chemical industry, for decades. This is essentially a call for executing PAT (ICH Q8[R2]) in its full definition.
- Use similar real-time environment design throughout the product life cycle. The development environment needs to truly reflect the manufacturing environment capabilities.

Multiparametric control strategies

In real-world applications of data science to parts of the overall biopharmaceutical manufacturing process, we face challenges related to the significant multidimensionality of CPP and CQA interactions. We must ensure that the control strategy allows operational decisions in this multidimensional space and is not reduced to single independent controls. The use of single independent controls would lead to the loss of all process understanding links gathered in the development of the control strategy. We should allow multiparametric feedback control to detect deviations and automatically adjust operations, decision support, and advanced operator support.

Production control strategies

Beyond the pure process control strategy discussed previously, we need to generate agile production control strategies that allow agile and flexible production beyond the control strategy in the submission file and act on the complete value chain illustrated in Figure 1. This will enable ICH Q10 pharmaceutical quality systems to enter the next era of life-cycle management described in ICH Q12. Many data science and digitalization aspects such as process maps and process data maps have recently been proposed [14].

CONCLUSION

As data science–trained engineers, we have the obligation to show the profits of integrated tools and workflows. The key enabler of digitalization in the bioprocessing industry is the ability to handle knowledge. In this article, we briefly identified prerequisites for data alignment, contextualization, and integration, as well as recommend standards and interfaces. We emphasized the need for future efforts to improve data security and data integrity, and the importance of having sufficient sandboxes and test environments.

As this article makes clear, we need to develop integrated digital twins linking complete process chains for predictive end product quality. We also need to increase our focus on the validation, evolution, and maintenance of digital twins. The full potential of digital twins will be apparent when these tools are implemented in real-time environments: We can use them for both process control strategies and production control strategies. The latter type of strategy will be addressed in the second part of this series, where we focus on the ICH Q12 product life cycle.

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THE HISTORY AND FUTURE OF VALIDATION

By Anthony Margetts, PhD, and Line Lundsberg-Nielsen

Across every industry today, digitalization is driving the use and value of data to disrupt traditional business models and ways of working. In pharmaceuticals, the promises of Industry 4.0 are expected, and needed, to finally modernize the legacy approaches that have evolved since the 1970s. Validation is an obvious target for digital disruption because of the inefficient, document-heavy methods in place and the huge costs and time wasted, and because it is a barrier to efficient and effective technologies that can advance safer and better quality products. This article reflects on the history of validation and anticipated future directions.

The lead author of this account has used personal experiences to help tell the story. For this reason, the article uses the first person in parts of the narrative.

THE FIRST 50 YEARS

This history begins with the perspective of a leading figure in validation, James Agalloco, who just achieved a great milestone: four decades of being involved with ISPE. He has stated that the origins of validation in our industry can be traced to terminal sterilization process failures in the early 1970s [1]. One case was the 1971 Devonport incident, in which a batch of 5% dextrose IV bottles that were not correctly sterilized reached the market and were administered to patients. Sadly, five patients at a Devonport, England, hospital died after receiving the contaminated solution [2]. I knew the manager involved, and such tragedies refocused everyone in the industry on the fundamental importance of the safety of our drug manufacturing processes.

The first UK "Orange Guide," titled "Guide to Good Pharmaceutical Manufacturing Practice," was published in 1971. The edition released in 1983 included wording on validation. Today, the UK Orange Guide covers EU GMP, rather than British GMP [3]. Such international efforts have encouraged the standardization of regulations.

In the US, the GMPs for drugs (21 CFR Parts 210 and 211) and medical devices (21 CFR Part 820) were first published in 1978 and, like the Orange Guide, included validation as a central term in 1983. Current versions of the GMPs are available from the US FDA website [4].

At the Parenteral Drug Association Annual Meeting in 1980, Ed Fry of the US FDA gave a talk titled "What We See That Makes Us Nervous," in which he expressed the need to improve pharmaceutical manufacturing processes. The FDA recognized that processes were not robust, and throughout the 1980s, the regulators considered how to make companies more effectively validate their processes and published a series of seminal guidance documents, such as the 1983 guide to inspection of computerized systems in drug processing [5]. The FDA's discussions included concepts of scientific understanding based on process development. Despite these discussions, when the FDA published "Guidance for Industry: Process Validation: General Principles and Practices" in 1987, the guidelines did not mention the design of the process [6].

In 1984, however, Ken Chapman published a paper about process validation [7], which introduced the life-cycle concept and explained that the ability to successfully validate commercial manufacture depends on knowledge from process development. Chapman was also very active in the early days of computer validation, and he developed the idea that a computerized system consists of software, hardware, operating procedures, people, and equipment—and sits in an operational environment that has to be managed. This model is very important and relevant today.

In 1987, with increased understanding that computer systems were being used in manufacturing, the US FDA sent four inspectors to a master of science program in applied computing at the University of Georgia, Athens. In 1991, an FDA inspector visited Glaxo and Imperial Chemical Industries Pharmaceuticals manufacturing sites in the UK and Italy and, for the first time, the regulators raised concerns about the lack of validation of computer systems. These inspections led to the formation of the GAMP® Community of Practice to develop an industry-wide response to meet the US FDA's expectations. (For a history of GAMP, see reference 8.)

Table 1: Stages in US and EU guidance on the process validation life cycle.

Stage	US	EU
1	Process design	Pharmaceutical development or process design (ICH Q8)
2	Process qualification (PQ)	Qualification and validation
2.1	Qualification of equipment and utilities	Qualification (Annex 15) Installation qualification (IQ) Operational qualification (OQ) Performance qualification (PQ)
2.2	Process performance qualification (PPQ)	Process validation (PV) Traditional Continuous process verification (CPV) Hybrid
3	Continued process verification (CPV)	Ongoing process verification (OPV)

In the early 1990s, the FDA launched their preapproval inspections to affirm that commercial materials had their basis in the pivotal clinical trial process and materials. I had the experience of witnessing an inspector stop an audit because we could not demonstrate that the process being operated was the one used for the clinical trials. In the same inspection, the inspector asked specifically for validation plans and validation summary reports, now considered a central element of the quality system needed for manufacture of drug products.

A sequence of FDA investigations of Barr Laboratories that started in 1989 became a huge problem for the company, as inspectors repeatedly observed Barr's failure to follow cGMPs while the company disputed those findings. Ultimately, the conflict landed in the US District Court of New Jersey. In the 1993 case, *United States v. Barr Laboratories, Inc.*, Judge Alfred Wolin declared that process validation is required by GMPs [9].

In 2004, the FDA published "Pharmaceutical cGMPS for the 21st Century—A Risk-Based Approach" [10]. This included a reference to the revised compliance policy guide (CPG) for process validation [11]. Then, in 2011, 30 years after Ed Fry raised concerns and 25 years after Ken Chapman published his paper, the FDA published "Guidance for Industry: Process Validation: General Principles and Practice" [12]. In this guidance, the FDA adopted a life-cycle approach, moving from process qualification to validation in three stages, Stage 1: Process Design, Stage 2: Process Qualification, and Stage 3: Continued Process Verification.

Between 2005 and 2009, the International Council on Harmonisation (ICH) produced a series of quality guidelines emphasizing the importance of pharmaceutical development, the life cycle, and the framework of quality risk management [13]:

- ICH Q8 Pharmaceutical Development (2005; minor updates 2009)
- ICH Q9 Quality Risk Management (2005)
- ICH Q10 Pharmaceutical Quality System (2008)

Among the ICH quality guidelines, Q6 (1999), Q7 (2000), Q9, and Q10 specifically require assessment and approval of suppliers. Use of approved suppliers is an important part of the quality process. Q7 covers the life-cycle approach for active pharmaceutical ingredients.

In 2007, the American Society for Testing and Materials (ASTM) with ISPE involvement published standard ASTM E2500, *Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* [14]. This introduced a risk-based approach to qualification of unit operations in GMP manufacturing that leverages engineering activities to reduce qualification risk.

In 2015, Annex 15: Qualification & Validation was published as part of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use [15]. The next year, the EMA published two process validation guidelines [16, 17]. These guidelines used a similar life-cycle approach to the one used by the FDA; however, staging terminology varies (see Table 1).

In FDA guidance, activities covered by "continued process verification" include routine monitoring of process parameters, trending of data, change control, retraining, and corrective and preventive actions (CAPA). In EMA definitions, "continuous process verification" operates in place of process validation.

At the same time that regulatory authorities were producing guidelines and standards, the pharma industry and others introduced many improvement initiatives, including operational excellence, lean manufacturing, and Six Sigma. Around the world, companies outside of pharma adopted ISO 9000 quality management standards [18] as a basis for their quality system improvements, and they could see the benefits in the supply chains. Some companies could see the benefit of understanding the process as part of validation, but this was in complete contrast to many pharmaceutical companies around the world. In the pharma industry, most did not see process validation as a benefit. Instead,

they saw only a necessity to perform three consecutive process validation batches and document that performance.

Throughout the early decades of validation history, I watched the battles between regulatory teams trying to get processes registered with as much information as possible, and production teams that did not want to be too specific because they knew that they might fail in process validation, or later during commercial manufacturing. Much of the resistance to specificity stemmed from the burden of filing regulatory variances for what should be minor process changes operating as part of continuous improvement.

