PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

May–June 2019 | Volume 39, Number 3

CONTINUOUS MANUFACTURING

CM Control Strategies, Sampling Considerations, & Regulatory Progress

Inline Dilution for Downstream Manufacturing

SPECIAL REPORT: Pharma 4.0

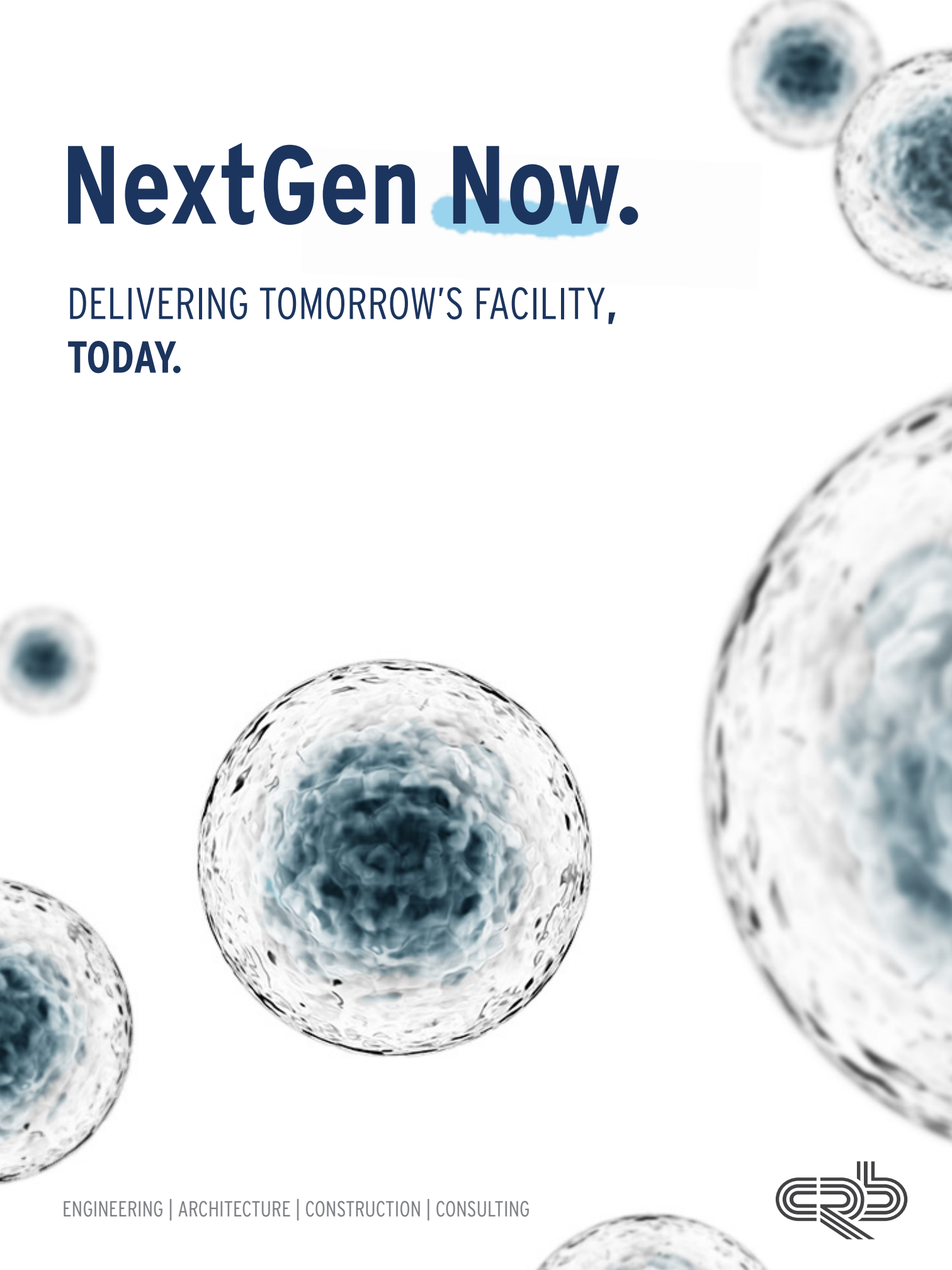
ISPE®

ispe.org/pharmaceutical-engineering


FLUOR DELIVERS.
Engineering Concepts and Building Capacity
in Life Sciences Worldwide
Fluor transforms the world by building prosperity and empowering progress in design, engineering, procurement, fabrication, construction, and maintenance.
Since 1912, Fluor has been designing and executing innovative solutions that bring our clients greater capital efficiency with improved cost and schedule certainty.
www.fluor.com
FLUOR®
© 2019 Fluor Corporation. All rights reserved.
Fluor is a registered service mark of Fluor Corporation.
ADGV180219

NextGen Now.

DELIVERING TOMORROW'S FACILITY, **TODAY.**



ENGINEERING | ARCHITECTURE | CONSTRUCTION | CONSULTING

PHARMACEUTICAL ENGINEERING®

MAY / JUNE 2019

10 HOLISTIC CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING

A control strategy developed using a science- and risk-based approach will ensure that reproducible product quality is achieved throughout the product life cycle, while maintaining the efficiency, robustness, and flexibility that continuous manufacturing has to offer.

ON THE COVER A conceptual representation of continuous manufacturing, the theme of this issue of *Pharmaceutical Engineering*.

FEATURES

DON'T BE A RISKY BUSINESS

INTEGRATE YOUR PROGRAM AND PROJECT TO AVOID SURPRISES AND ACHIEVE OPERATIONAL EXCELLENCE

Why do projects fail? Too often, aspects of program and project are not integrated, creating friction and non-productive conflict that waste resources and cause suboptimal output.

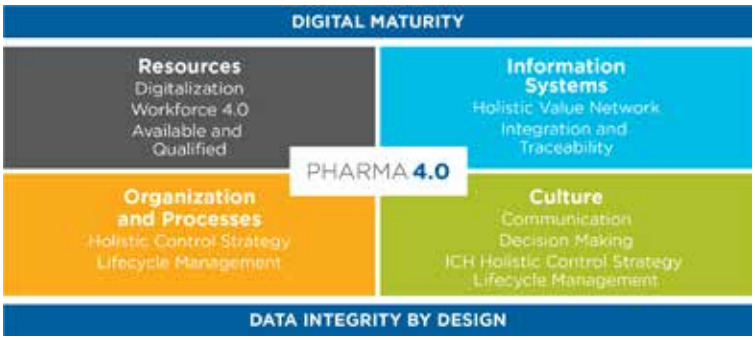
Our experts possess the technical knowledge and understanding of today's manufacturing processes, facilities, and equipment to integrate your program and project, helping you efficiently deliver your product to market on time and within budget.

CAI

WHEN YOU NEED TO MEET A HIGHER STANDARD™

cagents.com

ISPE | PHARMA 4.0



SPECIAL REPORT: PHARMA 4.0

The promise of Pharma 4.0 continues to unfold, as two updates in this Special Report demonstrate: The ISPE Pharma 4.0 Operating Model's Pharma-Specific Maturity Index (page 40) and Digital Reference Architecture Principles for a Data-Driven Pharmaceutical Factory (page 46).

DEPARTMENTS

TECHNICAL

ISPE

PHARMACEUTICAL ENGINEERING

Volume 39, Number 3
Published since 1980

Editorial Director: Susan Sandler, ssandler@ispe.org

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

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

ISSN 0273-8139

Pharmaceutical Engineering is published six times a year by ISPE.

Advertising and Sales
Deborah Bahr, VP Business Development & Sales
+1 301-364-9213 ext. 433 dbahr@ispe.org

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

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

Stock Photography and Illustration
iStock

Art Direction and Graphic Design
THOR Design, Inc., www.thor.design

Printing
Royle Printing

Letters to the Editor
Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, and organization. If published, letters may be edited for length and clarity. Send correspondence to ssandler@ispe.org.

US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
600 N. Westshore Blvd, Suite 900
Tampa, FL 33609 US

Periodicals postage paid at Tampa, Florida, US, and additional post offices

Canada Postmaster
Send change of address and undeliverable copies to:
Pharmaceutical Engineering Magazine
PO Box 122
Niagara Falls, ON L2E 6S8
Canada

Canada Post mail agreement #40012899

Pharmaceutical steam trap from Spirax Sarco

FDA approved, fully certified

The Spirax Sarco BT6-B is a high specification sanitary balanced pressure thermostatic steam trap that minimises contamination when steam is in direct contact with pharmaceutical product. Its unique design with certifications and approvals, ensures the BT6-B is economical and exceeds the capabilities of other models currently available on the market.

The only one in the market fully certified

- 'Gold Standard' EN10204 3.1 Certification, across all wetted parts, including FDA approved element fill as used in our proprietary steam trap technology.
- FDA and USP compliant.
- Full material traceability 3.1, including all wetted parts.
- Surface finish certificate available.
- Assembled and packed in ISO Class 7 clean room.