Since the new millennium, with the help of the FDA process analytical technology (PAT) initiative and ICH, more of us in the pharma industry have realized the importance of process development, risk assessment, and process understanding, and have come to understand that allowable limits for critical quality attributes (CQAs) and critical process parameters (CPPs) can establish a rational validation framework to help manufacture safe and effective products reliably.

In the era of science-based process validation and personalized medicine, the number of process performance qualification or process validation (PPQ/PV) batches must be justified for small molecules, large molecules, and advanced therapy medicinal products. We now realize that these processes require real-time monitoring of each batch to maintain them in a state of control. Fortunately, the EMA has stated that continuous process verification may provide a practicable method of managing batch-to-batch consistency, quality assurance, and quality control [16].

ISPE'S CONTRIBUTIONS

No history of validation can overlook the significance of ISPE's role in establishing GAMP and commissioning and qualification (C&Q) concepts.

GAMP

GAMP introduced a number of concepts that are important in validation today:

- The life-cycle model concept, which is now seen as fundamental for process validation.
- The expectation to see validation activity defined up front in validation plans and closed off by formally signed validation reports produced by the regulated company.
- The concept of the user requirement specification (URS) as a basis of qualification. This was developed further by ASTM E2500 [14] and by the ISPE C&Q guide [19].
- The concept of using approved suppliers, introduced in 1994.
- The concept of risk assessment, introduced in 2001.
- The V model to link specifications to verification, introduced in 1994. At that time, some companies wrote installation qualification (IQ) and operational qualification (OQ) documents that did not refer to any specifications. This link between specifications and verification is an important part of validation today.
- Key terms to help to focus risk assessment, including patient safety, product quality, and data integrity. In 2017, GAMP published an important guide dealing with data integrity [20], which is a fundamental part of process validation.

C&Q Concepts

The ISPE *Baseline Guide Vol. 5: Commissioning and Qualification,* originally published in 2001, was revised in 2019 [19]. The guide describes how systems are commissioned and critical aspects (CAs) and critical design elements (CDEs) are qualified. CAs and CDEs are linked to QCAs and CPPs. Facilities, equipment, and systems supporting processes should be qualified using these concepts to reduce the burden of non-quality-impacting documentation, and repeat testing, which were notable in the past.

Key aspects of C&Q include:

- Commissioning is executed and documented as Good Engineering Practice (GEP) [21].
- GEP verifies that the URS requirements are all incorporated, have been approved in the design review, and have been tested and documented as working in the acceptance and release report or qualification report.
- In GEP, everything is tested to ensure the system is fit-for-purpose.
- Systems are 100% (GEP) tested during commissioning, with approximately 10% of testing focused on the CAs/CDEs for qualification.
- The focus for qualification is on robust testing and documentation of the CAs/CDEs as appropriate to the level of risk controls applied.
- Lists of tests, test scripts, acceptance criteria, and traceability are all covered by GEP.
- Computer systems controlling equipment are qualified with the equipment.
- The C&Q guide is clear that quality does not approve commissioning documents. The guide notes that quality will approve the C&Q plan and the acceptance and release report.
- Typically, major pharmaceutical companies cover all the engineering associated with a new project in one C&Q plan and in the final acceptance and release report, so the role of quality assurance is limited to approval of these documents and the use of approved subject matter experts who oversee the qualification work.
- Much of the qualification supporting data can be provided by approved suppliers. The supplier assessment is an important step to deciding the validation strategy, and the validation plan should refer to the use of supplier qualification practices as much as possible.

LOOKING FORWARD

The following are important to incorporate into the proposed new "Validation 4.0" framework that will enable Industry 4.0 changes in the pharmaceutical industry.

Leveraging the Product Life Cycle

The life-cycle model concept builds on the importance of data from pharmaceutical development as a fundamental for process validation. Requirements are an output from development and needed as a baseline for everything—including processes, facilities, utilities, systems, and equipment—to define the CQAs, CPPs, CAs, and CDEs so that these can be verified later. Requirements can be handled as processes and more clearly understood by describing them using illustrative process maps. Processes are further detailed using data maps showing the flow and relevance of information at each step and activity across the end-to-end product life cycle.

Risk Assessment and Controls at Design

This part of the Validation 4.0 framework focuses on aspects of the process or system that are important to patient safety, product quality, and data integrity, and it allows the validation effort to be focused on critical areas.

Process and data maps are used to better understand the risks to the process, and the risks to data. Risk assessment and controls analysis should be started as early as possible during process and system development and specification. The control strategy is an important part of the design, and doing this work early allows for generation of suitable options that lower risk and a clear identification of the data that must be measured to ensure the state of control. Risk assessment can be used to evaluate data integrity to show where controls are needed to ensure that processes are operating correctly.

Data-Driven Process Validation

As noted previously in Table 1, the US FDA's structure for process validation has three stages:

- Stage 1 is the essential link to the development stage, covering process design and establishing the control strategy. It also includes the design of equipment and automation systems, assessment of input material attributes, process dynamics and variability, and development of strategies for process monitoring and control.
- Stage 2 has two parts: Stage 2.1, qualification of the equipment, utilities, and facility, demonstrates the equipment and systems work as intended. Stage 2.2 demonstrates the robustness of the manufacturing process and the adequacy of the control strategy (i.e., verification of the control strategy).
- Stage 3, continued process verification, provides continual assurance that the process remains in a state of control during commercial manufacture.

Annex 15 of the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme (PIC/S) GMP guide [22] describes the requirements for process validation in some detail and includes the points described earlier from US regulations. The PIC/S guide also states that for products developed by a quality by design approach, where it has been scientifically established during development that the control strategy provides a high degree of quality assurance, continuous process verification can be used as an alternative to traditional process validation.

CONCLUSION

Validation is here to stay—it is an integral part of regulatory requirements and of the manufacturing component of the healthcare environment. The added value of validation must be to demonstrate that the manufacturing system is fit for the intended use, and that the control strategy clearly reduces the risk to patient safety. Also, validation in itself should not be a barrier to innovation.

Continuous process verification is a key target for Validation 4.0. We need to develop methods that encompass the continuous monitoring of data, from the process and the risks to the control strategy, to ensure our processes are always valid. By building in feedback to the process, we enable a control model that can develop and respond to change, and we can monitor processes in real time.

Because parts of the model may change during operation, monitoring of the process and risks is necessary and will ensure that we constantly learn more about the process as it becomes mature through the product life cycle. Establishing this concept early and systemizing it in tools is expected to be an effective way to move toward the application of digital twins. A digital twin is a replica of an intended or operating process, which can be used to plan and analyze the process and understand the effect of design and proposed changes.

A stated goal of Validation 4.0 is to potentially eliminate Stage 2 of process validation (verification of the control strategy by testing). By bringing R&D and Stage 3 operations closer together and moving to continuous verification from real-time data, we can speed up the validation process, keep up with innovation in the new digital world, and reduce risks to patient safety.

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About the authors

Anthony Margetts, PhD, is Principal Consultant at Factorytalk in Thailand. He has 50 years of experience in the chemical/pharmaceutical/medical device industries and is an expert in the fields of GMP compliance and validation for the healthcare industries. He worked for AstraZeneca (formerly ICI Pharmaceuticals) leading teams responsible for new product introductions and preparations for European and US FDA preapproval and regulatory inspections. Tony was chairman for the editorial review of the latest version of GAMP® 5, now the global reference for computer validation in healthcare industries. He received his BSc in chemical engineering and PhD in chemical engineering from the University of Birmingham, UK. Tony has been an ISPE member since 1995.

Line Lundsberg-Nielsen runs her own consultancy business and works as a consultant for NNE supporting clients in developing and implementing manufacturing processes for pharmaceutical products. She has spent more than 20 years in the pharmaceutical Industry. She holds a PhD in PAT. Her work focuses on science- and risk-based approaches in QbD, PAT, control strategy, process validation, qualification, technology transfer, and Pharma 4.0™. Line has served in many roles as an ISPE member. She is currently the Chair of the global PAT & LCS CoP steering committee, serves on the advisory board of the Pharma 4.0™ SIG, and is a member of the Validation 4.0 working group. Line has been an ISPE member since 2001.

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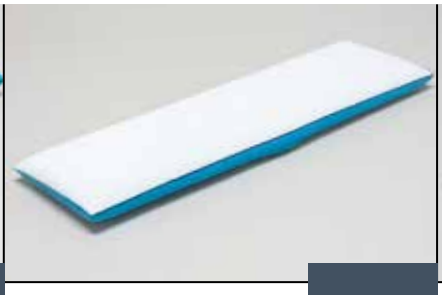

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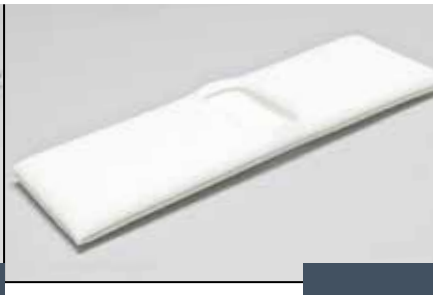

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BREAKING WITH TRADITION:
Laying the Foundation for Validation 4.0

By Michelle Vuolo and David Margetts

A fundamental GMP requirement is that processes, systems, and methods used to produce medicines and treatments are validated, meaning their fitness for purpose is demonstrated. If Industry 4.0 is to succeed in the pharma space as Pharma 4.0™, we need new paradigms for validation across the value chain that use new technologies to improve product quality and the safety of medicines and treatments for the patient [1]. We must transition from our old ways of approaching compliance to embrace this new age of data-powered technology. This article lays the foundation for shifting our mindset and achieving Validation 4.0.

Despite notable initiatives since the early 2000s from regulatory leaders such as ICH, the US FDA, and EMA, the pharma industry has struggled to move on from legacy quality management approaches. The original ICH statements that led to Q8 [2] were intended to modernize pharmaceutical quality systems through a focus on quality risk management [3] and quality by design (QbD). These concepts should have also been a basis for implementing new technologies, as the ICH concepts offer a framework to cope with inherent variability, and allow for a compliant flexibility needed for manufacturing increasingly sophisticated, even personalized medicinal products. However, for pharma organizations and regulators alike, the topic of validation has been a central obstacle to adopting new concepts for quality.

As we look to overcome this obstacle, several questions about validation must be addressed: What would it mean to not write documents in the regulated environment? What do QbD and data integrity mean when applied to a manufacturing facility? Can we move beyond three stages of process validation [1] to defining a control strategy and then continuously verifying that control? We invite you to think about what the answers to these questions might mean for you.

RETHINKING WHAT WE DO

To illustrate the need for a new mindset, let's start with a simple example derived from the definition of validation: establishing documented evidence of fitness for purpose. Generally, this principle has been interpreted as a requirement for documentation in either physical or electronic form. For example, during up-front validation testing, documents are used to record how the introduction of a process or system was controlled to ensure it operates correctly.

However, for Validation 4.0, we need to move on from creating historical documents of what was tested to focus instead on real-time verification of product quality by managing specification and evidence data around a process that is in a state of control throughout the life cycle. Standalone documents are clearly not suited to continuous verification, and the masses of documentation created by both suppliers and regulated companies in the name of validation are inefficient, difficult to maintain, and perhaps not auditable.

In the Industry 4.0 world, connected data and systems are subject to rapid and constant change for iterative improvement, and they are now being enabled for autonomous improvement. Instead of relying on difficult to maintain silos of documentation, we look toward digital artifacts managed with appropriate tools that can instantaneously provide reporting and notifications on the state of control. The systems used widely today by agile software developers for multitenant cloud solution providers are a good reference point for Validation 4.0: by adopting the usual tools of software engineers, we can leverage and integrate quality management efforts into our ongoing activities of continuous verification beyond what is possible with static documented evidence.

DATA IS THE FOUNDATION

Data integrity has been a buzz term for years now. A whole subindustry has been built around this concept, and yet we still fail to truly embrace what it means and how to implement it. Data is the foundational element of validation and the basis for decision-making. When we consider validation, we need to shift our focus to how we control the data that allows us to make GxP decisions, and look at validation under a QbD lens.

Validation 4.0 is a holistic and integrated approach to validation with process and data flows at its foundation. Let's follow the product journey that starts with an unmet patient need. To characterize a product intended to meet that need, QbD principles suggest that we begin by defining critical process parameters (CPPs) and critical quality attributes (CQAs). CPPs are defined to control the quality outputs, and we have to understand the critical quality, process, equipment, and material attributes to measure and control them within a defined range of variance that produces a quality product. This design space is an output of product development and the basis for handling inherent variability. It is then expected that as the product moves to actual production, real-time process data will be available and monitored so that the design can be refined. By bringing the QbD concept into Validation 4.0, we further encourage the early definition and use of data points to control and ensure the desired product quality attributes.

A quality risk management approach should be integrated with QbD and applied at the process and data flow level as a part of the design process (Figure 1). First, traditional user requirement specification (URS) statements are replaced by process and data maps (PDM). In Industry 4.0, data are referenceable, used throughout a process, and a basis for making effective decisions. By building a validation model that incorporates the process and key data early in design, we get a head start on defining the associated risks and the needed controls.

Following the initial process and data definition, the focus of validation changes from qualification testing to ongoing and constant assurance that the needed controls are in place and operating correctly. This continuous verification of the process and risk is the primary evidence that the process is in a state of control. By using real-world data to feedback into our process, data, and risk evaluation, we can be assured that our products are constantly manufactured and released based on sound data, and through this model, we can continuously reassess risk conditions and handle inherent process variability.

FROM PROCESS VALIDATION TO VALIDATION 4.0

As the US FDA has stated, "effective process validation contributes significantly to assuring drug quality" [4]. Process validation is a series of activities that occur over the life cycle of the product. Table 1 presents how the three stages of process validation can apply to Validation 4.0.

Figure 2 illustrates the holistic view of the Validation 4.0 life-cycle model and how it relates to the product life cycle. In this

Figure 1: Integrating quality risk management and data flow management during product design.

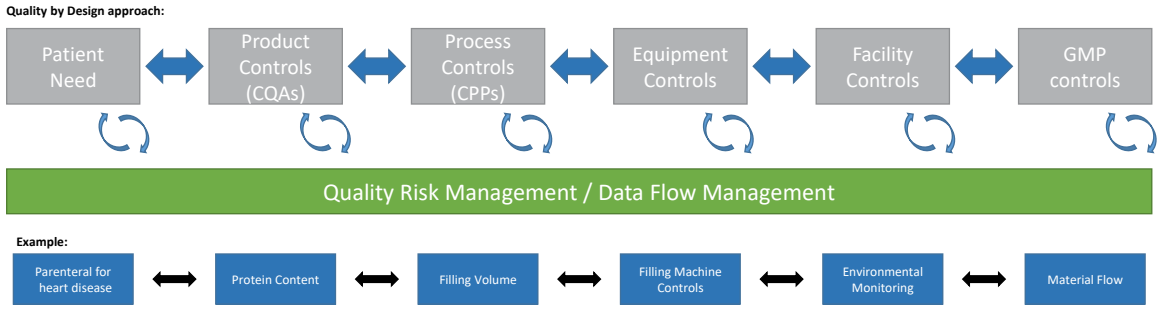
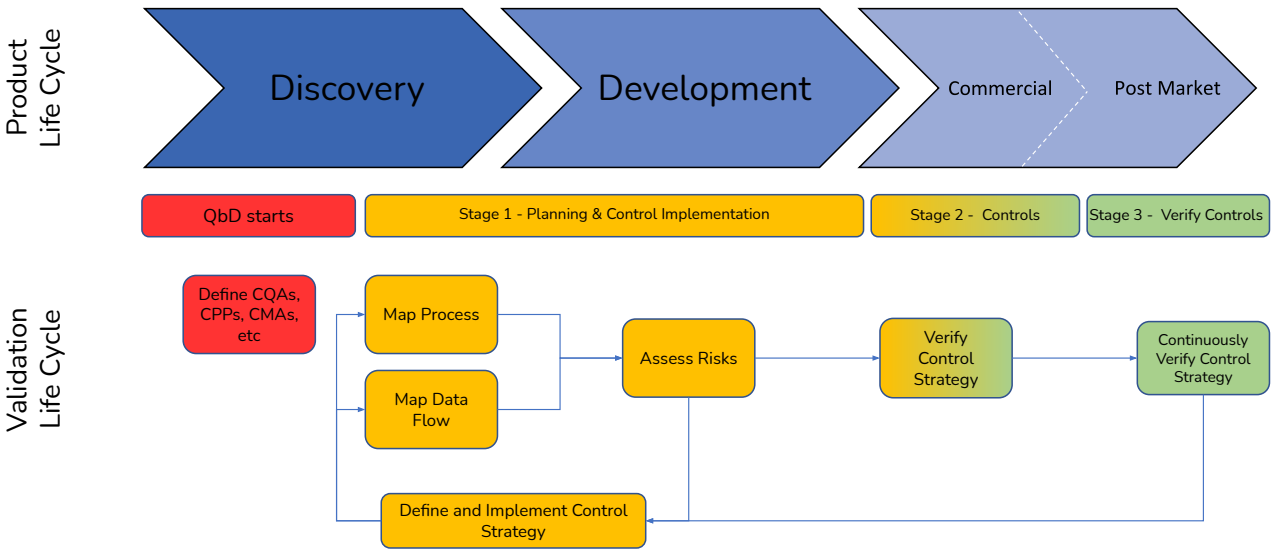


Table 1: Applying process validation stages to Validation 4.0.