Contact your local Spirax Sarco representative to learn more about the BT6-B.

First for Steam Solutions

EXPERTISE | SOLUTIONS | SUSTAINABILITY

spirax sarco

By Jim Breen

ISPE Conferences and More Strategic Changes

Jim Breen

During the winter and spring, ISPE has been very busy holding several very successful and heavily attended conferences, including the Facilities of the Future Conference 7–8 February in San Francisco, California, and the Aseptic Conference 18–19 March in North Bethesda, Maryland.

The ISPE Europe Annual Conference held 1–4 April in Dublin was a great success. I want to thank the Ireland Affiliate for their great work and for setting the bar high for our next Europe Annual Conference.

The ISPE Rocky Mountain Chapter held their 24th Annual Rocky Mountain Vendor Show on 7 March with over 110 exhibitors and 625 attendees. The ISPE Carolina-South Atlantic Chapter (CaSA) also held their 26th Annual Life Sciences Technology Conference on 12 March, which was also an outstanding success with over 1,000 attendees and 209 exhibitors. (Read more about these events in ISPE Briefs, page 54.) Great work by the CaSA and Rocky Mountain chapters! These shows are just some of the many conferences and events sponsored by ISPE's chapters and affiliates each year around the world and we encourage all members to participate.

STRATEGIC DEVELOPMENTS

After ISPE's tremendous success with Facilities of the Future programs over the past few years, we have decided to focus some resources on an equally important topic: Workforce of the Future. Research has shown that most jobs will require retraining and upskilling due to the impact of new technology in areas such as data analytics, machine learning, and the Internet of Things (IoT). ISPE will be developing articles, programs, and training opportunities to allow members to prepare and position themselves for future career opportunities in these areas. More information will be coming in the next months on the important issues affecting all industries on how to prepare the workforce for digitalization.

The ISPE Board has been working on a new five-year strategic plan, which we will announce to our members at the 2019 ISPE Annual Meeting & Expo 27–30 October in Las Vegas, Nevada. This new plan, commencing in 2020, will steer the Society into the future. Please stay tuned for more details.

MORE LEARNING OPPORTUNITIES AHEAD

There are more learning opportunities ahead this year, including the ISPE Biopharmaceutical Manufacturing Conference, 18-20 June in Boston, Massachusetts; ISPE Process Validation Workshop, 20–21 June in Boston; ISPE Europe Biotechnology Conference, 25–26 September in Brussels; ISPE Europe Pharma 4.0 Conference, 20–21 November in Manchester, England; and the ISPE Annual Conference & Expo, 27–30 October in Las Vegas.

For more information on these and other ISPE conferences, and to register, please visit https://ispe.org/conferences.

As the summer months begin, I hope everyone has an opportunity to relax and recharge while spending time with friends and family. Have a restful and safe vacation season.

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

ISPE
PHARMACEUTICAL ENGINEERING

Pretty cool Water for Injection

BWT OSMOTRON WFI &
BWT LOOPO WFI

The ultimate combination to generate "cold WFI" from drinking water, store and distribute - according to Ph. Eur. 0169 and USP <1231>. BWT's unique triple membrane barrier technology in the OSMOTRON WFI ensures best quality and efficiency in generation. Extensively tested with an independent university of applied sciences. The LOOPO WFI continuously ozonates your storage tank and monitors the WFI quality. Sanitization options include comfortable ozonization of the complete storage and distribution system or sterilization with superheated water at 121° Celsius. Maximum reliability and security. All in all: Best Water Technology.

bwt-pharma.com

By LeAnna Pearson Marcum


LeAnna Pearson Marcum

THE "F" WORD: How Failure Leads To Success

From the time when we were young, we have been taught to avoid failure. You are told to get the best grades in school, which will lead to getting into college. And when you graduate, you'll get a good job, work hard, and the promotions will come. At no point did anyone ever tell us to fail! But failure is part of life and we all have personal and professional failures despite our best efforts.

So why is failure so bad? What if we flipped the narrative and took the opportunity to look at failure as part of the process, perhaps as the precursor to innovation? As I started to think about this, I looked back at some of the great leaders in history and in our current climate. Many of them had failures along the way. They embraced those failures and have openly talked about how to fail is to grow. Jeff Bezos, the Chairman, CEO, and President of Amazon said, "Failure comes part and parcel with invention. It is not optional. We understand that and believe in failing early and iterating until we get it right." With this idea that failure is not optional, I looked back at my career and realized that many of my biggest challenges and successes included failure along the way.

EASING INTO A FEARLESS MINDSET

Many of my mentors, coaches, and leaders and those I aspire to be like have said, "Always push yourself outside of your comfort zone." This is easier said than done because as a society, we have been trained since we were small to be cautious and avoid failing. So how does one ease into this mindset of taking risks? I use a few tricks as I push myself both personally and professionally.

- **Stay positive.** It seems so very simple, but we are not all positive by nature. Pushing our boundaries makes us uncomfortable and this can lead us to be sensitive or even a bit negative. I try to focus on the small wins—no matter how slight or unimportant they might seem, they are still wins.

Taking failure and using it to learn a lesson and develop the tools to be better is the key to growth.

- **Laugh.** Sometimes when things go wrong, there is nothing else to do.
- **Turn a failure into a lesson.** Nobody is perfect, no matter how hard they try. We all juggle multiple things at any given time, so failure is bound to happen. Taking failure and using it to learn a lesson and develop the tools to be better is the key to growth.
- **Maintain focus on the present.** I am the worst at reliving a moment that already happened, but the simple fact is that you cannot change the past, so get over it. I have to remind myself every day to stay in the moment: that is what you can control and change.
- **Surround yourself with positivity.** My friends and family are amazing. Surrounding yourself with positive, happy people is empowering and is my secret weapon.

Don't let the "F" word scare you—take control of it and embrace it. You can only get better!

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

How did you get involved in ISPE? Join the conversation on the YP community page: http://cop.Ispe.Org/yp. To join the YP community, select it during registration or update your account on ispe.org.

"Fristams are the best pumps going."

- Plant Maintenance Manager, Midwest Production Facility

Ultraclean Reliability From Fristam

Fristam FKL positive displacement pumps are designed to safeguard the integrity of your product and keep your critical path up and running. From its simple, complete CIP and SIP cleaning to its low-shear operation, Fristam's ultraclean FKL series PD pump provides high process purity and gentle, reliable flow.

In addition, the FKL is available with the most comprehensive BPE documentation and the best service and delivery time in the industry.

Biopharm and Pharma Applications:

- Cough syrups
- Enzymes
- Protein solutions
- Cell broths
- Gelatins
- Intravenous dyes

Personal Care Applications:

- Lotions & creams
- Shampoos & soaps
- Ointments
- Toothpaste

Contact Fristam, your trusted resource for pharmaceutical pumps, to learn more.

Fristam PUMPS®

Engineered For Lasting Performance®

1.877.841.5001 | fristam.com/pharma

HOLISTIC CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING

By Christine M. V. Moore, PhD, Thomas Garcia, PhD, Douglas B. Hausner, and Inna Ben-Anat

Innovative technologies such as continuous manufacturing (CM) bring speed, efficiency, and agility to pharmaceutical manufacturing together with enhanced process robustness and assurance of product quality. During CM, material is simultaneously charged and discharged into process unit operations. Similar to batch manufacturing, CM requires a comprehensive and holistic control strategy throughout the product life cycle to ensure, in a reproducible and consistent manner, the intended product quality at the time of release and throughout the product's shelf life. A control strategy developed using a science- and risk-based approach will ensure that reproducible product quality is achieved throughout the product life cycle, while maintaining the efficiency, robustness, and flexibility that CM has to offer.

Control strategy is described in ICH Q10 as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control" [1]. Fundamentally, control strategy expectations for CM are the same as those for batch manufacturing, namely that the manufacturing process is capable of consistently producing quality product. However, there is at least one notable difference between traditional batch manufacturing and CM. Many traditional batch manufacturing processes have unit operations that are designed to be well mixed (e.g., fermenters, bin blenders) and quality concerns are therefore related to variability with location or space. In contrast, a major quality concern for CM operations is related to temporal variability. Consequently, CM control strategies frequently incorporate process analytical technology (PAT) that provides information related to the product and/or process in real time.

CM provides an opportunity to build quality into the process design and control strategy, consistent with quality by design (QbD) principles [2]. Because information is rapidly collected from CM systems, design space data can be readily obtained by varying settings and ranges of critical input parameters and analyzed by utilizing multivariate statistical design approaches (e.g., design of experiments [DoE]). A design space representing the multidimensional combinations and interactions of the critical attributes and parameters to demonstrate assurance of product quality is a potential element of a control strategy [3]. Inline

testing and modeling approaches, such as PAT, are other potential elements of a CM control strategy; these approaches provide an opportunity for real-time monitoring and control as well as real-time release testing (RTRT).

The overall control strategy for a CM process should be viewed in a holistic manner, with all elements of the control strategy working together to ensure product quality. There is no universal approach to a control strategy for CM, and multiple approaches can equally achieve quality and manufacturing goals. For example, a process that heavily incorporates in-process measurements and controls may have very little end-product testing, whereas an equally performing process may include fewer in-process measurements and extensive off-line analysis of finished product and process intermediates. Each manufacturer needs to decide on a control strategy approach that provides suitable mitigation of process risks while meeting business goals.

Simply having a well-developed control strategy alone is not sufficient to ensure manufacturing consistency and product quality. An effective pharmaceutical quality system (PQS) is integrated throughout the product life cycle to support the CM process [4]. The process control strategy is continuously reassessed and enhanced, if necessary, following quality risk management (QRM) principles. Adjustments to the controls are made, if required, through continuous improvement identified from product and process performance monitoring and tracking. Product-release considerations, such as deviation management, diversion process, and alternate testing approaches, also are part of the PQS.

This article discusses the main elements associated with a control strategy for CM of solid oral dosage forms such as tablets and capsules. Although many of the control strategy considerations are the same as for a traditional batch process, CM control strategies emphasize the importance of raw material characterization and management, in-process testing (including PAT), and nontraditional batch-release approaches such as RTRT. Whereas the focus of this article is the processing of pharmaceutical solids, many of the control strategy aspects discussed here, such as system dynamics, are equally applicable to fluid-containing systems such as chemical reactions, cell culture processes, and separation or purification processes.

RAW MATERIALS

Knowledge of the relationship between raw material attributes and the impact they have on product quality attributes is an important facet of product development, whether it is for CM or batch manufacturing processes. For a CM process, essential critical material attributes may differ from those for batch processing, with CM placing a stronger emphasis on dynamic powder characteristics, such as flowability, cohesiveness, and aeration. CM systems for solid oral dosage forms are heavily dependent on the ability of raw materials and intermediates to flow through the system. Therefore, the relationships of critical material attributes and process parameters to the critical quality attributes they affect should be understood. Understanding how critical raw material attributes impact flow, whether it involves drug substance or excipients being dispensed out of feeders or the dynamics of material movement through the equipment train, is of paramount importance [5, 6].

Physical properties of the drug substance and excipients, such as particle size, shape, and density, can affect feeder performance for raw materials. Poor feeder performance can have a negative impact on quality attributes such as assay or content uniformity, which can result in more material being diverted to waste and lower yields. When selecting a specific grade of an excipient, formulators should consider how different grades may affect manufacturability concerns such as compressibility and flow. If a batch process is to be converted to CM, the formulation ingredients used in the batch process should be reassessed to ensure that the material attribute specifications they possess will perform well in continuous processing.

The ability of the API to flow well is also essential to the smooth operation of CM for solid oral products. Particle engineering can be effective in crafting the physical properties of the API, if necessary, to provide appropriate flow characteristics. Where such efforts are not fruitful, alternative strategies can sometimes provide flowable material. In some cases, batch preblending of the API with a glidant excipient can provide material that flows well. In others, a drug product intermediate can be produced by spray-drying the API with excipients.

Raw material properties should be understood to ensure that the process is sufficiently robust to tolerate the introduction of different lots of raw materials, with no significant changes in the quality of the product or process performance. Changes in the particle size, shape, or density can impair flow and mixing, which leads to issues as the material traverses through the continuous processing equipment. This is of particular concern for extended campaigns that may consume different lots of the raw material over the course of the batch. A new batch of a raw material should not significantly affect the performance of material feeders because that could subsequently disrupt flow and alter the quality attributes of the drug product.

With appropriate understanding and controls, process operating conditions can be adjusted to compensate for the variability in a material attribute. When process controls are not successful in compensating for variation, material specifications should be adjusted to meet process needs. For example, to deliver a quality product, manufacturers may need tighter purchasing specifications for critical material attributes that are more restrictive than compendia requirements. In-process controls and specifications are both part of the control strategy.

Lot-to-lot variability of materials should be assessed, including the amount of variability that critical material attributes can tolerate without compromising product quality or manufacturability. Latent variable analysis on data from experimental results or quantitative values taken from the material certificates of analysis is one way to assess the amount of lot-to-lot variability in excipients [7]. Multivariate monitoring of raw material properties within the PQS can determine when new variability is outside the ranges previously examined. Materials that are out of the range of previous experience may merit additional characterization and flow performance studies prior to being introduced into the manufacturing process.


Christine M. V. Moore


Thomas Garcia


Douglas B. Hausner


Inna Ben-Anat

DETECTING AND CONTROLLING DISTURBANCES

For many continuous operations, such as solids blending prior to tableting, disturbances in time can propagate through the system and affect a small portion of the manufactured material, potentially leading to production of out-of-specification material. It is essential that the control strategy be designed such that those disturbances do not occur, are not significant, or are detected and managed. A common method for managing disturbances in continuous systems is to isolate the material downstream from the point of the disturbance [8]. Understanding the system dynamics of a continuous system is essential for appropriately isolating such process disturbances and ensuring the "to be released" product is of the appropriate quality.

The goal for any manufacturing process, regardless of the technology or control strategy, is to operate within a state of control. The ICH Q10 defines state of control as "a condition in which the set of controls consistently provides assurance of continued process performance and product quality" [1]. Although this definition was not derived specifically for CM, it is fully applicable.

MODULAR SOLUTIONS

The Power Of Certainty

- Integrated modular building & process system
- Innovative extreme modularization
- Certainty in Quality, Schedule and Cost
- Flexible and Cost-competitive Solution
- Maximize Project Safety

pharmadule
A Morimatsu Group Company
www.pharmadule.com

MORIMATSU
Your Needs · Our Drive
www.morimatsu-eng.com.cn

FROM CRITICAL EQUIPMENT TO TOTAL PROCESS SOLUTION

About US

We are a world leader in the delivery of innovative modular facilities and process equipment's solutions for the Life Science Industry. Originally founded in Sweden in 1986, Pharmadule is now part of Morimatsu Industry Group since 2011.

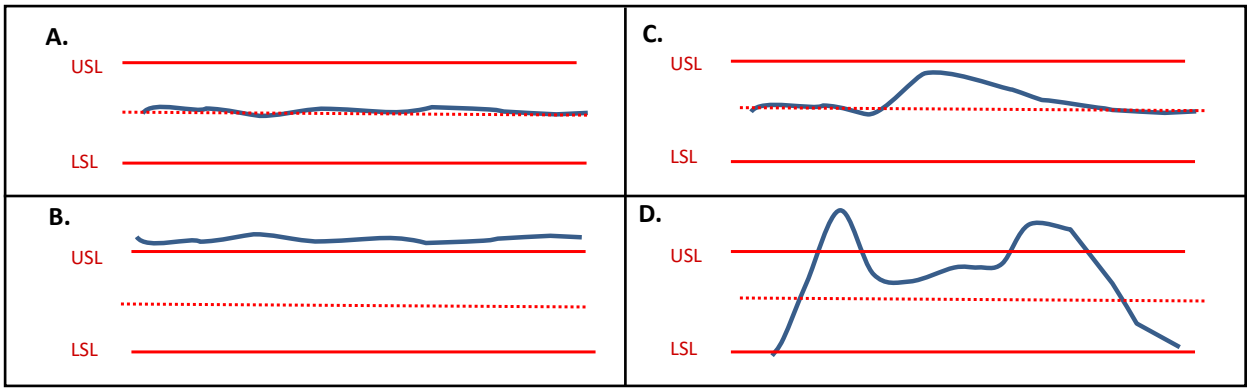
As a total solution provider we offer you cost-efficient and short delivery, predictability and reduced risk for your upcoming needs.

Europe. Headquarter, Stockholm Office
Danvik Center 28 131 30 Nacka
Sweden
E-mail: info@pharmadule.com
Tel: +46 (8) 587 42 000

U.S.A. Headquarter, New Jersey Office
33 Bernard Street Branchburg.
NJ 08876 USA
E-mail: info@pharmadule.com
Tel: +1 (908) 722-6845

Asia Pacific. Headquarter, Shanghai Office
No.29, Jinwen Road, Zhuqiao Airport
Industrial Park, Shanghai, China
E-mail: smp_info@morimatsu.cn
Tel: +86 21 38112058

Figure 1: Examples of steady state and state of control; USL = upper specification limit; LSL = lower specification limit.