Stage	Process Validation	Validation 4.0	Justification for Validation 4.0
1	Process design: • Build and capture process knowledge and process understanding. • Create quality target product profile. • Identify CQAs. • Design a process suitable for routine commercial manufacturing that can consistently deliver a product meeting the CQAs. • Define CPPs. • Establish a control strategy for ensuring the product will meet the quality requirements. • Conduct risk assessment(s).	Holistic planning and design: • Define requirements as process and data flow maps • Identify critical attributes and parameters from the process, materials, equipment, and external threats for ongoing monitoring. • Conduct process and data flow risk assessment at the design stage, incorporating criticality and vulnerability to define the control strategy, and to implement data integrity as a fundamental aspect of QbD.	• The output of this stage is a holistic control strategy that builds on knowledge from product development and focuses mitigation and decisions on the data. • Data-centric approach provides a basis for utilizing systemized tools for process design and enabling digital twins.
2	Process qualification/process validation: • Collect and evaluate data on all aspects of the process (from raw materials to finished and packaged materials, as well as the facility). • 2.1: Qualify facility and equipment (URS, factory and site acceptance testing, and design, installation, operational, and performance qualification). This may involve specific equipment qualification considerations. • 2.2: Evaluate the process designed in stage 1 to verify that it can reproduce consistent and reliable levels of quality.	Verification of controls: • Verify with evidence that the controls defined in the process and data flow risk assessment are in place and operate appropriately to provide the expected risk mitigation. • Automate to rapidly ensure that planned controls are in place/effective.	• Through model maturity and systemized tools, stage 2 may no longer be required because design includes the controls needed to ensure a product is fit for use; instead, can move directly to continuous verification. • Process results, risk controls, and parameter verification are moved to stage 3, where monitoring of process conditions and dynamic risk aspects and real-time data determines whether the process and controls are operating correctly.
3	Continued (ongoing) process verification: • Verify in an ongoing manner that the process continues to deliver consistent quality. • Detect and resolve process drift.	Continuous verification of implemented controls: • Link the operational-stage data back to the process and data maps and specifications to verify actual risk/control status continuously. • Incorporate data from across the value chain (from raw material suppliers to patients) and product life cycle to evolve the control strategy into a holistic control strategy.	• Handling inherent variability and change in process and risks is part of the overall method. • Real-time data are used to review whether initial assessments remain valid and to determine controls that enable flexibility in manufacturing (e.g., process analytical technology). • Through model maturity, opportunities are provided to apply digital twins,* analytics, and machine learning to simulate the impact of proposed changes before they are operationalized.

*A digital twin is a digital replica of a physical asset. It can be used for various purposes, including to evaluate the impact of one variable on another.

Figure 2: Stages of Validation 4.0.



Stage 2 ultimately ceases. Planning/Control Implementation moves directly into Verify Controls, which is a continuous activity.

model, data from across the product life cycle are key in creating holistic control strategies and continuously verifying them to demonstrate fitness for use, and real-time data from the actual operating process and its critical parameters are checked as part of continuous verification. Additionally, ongoing assessment of process/data risks is part of the overall integrated method to understand whether a process is in control, to evaluate inherent variabilities and refine control limits, and to consider dynamic risks as they change and trend over time.

CONCLUSION

By moving to a process- and data-centric approach to validation, and finally establishing a baseline for incorporating QbD, the pharma industry can move to continuous assurance of product quality throughout the product's life cycle, and at every point in time. The Pharma 4.0™ Special Interest Group recognizes that we do not yet have all the answers, but it is imperative that industry stakeholders work together now to ensure validation moves forward to take full advantage of the positive disruption of digitization, which may include automation, process analytical technology, and feedback loops, as well as data conversion and accumulation. The Validation 4.0 working group is currently working on next steps, including case studies. Please reach out to our working group via the authors with your comments, feedback, and any examples to help shape Validation 4.0.

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About the author

Michelle Vuolo leads the quality practice at Tulip Interfaces, Inc, which develops and sells an industrial operations platform where manufacturers from many industries can build digital content to manage their operations. Before that, Michelle spent over 24 years in the biopharmaceutical and medical device industries in many different roles, ranging from quality control laboratory, engineering technical support, quality assurance management, and computerized systems compliance. Michelle has been an ISPE member since 2008.

David Margetts is the CEO and Cofounder of Factorytalk, providing quality and technology consulting and solutions to the pharma and biotech industries. Dave has lived in Asia since 2004 and works extensively across the globe on key assignments to build businesses, develop ideas, and deliver projects through the leadership of successful teams. Dave's interests are to modernize pharma's quality approaches, and to design and enable solutions that bring Industry 4.0's benefits into GxP manufacturing. Prior to his move to Asia, Dave worked in engineering roles at ITS and AstraZeneca in the UK. He has been an ISPE member since 2004.

ISPE Aseptic Conference Turns 30

The ISPE Aseptic Conference will celebrate its 30th year with the virtual conference on 15–17 March. The conference has been setting the pace for the evolution of sterile manufacturing processes and technologies in the pharmaceutical industry. This year's virtual conference platform is providing a unique opportunity for expanded global participation by speakers and attendees.

For perspective on this important anniversary for the Aseptic Conference, *Pharmaceutical Engineering*® spoke with Jörg Zimmermann, Vice President, Vetter Development Service, External Affairs, at Vetter Pharma Fertigung GmbH & Co. KG, and Vice Chair of the ISPE International Board of Directors. Zimmermann is also Chair of the Program Committee for the Aseptic Conference.

What have been the most significant developments presented on at the Aseptic Conference?

This conference has been instrumental in moving developments forward in aseptic processing. When the conference started 30 years ago, processes had not been optimized much from the early days of sterile products, which had their breakthrough with the first hormone extracts in the 1920s and antibiotics during World War II.

When the conference started, RABS [restricted access barrier systems] and isolator barrier systems were still in their infancy and a lot of open questions needed to be resolved: How to design, qualify, and operate such advanced systems? Which previously manual operations can be automated? How about environmental monitoring? By exchanging experiences within this group of industry experts, the technical advancements were accelerated and have shaped the industry. The standards that we have today would not have been possible without this conference.

What was also instrumental was the open and honest exchange with representatives of the regulatory authorities. In the end, we have all helped improve the processes to get to the ultimate goal: to provide safe, sterile medicines to patients, free of microbes, particles, and pyrogens.

What is your favorite conference memory?

This is a difficult question because there are so many wonderful moments. We have had great conferences in Tampa, with cocktails by the pool in February, we met in Baltimore in the snow and people struggled to get there because of the snow, we had conferences in Washington within walking distance of the White House…but the best was always to meet old friends, and to get to know new people from all over the world, not only on a professional level but also on a personal level. Many friendships have formed over the years.


Jörg Zimmermann

What challenges have you faced in creating the conference each year?

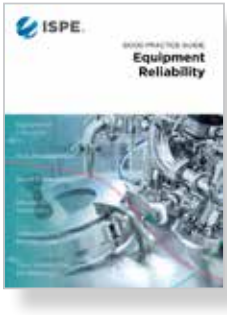
My most challenging task at one time was when a keynote speaker canceled less than 24 hours before going on and we had to rearrange the program—we had 300+ people coming in, expecting to hear the talk! We managed, but it was a close call. In another year, we were threatened by the government furlough, and there was a chance that the FDA representatives would not be able to join.

The key to success is that we have a wonderful program committee that does work year-round on the conference. We have sketches for the conference agenda two to three years out.

Why do you think that this conference has become such a tradition in the industry?

With all the developments that the conference has helped to shape, it has been established as the go-to gathering for aseptic processing. People know that they will hear about the latest and greatest; they know that they will meet the right experts and will get their questions answered. This helps them in their everyday jobs, whether they are new to the field or veterans. The high quality of the content and the open sharing of lessons learned from real-life projects is what makes the conference unique.

For more information about the Aseptic Conference, visit the ISPE Conferences site at ISPE.org/conferences



New Good Practice Guide on Equipment Reliability

Equipment reliability helps reduce and manage the risk of failures in equipment, providing focus on availability, fitness for purpose, and cost. Reliable equipment improves the likelihood of achieving reliable manufacturing operations, which improves the supply of critical therapies to patients worldwide.

ISPE's new *Good Practice Guide: Equipment Reliability* provides practical guidance to help pharmaceutical organizations proactively improve equipment reliability at all stages of the equipment life cycle, from design to decommissioning. This guide focuses on the systematic reduction of equipment performance variation and its operating impact through improved equipment design and management. It addresses the events and consequences of equipment failure, while providing guidance on effective tools and strategies for an effective reliability program.

Produced and reviewed by industry experts, the guide is a must-have reference for anyone who is involved with designing, implementing, operating, or maintaining equipment assets.

"As innovation extends to and transforms the supply chain, equipment life-cycle costs and availability become ever more relevant to maintaining a competitive advantage," said Michael Berkey, Guide Team Lead, and Associate Director, Merck & Co., Inc., Kenilworth, New Jersey, US. "The strategy and tactics of reliability can help companies maintain the value of their equipment throughout its useful life and mission, and the application of asset management principles can help companies leverage equipment toward a competitive advantage."

More information about this and other guides is available at ISPE.org/Publications/Guidance-Documents

—Marcy Sanford, ISPE Editorial Assistant

MEET THE ISPE STAFF

LINDA WALLS

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Linda Walls, Manager, Data Production and Analysis, Administration/Information Technology.

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

I joined ISPE in 2009 as a Data Services Coordinator. In 2013, I was promoted to Manager, Data Production and Analysis, and in 2019 the position moved from the Membership group to IT. This change increased the responsibility of data analysis and reporting from one department to supporting the entire organization.

In addition to data analytics, I troubleshoot association management systems (AMS) issues, test new enhancements, assist with event setup, and manage small projects.

I am a native Floridian (US) and a cum laude graduate of Florida A & M University. I hold a bachelor of science in computer information systems.

What do you love about your job?

To hear these five words from management and colleagues is very rewarding: "The data is very helpful."

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

I am a caregiver for my 88-year-old mother who has dementia. During the global pandemic, I enjoy reading (the best book ever written is the Bible) and taking walks with my dog, Roscoe.