"Steady state" is a commonly used term related to CM and should not be confused with "state of control." Generally, a steady-state condition can be described as a process state in which the quality attributes are kept approximately constant, or the rate of change with respect to time of those variables is approximately equal to zero over a relevant time span. Achieving steady state is neither sufficient nor specifically necessary to be in a state of control. For example, a small disturbance in the process could cause the system to move out of a steady state while remaining in a state of control. Additionally, it is possible to have a system that is not changing (i.e., in steady state) and to have material that is not within specified ranges of quality attributes and thus not in a state of control. Figure 1 depicts different scenarios of steady state and state of control. Figure 1A shows a process that is at steady state and in a state of control; 1B shows a process that is at steady state and not in a state of control; 1C shows a process that is not at steady state but in a state of control; and 1D shows a process that is not at steady state and not in a state of control. Knowledge and process controls ensure that small disturbances will result in a controlled process that is making acceptable product, as shown in Figure 1C. Figure 1D illustrates when a large portion of the material is within specifications, but collecting it as good product would be inappropriate.

Residence Time Distribution Studies

A control strategy for CM should consider system dynamics aspects to provide consistent and reproducible product quality. For continuous systems, it is typical to measure or model a system's residence time distribution (RTD), which describes the probability distribution of exit times for material entering the system [9]. The system's RTD provides an indication of the system's mixing efficiency, with the width of the distribution being proportional to the intensity of back-mixing in the system. The use of RTDs as a tool for traceability and process control is a regulatory expectation in many circumstances [10]. By measuring and modeling the RTD, material can be tracked forward through the system as a function of time. This approach enables appropriate diversion of potentially nonconforming product resulting from instances where the system was outside of a state of control or beyond the control limits for any unit operation within the system. In addition, it also allows for traceability between incoming lots of raw actives and excipients and the final collected product.

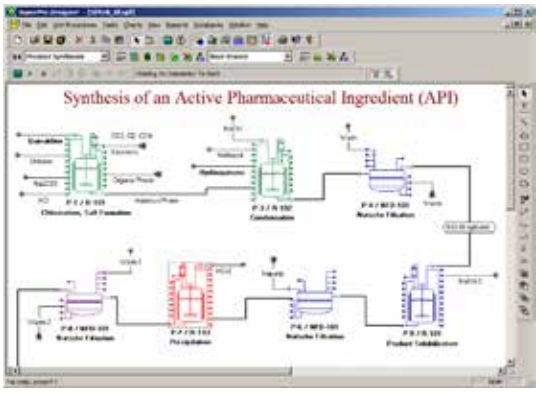
Conceptually, RTDs are somewhat straightforward, but the measurement of an RTD must be carefully considered if it is to be representative of the system's dynamic residence time within the set operational limits [11]. Two ways in which RTDs are commonly measured are with a pulse of a tracer or with a step change in composition (see Figure 2). In either case, it is crucial that the RTD determination conditions closely match the operational conditions. For tracer selection, a material with different physical properties may result in differences in how the tracer material flows relative to the operational blend, or it may change the blend properties overall. Similarly, for the step-change approach, where the concentration of API is monitored as the set point is changed, the stepped conditions will not be relevant if the resulting blend properties are significantly different. RTD characterization and validation efforts should evaluate both the sensitivity of the RTD to system variation and the validity of the RTD experimental and modeling assumptions. Instances where one set of blend properties vary significantly enough from another could lead to erroneous results for the RTD parameters.

Models utilizing the RTD can determine which disturbances will dampen out and not affect product quality and which disturbances dictate that material be diverted from the system. The

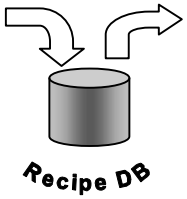
Intelligen Suite®

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

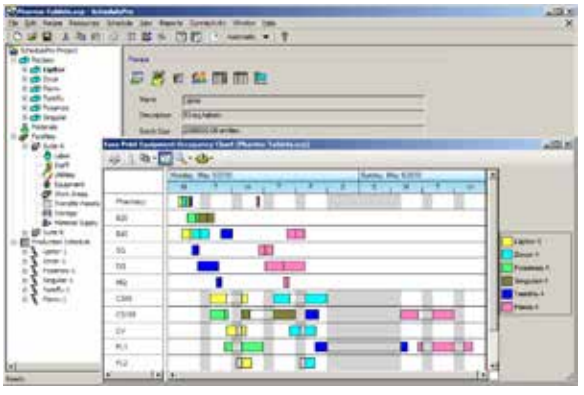
SuperPro®



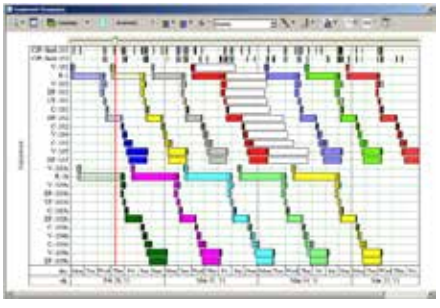
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

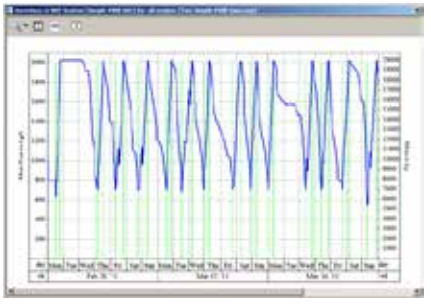


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

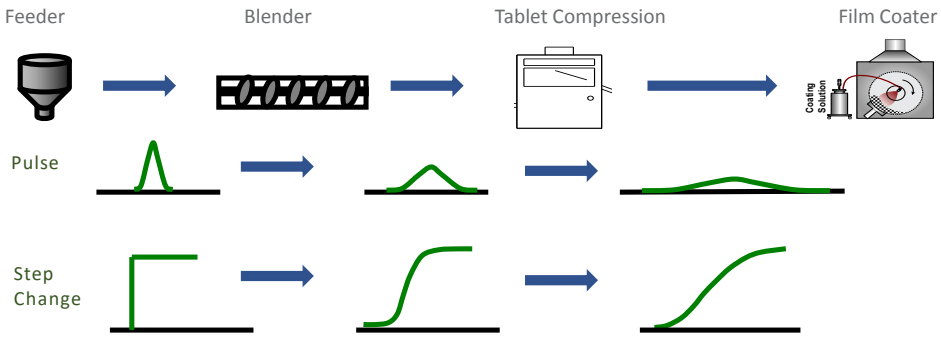
SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water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

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

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

Figure 2: Theoretical plot of concentration vs. time for pulse and step-change RTD measurements. The curves represent the RTD of a disturbance introduced at the feeder as it travels through the system. As the disturbance moves downstream, the intensity of the disturbance is dampened and the width of the disturbance broadens.



models can further inform how much material needs to be isolated. Sampling frequency and measurement capability are important considerations in these calculations to ensure appropriate detection of disturbances.

REFILL SCHEDULE

Refilling of the feeders, which introduce material into the process, is an inherent part of CM processes of solids. In nearly all cases, feeder refills introduce process disturbances of varying degrees [12]. Refill schedules can be optimized to minimize their effect on the system's process dynamics. Tools such as RTDs can be used to determine the conditions in which a refill may put product quality at risk, and how much (or how long) at-risk product may need to be segregated from the final collection stream. A refill schedule should be determined for adequate performance of the feeders. Figure 3 shows an example of disturbances for low and high feeder refill rates; the lower refill rate (Figure 3A) introduces a higher quantity of material, thus causing a greater disturbance than a more frequent higher refill rate (Figure 3B).

Start-up, Shutdown, and Pauses

Start-up and shutdown of continuous systems are process conditions where the system is not intended to be operating at a steady state and process conditions are known to be changing. This does not imply that the system is not in a state of control. If the process dynamics of start-up and shutdown have been appropriately characterized, a state of control can be maintained throughout the manufacturing process from start-up through shutdown. The value of the effort to demonstrate a state of control during the short periods of start-up and shutdown depends on product value and throughput. For large-volume commodity products operating at high throughputs and for long periods of time, lost material from start-up or shutdown may be insignificant.

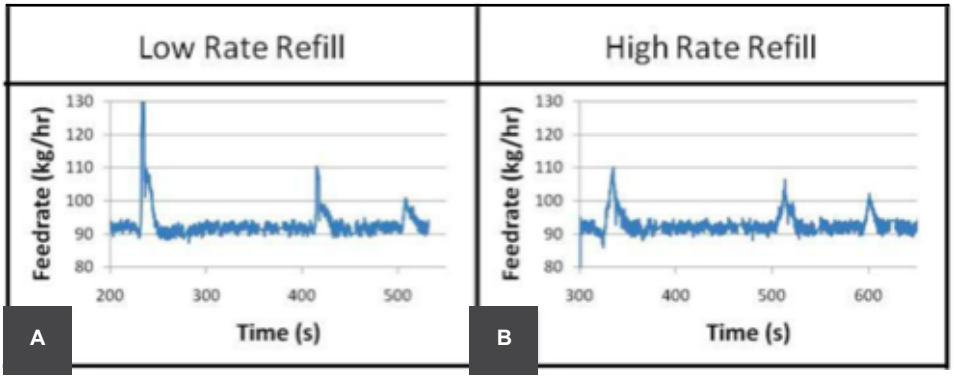
Material Diversion

Control strategies for CM are often designed to divert potentially nonconforming material when the process is not in a state of control. Material diversion can be planned or unplanned. An example of planned diversion is the removal of any nonconforming material that is generated during start-up, shutdown, or process pauses. Unplanned diversion or process interruption may be necessary when a trend or change in the material's characteristics or the process performance is detected. The PQS should include written and approved procedures that state how the process is to be shut down or paused, explain the circumstances in which an investigation into the root cause of the problem is required, outline when/how production can resume, and provide the steps for restarting the process.

The ability to perform diversions and partial lot rejections for CM is somewhat unique in pharmaceutical operations. In batch manufacturing, a lack of a state of control for the process commonly results in nonsegregable, nonconforming material and subsequent total batch failure. However, because of the high level of process understanding, traceability, and control in CM, portions of the batch containing potentially nonconforming material can be readily segregated from the remainder of the produced material that is verified to be of known acceptable quality. In most cases, the segregated portion of the batch will be rejected and discarded. However, in some cases, an investigation may reveal false signals leading to the diversion decision, such as data from a fouled measurement probe. In such a case, it could be justifiable to reintroduce the diverted material back into the acceptable product. Clear instructions for these types of decisions, as well as guidance on what supporting data are required, should be captured in the PQS.

A high or atypical number of diversion events or a large amount of rejected material can reduce confidence in the quality of the acceptable portion of the batch. Failure to comply with defined minimum yields for the batch may prohibit its release for commercial sale.

Figure 3: Examples of disturbances caused by feeder refill.



PROCESS MEASUREMENTS AND CONTROLS FOR CM

In general, process measurements and controls for CM can be described as a combination of in-process controls, process performance monitoring, equipment controls, and facility controls. A combination of all of these ensures that the manufacturing process remains in a state of control and consistently produces quality product. In-process controls are the checks during production that appropriately adjust the process to ensure conformance to specifications [13]; these are also known as "in-process tests" [14]. Process performance monitoring is not specifically defined in ICH guidelines, but it generally can be understood to be measurements that are used to assess process performance or consistency; these measurements can provide signals related to future quality issues. Equipment controls oversee the operation of specific types of equipment; examples include automatic adjustments or shutoffs. Typically, equipment controls are independent of the mode of manufacture. Facility controls for CM, such as room temperature and relative humidity, are the same as for traditional batch manufacturing.

The ICH Q10 definition for control strategy is very broad and includes many control strategy elements that are not included in the regulatory dossier. For example, in-process controls are typically discussed as part of the registered control strategy, whereas process performance monitoring, equipment controls, and facility controls are not included in the dossier. Aspects such as equipment operating conditions and frequency of monitoring are elements of the control strategy but are not typically included in the dossier.

PAT for Monitoring and Control

PAT can be incorporated into CM control strategies in many ways, such as by measuring product attributes in the process or by determining process performance. Measurement of product attributes can be direct or inferential and can be used for actionable control decisions or for monitoring purposes. Measurements can be taken at frequencies relative to the level of risk for the attribute, such as during changeover to a new lot of a drug substance or excipient.

A wide variety of PAT tools and approaches can be used to directly measure product attributes. The most common PAT tools for measuring product attributes in solids are spectroscopic, including near-infrared spectroscopy (NIR) and Raman spectroscopy. Although both spectroscopy tools can provide concentration measurements of multiple species, Raman spectroscopy can additionally provide information on solid-state characteristics, such as polymorphism [15]. Regardless of the PAT tools used, the purpose is the same: to provide real-time measurements of the system such that timely decisions can be made.

Process data, such as process parameter values, material attributes, and data from sensors, can be analyzed in a multivariate manner to determine process performance and process consistency. Multivariate approaches such as multivariate statistical process control can often reveal discrepant performance that univariate trending would not identify and can aid in early diagnosis of process or equipment failures [16].

Multivariate analysis also can be applied as a parametric approach to infer product quality data indirectly from process information. In a parametric, or "soft sensor" approach, a broad array of data from the process and materials is correlated in a multivariate fashion to help predict product quality attributes. Parametric PAT approaches are evolving from both a technical and regulatory perspective.

Many PAT systems, such as spectroscopy, require life-cycle maintenance and updates to the underlying models to ensure that they continue to function as intended [17]. All models used in-process control and monitoring are expected to be managed and maintained within the PQS. In some regions, regulatory reporting may be required for updates to models related to measurement of

PAT can be incorporated into CM control strategies in many ways, such as by measuring product attributes in the process or by determining process performance.

product quality. Typically, models for process monitoring of performance or consistency are maintained within the PQS without regulatory reporting.

Process Control Approaches

A robust control strategy for CM will emphasize controlling the product quality in response to potential variations in the process and equipment conditions over time, properties of incoming raw materials, or external environmental factors. The control strategy elements support the continued state of control, proper product collection, and product quality. The dynamic and integrated nature of CM increases the benefit of enhanced control strategies that employ control elements other than the traditional off-line end-product testing.

According to Lee and colleagues [8], control strategy implementation can be categorized into three levels based on the robustness, flexibility, and complexity of control elements and will depend on many factors, including the desired product performance, manufacturing process, and process dynamic characteristics (e.g., product heterogeneity and mixing patterns). The base level (Level 3), which is commonly used in traditional batch manufacturing, typically relies on tightly constrained material attributes and process parameters with extensive end-product testing to ensure product quality. The intermediate level (Level 2) has more flexibility in raw material attributes and process parameters through utilization of an established design space. The ultimate level (Level 1) has active process controls to monitor the quality attributes and adjust the process in real time. In practice, a control strategy for CM may display a combination of control elements at any of the three levels, provided that the risks to product quality are effectively controlled and mitigated.

Through flexible operations, where extensive process information is obtained during manufacturing, a Level 1 process can adjust for variability in raw material and equipment conditions to ensure on-target product is produced. In contrast, traditional process control schemes (Level 3) have predetermined, fixed operating points or ranges. In these cases, the quality of the product is only determined after the process is complete, with little or no opportunity to make corrections or adjustments.

CM control systems often use feedback and/or feedforward controls to adjust process parameters. An example of feedforward control is use of a loss-in-weight feeder data with an RTD model to predict the concentration downstream and determine diversion times for nonconforming material. An example of feedback control is adjustment of feeder flow rates based on inline blend NIR data. Other control configurations such as cascade control and ratio control are also possible.

No single set of controls or control strategies is appropriate for every continuous pharmaceutical manufacturing operation. The process controls should be based on the specific product, formulation, and process design as well as the associated risks to product quality. Processes with poorly flowing material or environmental sensitivity may need more in-process measurements or controls than is required for products and processes with fewer failure modes.

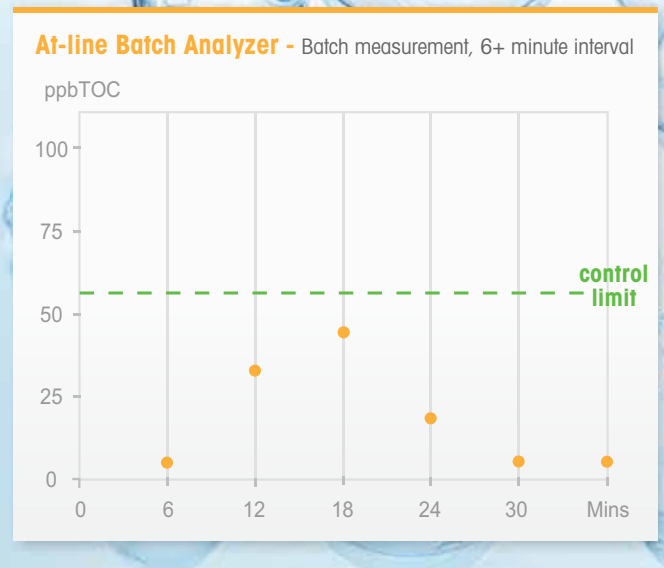
Alternative control strategies are also allowable [3] and, in some cases, expected. For example, in the event of a failure of a PAT control, a contingency plan should be developed to allow manufacture of the batch to be completed [18]. The contingency plan should be capable of detecting perturbations and, as appropriate, enable diversion of material that is out of specification; the diversion may need to be performed manually. Appropriate statistically based sampling plans and acceptance criteria are needed to provide confidence that the quality of the batch is acceptable for release. Drug product and intermediates may be tested with either off-line PAT or traditional analytical chemistry approaches.