AUTOMATING MACO CALCULATIONS in Cleaning Validation

By Puneet Sharma, Anthony Marrero, Matt Coates, and Bill Henry

For a multiproduct facility where equipment is shared, there is always risk from cross contamination. The correct calculation of the cleaning validation limits from maximum allowable carry over (MACO) of a marker compound to the next product is vital for the integrity and success of the cleaning validation program. However, the process yielding those limits often involves cumbersome, error-prone manual calculations. Herein, we describe an innovative yet simple tool that uses a combination of spreadsheet software and a statistical platform to fully automate science- and risk-based MACO calculations in pharmaceutical cleaning validation.

A reliable cleaning validation program is essential to GMP manufacturing and helps enable a manufacturing unit to deliver quality products on time and in full to market. The success of this program—along with other quality and compliance programs such as process validation, corrective and preventive action (CAPA), and change control systems—is an important prerequisite of a well-instituted quality management system.

The pharmaceutical industry has come a long way in embracing the value of cleaning validation programs for seamless manufacturing. Health and regulatory agencies such as the US FDA [1], EMA [2], and Health Canada [3] and organizations like ISPE [4], the Parenteral Drug Administration [5], Active Pharmaceutical Ingredients Committee [6], and ASTM International [7] are deeply committed to educating the pharmaceutical community by developing and sharing content built on the foundations of good GMP principles and best practices.

In the past two decades, there has been considerable discussion on how to identify the marker compound (the product most difficult to clean based on solubility, toxicity, therapeutic dose, and degradation potential, also referred to as the worst-case product) and calculate MACO risk of the marker onto the next product. The industry has made a significant leap from releasing equipment solely based on visual criteria to establishing acceptance cleaning limits based on science and an understanding of the risks associated with manufacturing different products/dosage forms in a facility. Today, the criteria for both visually clean and acceptable residue of the active substance/cleaning agent for equipment release are embedded in most companies' quality management systems.

There is general agreement among health authorities and technical groups that the MACO should be scientifically calculated through one or more industry-recognized approaches (health-based, therapeutic, toxicological, and 10 parts per million [ppm] methods), leading up to derivation of a cleaning validation acceptance limit. There are, however, differences of opinion and differences of approach both within and between companies regarding the ways MACO is calculated and reported. The objective of this paper is not to recommend one approach over another but to describe the creation of a program that would harmonize the standards within the company, remove confusion, and produce error-free output for cleaning validation limits while allowing users to have all available information. The final decision of which limit to choose resides with the technical and quality staff and requires appropriate justification. The goal throughout the selection process is to demonstrate that the carryover amount of an API will not pose a safety risk to the end user.

As reported by Walsh [8, 9], the methodology used to calculate and maintain cleaning validation limits can be cumbersome and, at times, error prone. The results are calculated and generally reported as data tables in a spreadsheet (e.g., Microsoft Excel). With time, as new products and equipment are introduced and others decommissioned, these spreadsheets grow and can become difficult to maintain and comprehend. It is not uncommon to find

that information about the marker compound and MACO is not updated with the introduction or decommissioning of products or equipment. This can cause serious issues, perhaps leading to noncompliance and/or recall, depending on the gravity of the miss. There is also a risk of knowledge loss during the transfer of these documents, especially in organizations that rely heavily on manual processes.

The authors of this paper (referred "we" or "the central team") have developed and validated an innovative yet simple tool to fully automate cleaning validation calculations in a compliant and user-friendly manner. This original paper presents the prerequisites, methodology, validation, and technology used to develop the program. We also describe the final report containing data tables, graphs, contextual text, and concluding remarks, along with raw data and formulas, which can be treated as a GMP document for audit and inspection purposes. We refer the tool as the cleaning validation limit macro (CVLM).

CVLM OVERVIEW

In its original usage, a macro is a user-defined function designed to reproduce a sequence of inputs performed within a software application, often created by recording a sequence of actions. Within Microsoft Office applications, Visual Basic for Applications (VBA) replaced the macro languages that existed in earlier versions. Programs written in VBA and similar application-specific languages are thus often referred to as "macros," even though the programs concerned are often a great deal more sophisticated than a simple recorded automation sequence.

The CVLM is written in Statistica Visual Basic (SVB), a Visual Basic variant that allows automation of the data analysis and graphical capabilities of Statistica. The program is not an algorithmic model in its strictest sense, but it utilizes a set of deterministic equations. The macro exploits these capabilities to produce customized graphs and tabular output, which are embedded in a time-stamped report document, along with dynamically produced explanatory text.

The CVLM is deployed via a secure enterprise-level system, ensuring that all users have access to the most recent validated version.

DEVELOPMENT PROCESS

With support from leaders of manufacturing sites, we identified validation, quality, technical, and engineering representatives to establish a "local-team" framework. The local teams collaborated with the central team to provide

- the list of the products manufactured (and APIs used) in their respective sites;
- physicochemical data on the APIs' solubility, toxicity, potency, and cleanability to be used in calculating the MACO;
- the list of cleaning agents with their composition, acceptable daily intake (ADI), and safety data; and
- relevant local and regional regulatory policies affecting cleaning validation.

The criteria used to select the internal manufacturing sites were based on the sites' geographical locations, experience with manufacturing different dosage forms, competency levels, and readiness to support this program. The decision to initially include only a few manufacturing sites complemented the "agile development" approach of the program, which allowed feedback to be received at the development stage and used to address gaps in real time. The contract manufacturing organization/third-party sites were not included in the program scope due to contractual limitations and complexities associated with managing the multiple and diverse quality management systems under one program.

Based on the knowledge gained of the program "wants" from local teams, we developed a blueprint or user requirement specification (URS) for the CVLM program with the following design principles in mind.

Science- and Risk-Based Program

The literature offers, with some nuances, plenty of information on ways to identify the marker compound and calculate MACO. The approaches currently used in the industry are varied, and at times disjointed, and may sometimes involve data sources and modes of calculations that are incorrect or unverifiable. The lack of a reliable validated system can promote the overuse of "visual clean" (equipment dried and free of visible dirt on the surface) as the sole criterion for equipment release after cleaning. In addition to reducing the complexity of identifying the marker compound and making the calculations error-proof, the CVLM program is at its core based on the use of science- and risk-based principles where quantitative determination of MACO/cleaning limits through swabbing or rinsing is used to make quality decisions.

Thus, it was decided that the CVLM program shall leverage already established science on MACO through four commonly used methods and use of a product-equipment matrix. The program should be flexible, defensible (stand the test of regulatory inspections), and relied upon for quality decisions.

Data Management Tool

The CVLM has a standardized file format where data on actives, cleaning agents, manufacturing, cleaning, and so on, will reside. Excel was selected because of its familiarity, ubiquity, and the ability to implement audit trail/traceability functionality.

Statistical Software

Statistica was chosen for the analysis platform because it is the standard, validated, statistical software used in our organization, which has trained users at every site. We started with version 12.0 and the most recent version installed is version 13.5. Any other similar tool with an integrated macro language (e.g., JMP or Minitab) and the capability to import external data files could have been used.

COMPUTATIONAL DETAILS

It is not our intent in this paper to dive deeply into the history of the MACO evolution, but a brief discussion is necessary to apprise

Table 1: Physicochemical properties criteria of APIs.

Solubility Definition	Parts of Water Required for 1 Part of Solute	Risk Rating
Very soluble (VS)	<1	1
Freely soluble (FS)	1–10	
Soluble	10–30	
Sparingly soluble (SPS)	30–100	3
Slightly soluble (SS)	100–1,000	
Very slightly soluble (VSS)	1,000–10,000	5
Practically insoluble	≥10,000	
Toxicity	**Oral LD_{50} (single dose to rats), mg/kg**	**Risk Rating**
Practically nontoxic	>5,000	1
Relatively harmless		
Moderately toxic	500–5,000	3
Slightly toxic		
Extremely toxic	≤500	5
Highly toxic		
Potency	**Concentration, mg/kg**	**Risk Rating**
Low risk	>10	1
Medium risk	0.5–10	3
High risk	<0.5	5
Ease of Cleaning		**Risk Rating**
Easy	*Criteria based on operator/cleaning specialist feedback*	1
Moderate		3
Difficult		5

readers of the criteria followed for risk rating and identification of the marker compound.

Marker Compound Identification

Factors such as solubility, toxicity, potency, and cleanability of an API play a pivotal role in the development of a cleaning process. The marker compound is determined from the formula with risk factors that are unique to each API. We employ the following formula for risk rating, where the APIs' parameters, based on their role and criticality in cleaning, follow the order of solubility (SOL) > toxicity (TOX) > potency (POT) > ease of cleaning (EOC):

$$\text{Risk rating} = (\text{SOL} \times 10) + (\text{TOX} \times 6) + (\text{POT} \times 4) + \text{EOC}$$

The parameters are assigned a severity rating of 1, 3, or 5, based on the API's physical, chemical, and toxicological data from USP [10] and the OPP/GHS [11] ratings (Table 1). The assigned value of each parameter is multiplied by an arbitrary number of a magnitude that brings adequate separation and matches with the order of criticality. However, the formula could be modified according to any organization's product range and quality requirements.

When the formula is executed, it assigns a risk value to each of the actives in scope. The API receiving the highest value is identified as the marker compound. Where two or more APIs show the exact same risk rating, the selection can be based on relative toxicity, frequency of batching, or any other factor as justified.

MACO Calculation

The CVLM program calculates MACO using four methods: health-based exposure limit (HBEL), therapeutic dose, toxicological, and 10-ppm approaches. Different safety factors were used, depending on the route of administration, and as accepted widely by the industry. Table 2 shows the formulas used in the CVLM [12].