Scale-up of CM

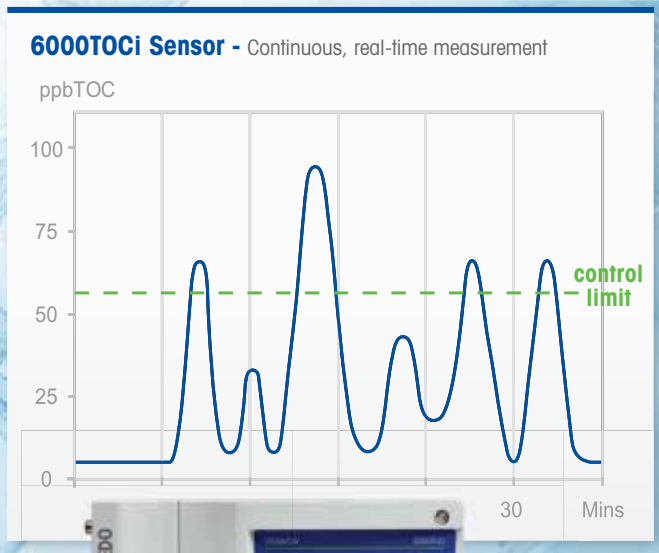
In traditional batch manufacturing, the term "scale-up" usually refers to the manufacture of greater quantities of materials through use of physically larger equipment. For CM, however, manufacturing of greater quantities of material usually occurs simply by running the same equipment for a longer time and/or at a faster rate.

CM rigs are often referred to in terms of throughput rather than equipment size or scale. Throughput is the amount of material processed by a system and is typically represented in units of mass per time, such as kg/hr. In some cases, manufacturing lines will be named based on the range of achievable throughputs (i.e., a 25 kg/hr or 50 kg/hr line), but, in reality, the throughput on a given line will likely be formulation dependent. On a specific system, the upper and lower bounds of throughput or achievable flow rate while a state of control is maintained may be different for each formulation or material attribute characteristic. Therefore, process development and validation activities are typically performed at a specific throughput or set of throughputs.

THORNTON
Leading Pure Water Analytics



VS.



Audit-Ready TOC Compliance
for Pharmaceutical Water Systems

The 6000TOCi sensor monitors Total Organic Carbon contamination in real-time, giving you the control over your water system required to meet global TOC regulatory standards.

- Measure continuously instead of with batch measurement at 6+ minute intervals
- Know your sensor is working properly with adaptive, advanced diagnostics
- Achieve clear record-keeping with maximum TOC and trending reports

Gain audit-ready control over the TOC in your water with the 6000TOCi!

Learn how the 6000TOCi can optimize your measurements:

www.mt.com/6000TOCi-ISPE

METTLER TOLEDO

The control strategy elements for CM primarily remain the same for different batch sizes or "scales." However, there are some time-dependent aspects of longer run times that should be considered in the development of the control strategy and validation plan; these include, but are not limited to, effects of equipment wear, potential for accumulation of material in the system, and possibility of microbial growth.

PRODUCT SPECIFICATIONS AND RELEASE CONSIDERATIONS

Product specifications are part of the control strategy and address the quality attributes' ranges and targets that must be achieved to ensure the safety and efficacy of the product. Although the quality standards for the release of intermediates and finished products remain the same as those applied to batch processes, nontraditional analytical methods and acceptance criteria can be used to demonstrate compliance with quality attributes. In a traditional approach (Level 3 control), end-product testing to product specification provides the primary assurance of product quality. In a more advanced control strategy, the primary assurance of quality is through process controls, including in-process tests, and the primary purpose of any end-product testing is to confirm that the process is operating as intended.

Different approaches can be used for the release of intermediates and finished product, including RTRT, traditional methods, or a hybrid approach. Continuous processes typically employ more PAT methods than batch processes, which facilitate the use of RTRT for in-process controls and release testing. Although advanced control strategies are frequently used in CM, the use of traditional approaches (i.e., off-line testing of in-process samples and end-product testing) for batch release remains a viable option, especially for backup systems in the event of PAT failures.

Real-time Release Testing

RTRT is used to evaluate and ensure the quality of in-process materials and/or final product based on process data that typically include a valid combination of measured raw material attributes and process controls [2]. In this context, implementation of RTRT to CM processes requires establishing clear relationships between the final product's critical quality attributes and the control elements incorporated into the process (e.g., quality attributes of raw and in-process materials, process parameters).

NIR spectroscopy is commonly used in CM of solid oral dosage forms and lends itself readily to an RTRT approach for identity, assay, and content uniformity (e.g., through NIR analysis of the blend prior to compression). Content uniformity can be calculated from the combination of NIR blend potency and weight uniformity of the dosage forms. A more complex example of an RTRT approach is a dissolution model based on the real-time measurements of in-process material or end-product quality attributes (e.g., drug concentration, tablet hardness, weight, and particle size distribution) and use of an appropriate mathematical model to predict the tablet dissolution performance [19]. When using an RTRT approach for product release, redundant testing for that particular attribute (i.e., wet chemistry) can be eliminated. However, traditional laboratory testing methods must be available to aid in postmanufacturing analysis.

An RTRT approach warrants careful consideration of the sampling strategy that accounts for equipment dynamics and the RTD for material passing through the system. The selected sample size and frequency should be representative of the batch and justified statistically to provide an adequate confidence level and coverage. Given the high frequency of data collection, appropriate statistical methods for large sample size can increase the confidence level that the batch conforms to the desired quality [20].

In the event of PAT equipment failure, established alternative procedures can be used for process monitoring and batch release [18]. These procedures could include end-product testing or the use of surrogate measurements to ensure that products demonstrate an acceptable level of quality.

Hybrid Release Specifications

As previously stated, an approach that combines traditional and RTRT release methods can also be used. For instance, identity, assay, and blend/content uniformity may be determined by NIR, with dissolution and impurities being determined through traditional laboratory analysis. Some tests, such as microbial content, may not be possible for PAT, which may prevent a full RTRT approach to release testing.

Traditional Release Specifications

Traditional product-release tests can be used with CM and, in some instances, may be preferred. For example, if the manufacturing process is a hybrid of both batch and CM processes, or if the final step (e.g., film coating) is conducted as a batch process, it may be easier to perform product-release testing on manual samples using traditional analytical methods and acceptance criteria. For any control strategy approach, sufficient assurance of quality should be justified through appropriate raw material specification, process parameter controls, in-process tests, and end-product testing.