In the case study later in this article, the median lethal dose (LD_{50}) was used to calculate ADI. However, depending on the stipulations of the quality management system in the organization,

ADI determined from animal toxicological studies (overt toxicity, biomarkers, exaggerated pharmacodynamic effects) to derive a safe starting dose in humans can also be used, if available. Irrespective of the approach used, the macro can easily be adapted to incorporate future changes.

Cleaning Validation Limit/Acceptance Criteria

Before the cleaning validation limit is assessed and applied, an analytical method with adequate sensitivity, specificity, and recovery should be developed and validated. The sampling of the cleaned surface with a suitable swab material or rinse solvent is an important next step to calculate the cleaning validation limit. Generally, predefined areas (usually 10 cm × 10 cm) are swabbed or rinse samples are collected with a known volume of solvent. The formulas used to calculate the swab or rinse limit for each MACO are as follows:

$$\text{Swab limit (mg/swab)} = \frac{\text{MACO (mg)}}{\text{Surface area (cm}^2\text{)}} \times \text{Swab area (cm}^2\text{)}$$

$$\text{Rinse limit (mg/rinse)} = \frac{\text{MACO (mg)}}{\text{Rinse volume (mL)}}$$

For each method of calculation, the lowest MACO and cleaning limit are obtained and proposed as acceptance criteria for cleaning validation. For most cases, the selection of the limit is straightforward and based on patient safety; however, there are other factors that could impact the selection, requiring further assessment. The technical and quality staff are responsible for the final decision with appropriate justification.

EXCEL DATABASE

The Excel database (the structure of which is described in detail later) used to manage the source data for the Statistica CVLM has multiple worksheets. For example, an API table worksheet contains data for HBEL, LD_{50}, and solubility ratings for each API, and a formula table contains data for the minimum batch size of the next product (grams), ease-of-clean risk, and adult/child designation for each formula. If the product is meant for both adults and children, the user is instructed to use the child bodyweight for a conservative estimate. Details that could be helpful in developing an equivalent system include:

- The system checks for duplication of data, such as multiple entries for the same API or formula.
- The system alerts the user with warning messages when any inconsistent information is entered.
- The system allows some cells to be left blank and the database saved for later completion.
- The Windows clipboard may be used to paste information, provided that the validation rules are met.
- A non-editable audit trail is created automatically, logging all changes to the data, with user ID and time stamp.

Table 2: MACO calculation formulas.

MACO Type	MACO Formula
HBEL	$\frac{\text{HBEL} \times \text{MBS}}{\text{MDD}}$
Therapeutic	$\frac{\text{MTD} \times \text{MBS}}{\text{SFt} \times \text{MDD}}$
Toxicological	$\frac{\text{ADI} \times \text{MBS}}{\text{SFt} \times \text{MDD}}$
10 ppm	$(10 \times 10^{-6}) \times \text{MBS}$

Key: ADI: Acceptable daily intake, (mg); HBEL, health-based exposure limit value of the previous product (mg/day); MBS, minimum batch size of the next product (mg); MDD, maximum daily dose of the next product (mg); MTD, minimum therapeutic dose of the previous product (mg); SFt, therapeutic safety factor. SFt was set at 1,000; being in the denominator, it makes the result more stringent. The program converts all values to milligrams for ease of data manipulation.

As described later in this article, the database template was validated before the official rollout of the program. For the scoping brief, six global pilot sites were identified and, after validation, the sites were advised to save the master template as a local copy and populate it with their own data, as necessary.

In use, the database is maintained and controlled by the sites for all products manufactured. Once fully populated, the database file can be quickly updated to add or remove any information and assess the impact on existing cleaning validation procedures. The audit trail is a key feature of the database as it records all data entry, modification, and deletion actions. It also serves as a control mechanism for GMP review and audits.

MACRO DESIGN AND OPERATION

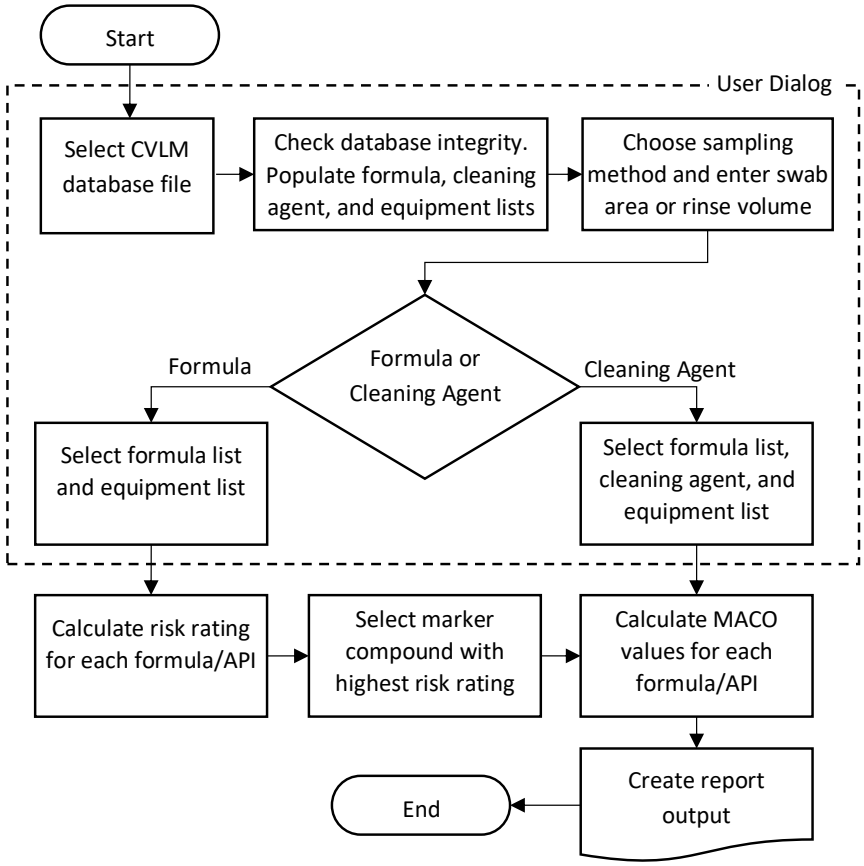
The macro is modular in design to allow easier maintenance and future updates, such as new methods of calculation or changes to address regulatory requirements. Separate subroutines were written for each method of calculating MACO, risk ratings, and limit values; each graph and table of results; and supporting functions such as report creation and text formatting.

Graphical and Tabular Output

The calculated results are reported in tables and graphs. The graphical output can be used to quickly and easily compare results, whereas the tables provide additional detail and full numerical precision.

Two graphs are produced and included in the report output (see the case study later in this article for an example):

Figure 1: Macro operation flowchart.



- A risk rating plot shows the overall risk rating for each formula/API combination, sorted so that the compound with the highest risk (the marker compound) appears at the top. The plotting symbol and color are determined by the toxicity rating, whereas the batch size is displayed as a label.
- A MACO plot shows all four calculated MACO values for each formula/API combination, sorted so that the compound with the lowest MACO value (from all the methods) appears at the top.

Program Operation

The flowchart in Figure 1 shows the steps that are processed within the user dialog during program operation. These are illustrated further in the case study.

User interface

On execution, a dialog is displayed that allows the user to select a CVLM database file. A database integrity check is then performed to verify that a valid database file containing at least the minimum required information has been selected. The dialog then allows the user to choose a sampling method and quantity (area for "swab," volume for "rinse") and either "formula" or "cleaning agent" approaches. If the cleaning agent option is selected, dialog controls offering the formula, cleaning agent, and equipment lists obtained from the database file are activated. If the formula option is selected, only the formula and equipment list controls are shown. The formula and equipment controls both allow multiple items to be selected, whereas the cleaning agent control allows only a single item to be selected.

The dialog checks that all necessary information has been provided before allowing the calculations to proceed. A secondary dialog is used to collect the number (count) of each selected piece of equipment required for the current equipment train, up to the maximum number specified in the database file.

Computations and report output

After the user selections have been completed, the macro proceeds to perform the necessary calculations and produce the output report.

The individual tables and graphs, along with other supporting results, are also stored in a Statistica output workbook, where the output can be further customized or used as input for other analyses.

MACO calculations can only be performed where complete information is available. For example, if the database is missing the therapeutic dose variables for an API, only the HBEL, toxicological, and 10-ppm MACO values will be calculated for this API. Both the Excel database and the macro program have built-in notifications that alert the user of any missing data, and the program will not run if any critical pieces of information are missing. However, we took the approach that the software should perform all calculations possible with the available information, rather than simply refusing to proceed. The final decision about which method(s) to use is left to the user in accordance with company policies.

In addition to the main report, an event log, including any warning messages generated during the execution of the macro, may also be produced. The warnings produced may relate to the database integrity check, any APIs that are missing critical information, or any other issues that were encountered in the calculation of the risk rating, MACO values, and so on.

CASE STUDY

The use of the CVLM is illustrated using an arbitrary example wherein two single-API products (A and B) share manufacturing equipment and their cleaning validation may be impacted by the introduction of a third product (C, with two actives C1 and C2). The products described here as examples are all oral solid, non-film-coated tablets with one or multiple APIs.

Database File Setup

Multiple worksheets in the database are set up to provide the data needed to calculate MACO per the formulas shown in Table 2. The worksheets contain data on API, formula, API/formula (identifying the APIs within each formula), equipment, and cleaning agent, as shown in Table 3.

Running the Macro

The process to execute the macro is simple and consists of the following steps:

1. Open Statistica Enterprise and run the CVLM application.
2. Select the Excel database file.
3. Specify the parameters for the analysis, including swab area/rinse volume, formula list, equipment list, and, optionally, cleaning agent.
4. Specify the count for each item of equipment used.
5. Perform calculations and create report.

The CVLM Report

The final report, which includes tables of results, graphs, and contextual text, is presented in a PDF file. The report also includes details on the formulas used, raw data, and products and equipment selected for analysis. The report may be added as an

Table 3: Database setup example.

API				
API	**HBEL (µg/day)**	**LD_{50} (mg/kg)**	**Solubility Rating**	
A	2,000	205	5	
B	400	415	3	
C1	2,000	371	1	
C2	250	840	1	
Formula				
Formula	**MBS (g)**	**Ease-of-Clean Rating**	**Child/Adult**	
A	160,000	1	Child	
B	420,000	1	Adult	
C	316,800	3	Adult	
Formula/API				
Formula	**API**	**MTD (mg)**	**MDD (mg)**	**Label Claim (mg)**
A	A	200	400	200
B	B	20	40	20
C	C1	30	180	30
C	C2	1.25	7.5	1.25
Equipment				
Equipment ID	**Surface Area (cm^2)***	**Maximum Number****		
1	14,350	1		
2	29,183	1		
3	72,197	1		
4	2,266	6		
5	60,560	4		
Cleaning Agent				
Cleaning Agent	**LD_{50} (mg/kg)**			
CA1	450			
CA2	1,153			

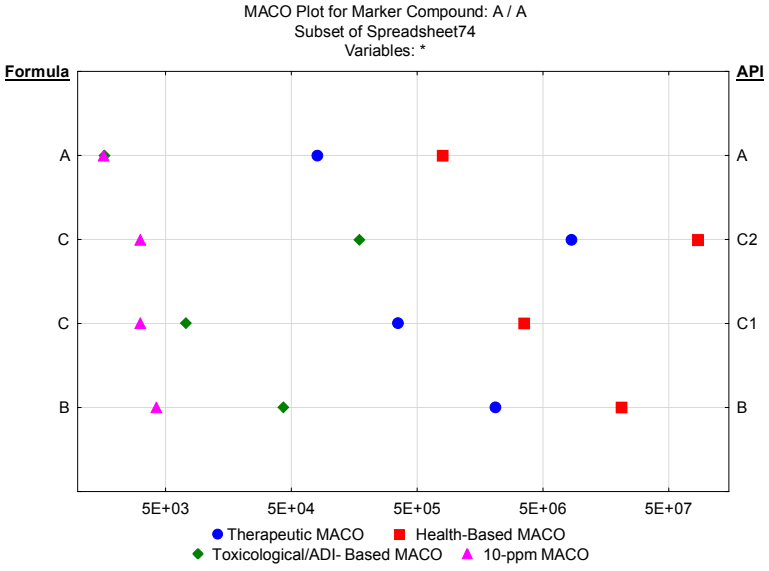
*The program adds a 10% safety factor to the total surface areas.

**The maximum number refers to the pieces of equipment available for use in the manufacturing of a product. The actual number used is selected by the user at run time.

Figure 2: MACO results from four calculation methods.

MACO Results for Marker Compound: A / A

The following graph shows the calculated Maximum Allowable Carryover (MACO) values for each API within the selected Formulas, sorted by the minimum MACO value (from all methods).



For each method of calculation, the lowest MACO and cleaning limit values were first found. The 'next' Formula/API(s) resulting in these values for each method were then identified and are shown in the following table. Limit values are calculated for a swab area of 100 cm^2.

MACO Calculation	Formula	API	MACO (mg)	Limit (mg/cm^2)	Swab Limit ($mg/100cm^2$)
Therapeutic	A	A	80000.00	0.1957	19.57
Health-Based	A	A	800000.00	1.9573	195.73
Toxicological/ADI-Based	A	A	1640.00	0.0040	0.40
10-ppm	A	A	1600.00	0.0039	0.39

attachment to a validation protocol/report and made available to support any questions during an audit.

The graphical components make the report easy to understand and can be exported to other applications (e.g., slide presentation software) for management review. Figure 2 shows an excerpt from the report output.

Based on the results shown in Figure 2, the 10-ppm method shows the lowest MACO and cleaning validation limit for marker compound A. In this example, the lowest limit (390 µg/swab area) is indeed less stringent than visual clean, as most residue would be visible on the surface at this limit. So, for routine cleaning, an argument can be made that visually clean could be the sole criterion for final equipment release, thus removing the need for swabbing and testing (periodic monitoring may still be needed). Showing all the calculations makes the final decision robust and defendable.

VALIDATION

Because the database and the Statistica macro both use GxP data and the macro output is used to make product quality and compliance decisions, the database and macro required validation. The validation was protocol driven and similar in design to computer systems validation, as test cases were created and executed with predefined acceptance criteria, including the following stages:

- Requirements specification: This details the system requirements, business requirements, and any other GxP requirements.
- Design specification: Both the Excel and Statistica components included custom-written code and, as such, needed a design specification with application-specific configuration details.
- Code review: This confirms that the code developed will accommodate the system requirements and will function as described in the design specification.
- Testing: All GxP requirements require testing.
- Report: The report provides a reference to testing protocols and a summary of how the deliverables of the validation have been met.

A pilot group of selected production sites used the system extensively during development. Any identified bugs were reported,

and issues addressed, before a new release was uploaded into the development area for further testing by the pilot group.

PROGRAM BENEFITS

The program offers multiple benefits, such as the following:

- Error-proof MACO results for all four recognized calculation methods
- The program can be built in-house using existing software, with no extra licensing fees
- Efficiency—report output is already a GMP document and takes only a few minutes to create
- Rapid and traceable results with easy-to-update variable data
- Allows calculation of acceptance criteria for swab and rinse samples

CONCLUSION

The development, execution, and validation of the CVLM provides a reliable tool to simplify and automate the cleaning validation calculations to support a compliant cleaning validation program. Thus, the CVLM program can help sites make informed decisions to continue supplying products to market on time.

About the authors

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MATERIAL PROPERTIES DATABASES

to Advance Pharmaceutical Processing

By Jamie Clayton

Pharmaceutical manufacturers rely heavily on powder processes, the majority of which are designed and operated on the basis of empirical correlations between material properties and performance. The development of material properties databases for pharmaceutical excipients and active pharmaceutical ingredients (APIs) has the potential to enhance such correlations and, more generally, to facilitate activities throughout the pharmaceutical life cycle. A growing body of work in this area shows exciting promise, illustrating the capabilities of material properties databases to add value within the quality by design (QbD) environment that now prevails.

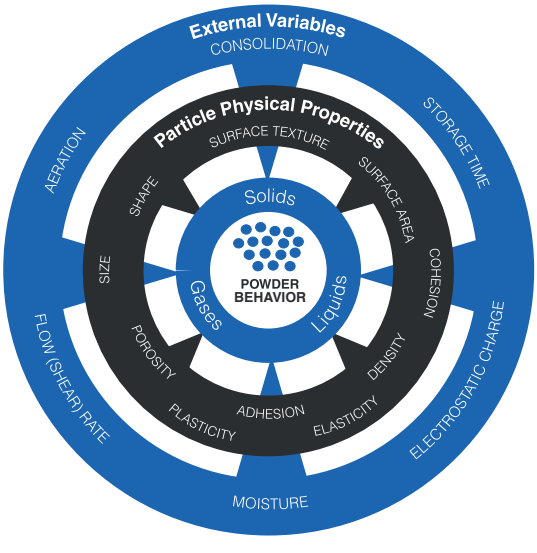
The pharmaceutical industry's current focus on manufacturing efficiency can be traced back to the early 2000s, when QbD was introduced and generic activity increased. These nearly simultaneous developments resulted in a compelling alignment of regulatory and commercial interests. As the US FDA made clear in 2004 [1], "quality and productivity improvement share a common element—reduction in variability through process understanding." To compete effectively in today's marketplace, manufacturers require knowledge of how to process materials to a highly consistent product and, by extension, a robust understanding of which material attributes influence in-process behavior. In this context, material properties databases can help advance the science of pharmaceutical processing.

BARRIERS TO SUCCESS

Establishing design protocols for powder processes presents a considerable challenge because the behavior a powder exhibits within the process environment is the net result of a complex web of interactions between many variables (see Figure 1). Although chemical properties are critical in powders, as they are in gases and liquids, powder behavior is governed by a wide range of physical variables. Relevant particle properties include size and shape, density, surface roughness, and propensity to accumulate electrostatic charge. Equally influential are system variables such as the amount of entrained gas in the powder, humidity levels, and degree of consolidation.