CONCLUSIONS

Control strategies for CM should be holistic in their design, appropriately utilizing a combination of raw material specifications, in-process tests, process monitoring and controls, and end-product testing to specifications. There is no one-size-fits-all approach to CM control strategies. Each process and product has its own risks that the control strategy mitigates through science- and risk-based approaches along with a robust PQS. Although advanced controls are commonly used in CM for solid oral dosage forms, they may not necessarily be required, depending on the level of process understanding, manufacturing experience, and specific process risks. A comprehensive and holistic view of all elements of the control strategy provides continued assurance of product quality over the product and process life cycle.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System Q10." Published June 4, 2008. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Pharmaceutical Development Q8 (R2)." Published August 2009. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Endorsed Guide for ICH Q8/Q9/Q10 Implementation: ICH Quality Implementation Working Group Points to Consider (R2)." Published December 6, 2011. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Quality Risk Management Q9." Published November 9, 2005. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf
5. Allison, G., Y. Cain, C. Cooney, T. Garcia, T. G. Bizjak, O. Holte, N. Jagota, et al."Regulatory and Quality Considerations for Continuous Manufacturing, May 20–21, 2014 Continuous Symposium." *Journal of Pharmaceutical Sciences* 104, no. 3 (March 2015): 803–12. doi:10.1002/jps.24324
6. Nasr, M. M., M. Krumme, Y. Natsuda, B. Trout, C. Badman, S. Mascia, C. Cooney, K. D. Jensen, A. Florence, C. Johnston, K. Konstantinov, and S. L. Lee." Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice: September 26–27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals." *Journal of Pharmaceutical Sciences* 106, no. 11 (November 2017): 3199–206. doi:10.1016/j.xphs.2017.06.015
7. Kushner, Joseph. "Utilizing Quantitative Certificate of Analysis Data to Assess the Amount of Excipient Lot-To-Lot Variability Sampled During Drug Product Development." *Pharmaceutical Development and Technology* 18, no. 2 (March–April 2013): 333–42. doi:10.3109/10837450.2011.604784
8. Lee, S. L., T. E. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, and L. X. Yu. "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production." *Journal of Pharmaceutical Innovation* 10, no. 3 (September 2015): 191–9. doi:10.1007/s12247-015-9215-8
9. Gao Y., A. Vanarase, F. Muzzio, and M. Ierapertritou. "Characterizing Continuous Powder Mixing Using Residence Time Distribution." *Chemical Engineering Science* 66, no. 3 (February 2011): 417–22. doi:10.1016/j.ces.2010.10.045
10. Kourti T., R. Madurawe, K. Brorson, D. Doleski, D. Hernán Pérez de la Ossa, J. Hu-Primmer, C. Airiau, et al. "ISPE 2016 Continuous Manufacturing Conference Highlights." *Pharmaceutical Engineering* 37, no. 3 (May/June 2017): 35–42.
11. Escotet-Espinoza M., S. Moghtadernejad, S. Oka, Z. Wang, Y. Wang, E. Román A, Schäfer, P. Cappuyns, et al. "Effect of Material Properties on the Residence Time Distribution (RTD) Characterization of Powder Blending Unit Operations. Part II of II: Application of Models." *Powder Technology* 344 (February 15, 2019): 525–44. doi:10.1016/j.powtec.2018.12.051
12. Nowak, S. "Improving Feeder Performance in Continuous Pharmaceutical Operations." *Pharmaceutical Technology* 40, no. 10 (October 2, 2016): 68–73. http://www.pharmtech.com/improving-feeder-performance-continuous-pharmaceutical-operations
13. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7." Published November 10, 2000. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf
14. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11." Published May 1, 2012. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf
15. Romero-Torres, S., J. Huang, and P. Hernandez-Abad. "Practical Considerations on PAT Analyzer Selection—Raman vs. NIR Spectroscopy." *American Pharmaceutical Review* no. 12 (December 1, 2009): 5–10.
16. Kourti, T. "Process Analytical Technology Beyond Real-Time Analyzers: The Role of Multivariate Analysis." *Critical Reviews in Analytical Chemistry* 36, no. 3–4 (2006): 257–78. doi:10.1080/10408340600969957
17. Wise, B., and N. Gallagher. "The Process Chemometrics Approach to Process Monitoring and Fault Detection." *Journal of Process Control* 6, no. 6 (December 1996): 329–48. doi:10.1016/0959-1524(96)00009-1
18. European Medicines Agency. "Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)." Published March 29, 2012. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-real-time-release-testing-formerly-guideline-parametric-release_en.pdf
19. Pawar, P., Y. Wang , G. Keyvan, G. Callegari, A. Cuitino, and F. Muzzio. "Enabling Real Time Release Testing by NIR Prediction of Dissolution of Tablets Made by Continuous Direct Compression (CDC)." *International Journal of Pharmaceutics* 512, no. 1 (October 15, 2016): 96–107. doi:10.1016/j.ijpharm.2016.08.033
20. European Directorate for the Quality of Medicines. "Chapter 2.9.47: Demonstration of Uniformity of Dosage Units Using Large Sample Sizes." In *European Pharmacopeia*, 9th ed. 2019. http://online6.edqm.eu/ep908

About the authors

Christine M. V. Moore, PhD, is Global Head and Executive Director, GRACS CMC–Policy at Merck & Co., Inc., Kenilworth, New Jersey, US. Christine joined Merck after more than a decade in various positions in the US FDA, including Acting Office Director of the Office of New Drug Quality Assessment and the Office of Process and Facilities. Prior to working at FDA, Christine spent 10 years in small and large molecule process development, including process analytical technologies. She holds a BS in chemical engineering from Northwestern University and a PhD in chemical engineering from Massachusetts Institute of Technology. Throughout her career, Christine has focused on the development of scientific and regulatory approaches for advancing pharmaceutical manufacturing technologies, modernizing regulatory guidance, and progressing international harmonization. She has been a thought leader in progressive regulatory approaches in the areas of quality by design, process analytical technology, and continuous pharmaceutical manufacturing. Christine has been an ISPE member since 2012.

Douglas B. Hausner is the Associate Director of the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) based at Rutgers University in New Jersey. C-SOPS focuses on the science-based development of pharmaceutical products and processes. C-SOPS has been directly involved in working with major pharmaceutical companies and the FDA on some of the first processes for continuous manufacturing of pharmaceutical solid dose products. Doug has a PhD in physical chemistry and has been a member of the Department of Chemical and Biochemical Engineering at Rutgers for eight years. He has been an ISPE member since 2011.

Thomas Garcia, PhD, is a Research Fellow in Global CMC at Pfizer Inc., Groton, Connecticut. Tom has 30 years of industry experience: 14 years in pharmaceutics and 16 years in CMC regulatory. He has published extensively in the area of blend and content uniformity and has led ISPE and PQRI (Product Quality Research Institute) groups on this topic. Tom implemented regulatory strategies for Quality by Design (QbD) dossiers during its inception, and is currently doing the same with Continuous Manufacturing. He is a member of the ICH Q 13 Expert Working Group. Tom was also a member of the SUPAC IR Industry Training Committee and multiple ISPE teams. He is an Adjunct Associate Professor in Pharmaceutical Sciences at Albany College of Pharmacy and Health Sciences. Tom received a BS in pharmacy from Albany College of Pharmacy in 1983, and a PhD in industrial and physical pharmacy from Purdue University in 1989. He has been an ISPE member since 2007.

Inna Ben-Anat is Executive Director, Global Quality Management Systems (QMS), at Merck & Co., Inc., Kenilworth, New Jersey, US. Inna leads the Technology Transfer and Commercialization Chapter within Global QMS, ensuring sustainable compliance and providing leadership and technical direction on regulatory requirements for technology transfer and commercialization processes. Inna joined Merck from Teva Pharmaceuticals, where she served at various roles within MS&T, R&D, and operations functions, leading quality by design implementation, new products introduction, and product robustness strategies. Inna holds an MSc in quality assurance and reliability and a BSc in chemical engineering, both from the Technion, Israel Institute of Technology. She has been an ISPE member since 2008.

PROCESS VALIDATION

in the Context of Small-Molecule Drug Substance and Drug Product Continuous Manufacturing Processes

By Jonathan B. Wade, PhD, and Robert Ievers

Continuous manufacturing (CM) technologies have recently been implemented in the pharmaceutical industry for process development, clinical trials, and commercial supply. This article is a high-level summary of a recently published ISPE Discussion Paper that details unique aspects of CM related to each stage of the process verification (PV) life cycle.

Although concepts from the three-stage PV life cycle can be applied to the CM process, several aspects of PV for the CM process diverge from PV for the traditional batch manufacturing process. Both the article and the Discussion Paper aim to acknowledge differences between CM and traditional batch manufacturing and to review additional considerations for CM processes without creating new definitions. In some cases, the concepts covered in the Discussion Paper may apply universally; however, the intended focus is on small-molecule drug substances and drug products that leverage CM processes, whether for a new product development or the postlaunch conversion from batch manufacturing to CM.

This article summarizes the three sections of the Discussion Paper that are aligned with the three PV life-cycle approach stages: process design, process qualification (PQ), and ongoing process verification (OPV). Additional considerations needed during the development and validation of a CM process are emphasized.


Jonathan B. Wade


Robert Ievers

Readers are highly encouraged to refer to the entire Discussion Paper for more details as well as a fictional case study that provides additional context for the concepts.

STAGE 1—PROCESS DESIGN

In stage 1 of the PV life cycle, the commercial manufacturing process is defined based on knowledge gained through development and scale-up/scale-out activities. The control strategy is defined and refined to ensure that the process is ready to progress to stage 2. One of the primary aims of stage 1 is to develop a control strategy to make sure that the output consistently meets the expectations described in the Quality Target Product Profile (QTPP).

At a high level, the main science- and risk-based steps completed in stage 1 are the same for both traditional batch and CM processes. However, the following are some of the considerations unique to the development of CM processes:

- **Process disturbances:** CM within a controlled and reproducible operation may have periods of process disturbance (e.g., raw material feed-rate fluctuations during process start-up). The potential for these disturbances should be considered and

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

MULTIPLE EFFECTS DISTILLATION UNIT 12M³H

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURNKEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

criteria developed to define and maintain the process in a state of control. When process performance is deemed to be outside of its state of control, a process pause and/or a decision to isolate material can be engaged. Additionally, it is important to recognize the impact that a disturbance in a unit operation could potentially have on downstream unit operations if they are integrated as one module.

- **Material diversion:** As noted in the previous point, a unique consideration with CM is the concept of material diversion during an identified process upset. A known process upset traveling through a continuous processing equipment set with a known residence time has a known dispersion and, subsequently, a known clearance time on return to normal conditions. Predictive models, including residence time distribution (RTD) models, and process analytical technology (PAT) applications are useful approaches for determining the amount of material that requires diversion.
- **Process development using commercial-scale equipment:** Stage 1 development entails experimentation to develop an understanding of the process dynamics required for integrated monitoring and control technology. Commercial equipment may be used to perform most stage 1 experimentation at scale, eliminating the need for scale-up activities to assess process risks at the commercial scale required for traditional batch manufacture. Although continuous processes may inherently reduce the need for equipment scale-up activities, it is important to note that because rate (mass per unit time) can become one of the scaling dimensions for a continuous process, there is a burden to characterize critical quality attribute (CQA) performance and processing risks as a function of time/throughput rate (e.g., material buildup on equipment surfaces). It may not always be possible to fully characterize a commercial time scale during stage 1; therefore, this may be carried into stage 2 as a residual risk.
- **Spectroscopic tools:** Spectroscopic tools, such as PAT, that require advanced chemometric and/or process models may be employed in stage 1, and process automation often becomes an integral part of the control strategy. Real-time release testing (RTRT) strategies integrate these concepts.