This complexity directly affects powder testing. In particular, manual techniques and techniques that lack a precisely defined methodology or apparatus suffer from poor repeatability and reproducibility, primarily due to the impact of operator-to-operator variability. Because so many variables can impact the outcome of a test, conditions, methods, and apparatus must all be precisely controlled to generate robust data. Furthermore, many powder testing techniques offer minimal facility to control the test

Figure 1: Powder behavior is the result of a complex network of interactions between particle properties and system variables.



environment to produce data relevant to the process of interest—instead, they generate only a single parameter that is meant to reflect the diversity of powder behavior. Relevance and sensitivity are major issues in powder testing. For example, how useful and discriminating are angle of repose data for predicting optimal conditions for a specific formulation in a process as complex as tableting?

Efforts to build a more secure knowledge base for powder processing are crucial but potentially time consuming, and such efforts are carried out against a backdrop of

- intense pressure on research and development's productivity and time to market,
- significant variability in raw material supply chains, with supplies potentially varying in terms of chemistry (e.g., impurity type and level) and physical properties, and
- complex multistep manufacturing trains, potentially across different locations.

However, significant progress is being made.

DATABASE BENEFITS

Recently published studies highlight collaborations between academic institutes and major pharmaceutical companies such as GSK, Janssen Pharmaceutica, and AstraZeneca [2–4] to develop extensive material properties databases for pharmaceutical excipients and APIs. Those leading the way in troubleshooting and raw material selection are also increasingly open about the merits of a material properties database–based approach [5]. Whether in-house or shared, comprehensive material properties databases for materials in routine use offer considerable potential to:

- Develop robust process models—this is particularly important for the successful adoption of continuous manufacturing, which relies on establishing process control protocols that respond optimally to variability in process materials.
- Rationalize the number of characterization techniques routinely applied, which is critical for materials in short supply, such as APIs.
- Support the use of surrogates and analogues to overcome limitations with material availability during process development and effectively identify formulation components for generics.
- More effectively set specifications for commercial supplies to more rigorously assess alternatives and secure a robust supply chain.
- Improve process capability metrics by supporting the identification and elimination of potential sources of variability.

These benefits add up to a compelling case for investing in the development of material properties databases.

DATA ANALYSIS STRATEGIES

The first step in establishing a material properties database is to consider what can be measured. The number of techniques available for powder characterization studies is now substantial, as evidenced by the extensive study carried out by Van Snick and associates [2], which describes the generation of 100 raw materials descriptors for each of 55 different commercially available APIs and excipients. These descriptors include:

- Particle properties—for example, particle size by laser diffraction, particle morphology by static image analysis, and specific surface area by gas adsorption.
- Bulk powder properties, such as bulk and tapped density, permeability and compressibility, true density by gas pycnometry, moisture sorption and desorption by dynamic vapor sorption, and moisture content by loss on drying. Bulk powder flowability is a focus and was tested via a range of techniques, including shear cell analysis, tapped density, flow through an orifice, angle of repose, avalanche angle, and powder rheometry.

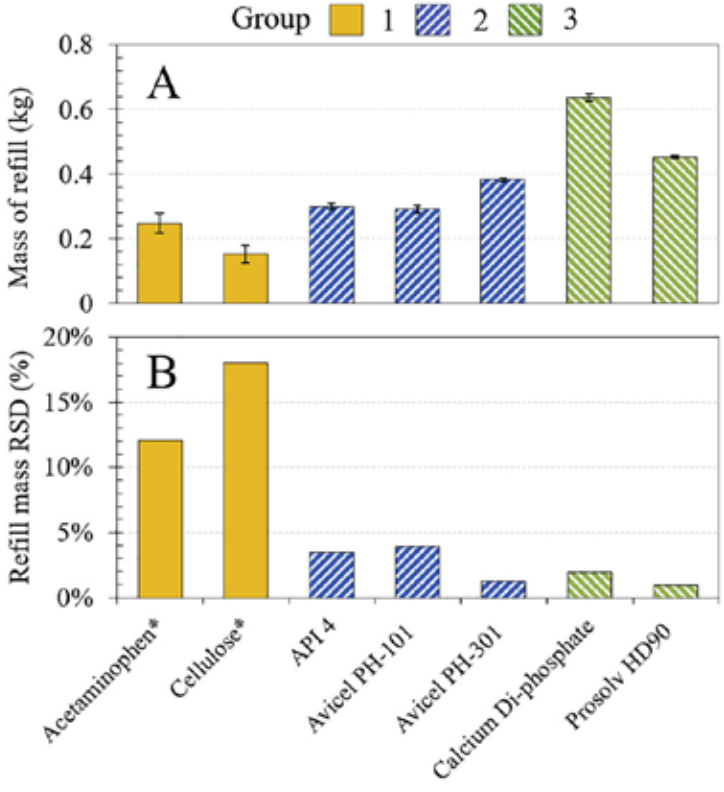
Casting a wide analytical net is essential, but rationalization of the resulting data is key when it comes to the practical application of material properties databases. Multivariate data analysis strategies that have been successfully applied include principal component analysis (PCA) and clustering analysis (CA) [2–4].

PCA combines individual variables into a limited number of components that capture an acceptable level of the variability in the original data set. The application of PCA by Van Snick and colleagues [2] identified four distinct components and highlighted flow, cohesion, compressibility, particulate descriptors, permeability, shear descriptors, and water uptake, among other factors, as critical material attributes for the powders tested.

An interesting point to note about PCA is the potential importance of removing multiple highly correlated variables, such as particle size descriptors [2]. Laser diffraction produces a range of very highly correlated particle size metrics—including Dv10, Dv50, and Dv90—which can result in an overweighting of the technique relative to one that provides a single descriptor, such as specific surface area. This point highlights a critical aspect of instrumentation choice. Some systems produce a single parameter, which may or may not be critical; others produce multiple parameters that are highly correlated; and yet others produce multiple parameters that are independently valuable. For example, dynamic, shear, and bulk properties, which quantify many of the critical material attributes listed previously, can all be measured with a single tester (FT4 Powder Rheometer, Freeman Technology). This is an important consideration when comparing the value of different instruments.

CA is a machine learning technique that groups or clusters data points on the basis of similarity or dissimilarity. It can therefore be used to cluster materials with similar properties, as demonstrated by Escotet-Espinoza and coauthors [3]. On the basis of CA, a group of 20 materials (with 32 material attributes measured for each) was split into three distinct groups. Flowability and tendency to adhere to processing equipment were identified as key differentiators of the materials in the three groups, with each group then being extremely helpful for identifying surrogates and analogues.

Figure 2: Correlating refilling performance with powder properties illustrates how material properties databases can be used to identify materials with comparable process performance. Materials marked with an * exhibited arching during the experiment. RSD = relative standard deviation.



PCA and CA provide valuable insight into the behaviors of pharmaceutical powders, highlighting properties that are correlated or anti-correlated, and the techniques that are most useful. Assessing whether powders with comparable property profiles exhibit equivalent process performance is the crucial final step in confirming the validity of using an material properties database to enhance process-related studies.

DATABASE APPLICATION EXAMPLE

Figure 2 shows how a selection of seven characterized powders, clustered into the three groups previously described, behave in a feeder refill unit (GEA Process Engineering, Belgium [3]). This unit consists of an 8-liter hopper located above a rotating cup system; a fixed cup volume of 0.8 liters was used. The mass dispensed into the cup, per actuated refill, was measured for eight refills using a catch scale system (Coperion, K-Tron, Sewell, NJ). Performance was assessed in terms of the mass dispensed per refill, averaged over four refills (Figure 2a), and variability in the mass dispensed per refill (Figure 2b).

The results show that refill mass and the variability associated with dispensed mass are aligned with cluster. Notably, group 1 powders (acetaminophen and cellulose), which have poor flowability, exhibit the most variability in this equipment, dispensing least consistently into the cup. Because these two powders also exhibited arching, it was necessary to hammer the hopper between refills to promote powder flow. More generally, powders lying within the same cluster exhibit similar behavior in the filling operation and indeed in feeder and blender systems, as evidenced by subsequent experiments.

This simple analysis helps illustrate the potential to use material properties databases to develop models for specific unit operations and shows the value of certain measurements for identifying surrogates/analogues. Here, comparability was successfully determined on the basis of dynamic, shear, and bulk properties and particle size data. More specifically, the study highlights the importance of bulk density, permeability, and compressibility in defining process performance, and how dynamic flow energy measurements and shear cell analysis provide independent insights into powder behavior.

LOOKING AHEAD

Powder processes are critical for pharmaceutical manufacturers, and there is considerable merit in collaborative efforts to improve

the knowledge base that underpins their application. The establishment of material properties databases is a pragmatic and productive strategy that we have seen successfully applied by customers across a range of industries.

Over the long term, material properties databases could transform the pharmaceutical industry's ability to formulate and manufacture with confidence and efficiency. They offer the capability to accelerate the identification of critical material attributes and other aspects of development; develop formulations with specific, predictable physical characteristics; establish appropriately responsive process control protocols; and optimize raw material supply chains. Equally important, material properties databases help differentiate those techniques and instrumentation that offer the most value, supporting the refinement of productive and cost-effective analytical strategies that meet industrial requirements.

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About the author

Jamie Clayton is Operations Director at the powder characterization company Freeman Technology, based at the company's headquarters in Tewkesbury, UK. He graduated from University of Sheffield with a degree in control engineering and is responsible for overall management of company activities, including the R&D, production, sales, and customer support teams. During his time with the company, Jamie has worked as a mentor with several academic groups, and he is an active member of ASTM F42. Jamie is also a regular contributor to conferences and workshops on the topic of powder rheology and works closely with clients on the application of the company's technology.

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