To achieve success in CM development, manufacturers will need a cross-functional, collaborative team with a high level of understanding of the concepts listed here.

STAGE 2—PROCESS QUALIFICATION

Before commercially distributing a drug product, the manufacturer is obliged to successfully complete PQ. During the PQ stage of PV, the process design is evaluated to determine whether it is capable of reproducible commercial manufacture. In general, equipment and utilities qualification and manufacturing facility design involve the same steps for both batch and CM. However, the complexity of the qualification activity may be greater for CM because of the integrated nature of the unit operations. The complexity

In general, equipment and utilities qualification and manufacturing facility design involve the same steps for both batch manufacturing and CM. However, the complexity of the qualification activity may be greater for CM because of the integrated nature of the unit operations.

BPE BIOPHARMA ENGINEERING

EXPERTS IN CONTINUOUS MANUFACTURING

Continuous API Manufacturing Facility

Client: **CONFIDENTIAL**

Value: **€30M**

Location: **IRELAND**

Duration: **24 MONTHS**

From concept to completion, download our full case study at www.biopharma.ie

T: +35321-2307120 | E: info@biopharma.ie | www.BioPharma.ie

Compared with most traditional batch manufacturing operations, CM processes will likely generate more in-process data and, perhaps, more finished-product data.

also increases when PAT and automated control and data management systems are utilized. Similarly, although the high-level science- and risk-based steps completed in process performance qualification (PPQ) are the same for both batch and CM processes, there are a few unique PPQ considerations for CM.

CM-specific issues for stage 2 include the following:

- **Justification for the quantity of validation batches:** When justifying the number of validation batches, the desire for flexibility in batch size and/or mass throughput should be considered. A risk-based approach should be taken when determining whether the intended worst-case run time (defined by time, number of units, mass of product, etc.) and/or selected throughput(s) should be included in the PQ exercise. To do this, consideration would be given to product understanding, process knowledge, and detectability of unexpected performance in relation to the specific risks associated with increases in run time (e.g., microbial growth, material build-up/equipment performance, cleanability). In many cases, a PV with fewer than three batches may be supported, although global acceptance of such an approach remains a topic of discussion. Increases to batch size require thorough risk management; however, with appropriate understanding of the system dynamics, a single batch may be suitable to supplement the initial PPQ.
- **Process performance metrics:** It is good practice to measure process performance metrics (yield, mass balance, etc.) in stage 2 for process performance monitoring and continuous improvement, rather than treating those metrics as PV acceptance criteria. The robustness measurement techniques explored in stage 1—such as mass balance, yield, and the percentage of time the process remains in a state of control from the planned product collection of the continuous processing batch—would be appropriate process performance metrics.
- **Volume of data:** Compared with most traditional batch manufacturing operations, CM processes will likely generate more in-process data and, perhaps, more finished-product data. Furthermore, the structure of the data collected (e.g., systematic or nested samples associated with solid dosage uniformity testing) may require more advanced statistical modeling to accurately describe process performance and capability. It is important to clearly define the scope of data so it is directly tied to the manufacturing control strategy and/or product disposition. The stage 2 statistical analyses and related sampling plans (i.e., defined sampling points and amounts used to support stage 2 statistical analyses) will focus on the CQAs, critical process parameters, in-process controls (IPCs), and other variables relevant to assessing product quality and process control that were identified in the criticality analysis in stage 1.

The data-analysis objectives in stage 2 are the same for CM and batch processes: to evaluate intrabatch variability and capability, and to provide initial assessments of reproducibility and consistency between batches. Based on these assessments, decisions are made regarding 1) the readiness of the process to proceed to stage 3; 2) whether, and to what degree, enhanced sampling (i.e., more frequent sampling and/or greater-than-routine amounts) is needed in stage 3; and 3) if enhanced sampling is required, how many batches will be sampled before another evaluation. Considering the special considerations for PAT and similar tools, and the related implications for statistical methodologies for continuous processes discussed previously, the stage 2 performance evaluation for a CM process is not substantially different than that for a batch process.

STAGE 3—ONGOING PROCESS VERIFICATION

The goals and expectations for OPV are the same for batch and CM processes: to provide ongoing assurance that the process remains in a state of control by monitoring it through a periodic trending program. This program will help manufacturers understand routine variability, detect unusual variability (i.e., special cause), and enable process improvement to maintain a state of control.

As noted in the previous section on PQ, one of the most distinctive aspects of the CM process relates to the volume of data that may be collected. Given the large amount of data that may be routinely captured for a CM process during OPV, it is important that the trend analysis focus on the critical parameters that are predictive of product quality (e.g., control strategy parameter criticality, IPCs). The process measurements to be statistically trended in the OPV program should be selected using quality risk-management tools and specified in an OPV plan. Careful assessment of statistical assumption violations is needed. The OPV plan should also address the statistical trending tools to be used, the frequency of data review, the duration of data collection, the roles and responsibilities of team members, and which events will trigger actions as well as the actions that must be taken.

An ideal OPV program will capitalize on the additional data generated and allow for a periodic refinement of the control

We understand how leading-edge products and process improvements are critical in your business.

INNOVATE + ACCELERATE

You are enabled to achieve a faster time to market, improve plant productivity and reduce risk.

Improve your processes with our comprehensive portfolio of measuring instruments:

Micropilot FMR6x:
The 80GHz radar with all certificates runs clear, reliable signals even in small tanks with baffles.

Promass P 100:
The flow measurement specialist with an ultra-compact transmitter is designed for sterile processes.

iTHERM TrustSens TM37x:
The world's first self-calibrating compact thermometer slashes the risk of process failures.

Do you want to learn more?
www.endress.com/life-sciences

Endress+Hauser

People for Process Automation

strategy. This type of program provides an opportunity to determine the root cause of special cause events and further increase the knowledge base of the product, with the optimal goal of continually improving the process.

Other considerations when designing an OPV program for a CM process include model maintenance, which is an additional requirement often associated with CM processes that use technology such as PAT. Process models (such as an RTD), PAT models, and other models supporting RTRT require a model maintenance plan based on their respective risks and roles within the control strategy.

CONCLUSION

PV in the context of CM is fundamentally the same concept used in the context of batch processes. A life-cycle approach consisting of three stages (process design, PQ, and OPV) forms the basis of the approach. However, multiple unit operations linking in CM processes may lead to an increased volume of data and may require integration of process models and tools such as PAT for feedback/feed-forward controls, as well as the implementation of RTRT strategies. Therefore, opportunities to refine PV for CM processes will require further consideration as the industry continues implementation. The authors of the ISPE Discussion Paper are interested in receiving feedback on the CM topics presented in the full document, including lessons learned through regulatory agency feedback during review and inspection. Please email wade_jonathan@lilly.com or Robert.ievers@merck.com.

About the authors

Jonathan B. Wade, PhD, earned his BSc degree in medicinal and pharmaceutical chemistry from Loughborough University, UK, and a MSc degree in pharmaceutical technology and PhD in pharmaceutical science, both from King's College London, UK. Jon has over 17 years of experience across late-stage product development, scale up, technology transfer, process validation, and post-launch optimization with a focus in solid oral dosage forms. He has extensive hands-on experience designing, executing, and defending process validation strategies associated with new product introductions, technology transfers, and periodic revalidations for legacy products. Currently, he is leading the harmonization and implementation of batch and continuous process validation life-cycle approaches for the Eli Lilly Global Dry Product Network.

Robert Ievers is a Director in the Global Technical Operations Sterile & Validation Center of Excellence at Merck & Co., Inc., Kennilworth, New Jersey, US, where he provides process and cleaning validation support to internal and external partner manufacturing sites throughout the world. He has 20 years of experience in technology transfer and manufacturing technical operations organizations, holding positions of increasing responsibility during his career. Bob holds a bachelor of science in chemical engineering from Rensselaer Polytechnic Institute.

Acknowledgments

This article is a summary from the Discussion Paper with the same title published in January 2019. The full article can be accessed at https://ispe.org/publications/papers. Contributing authors to the full Discussion Paper posted on the ISPE website include Matthew McMenamin, Manager, Systems and Technology, Glaxo Smith Kline; Carly Evans, Senior Director Regulatory, Akebia Therapeutics; Declan Hurley, Consultant Scientist, Eli Lilly & Co.; and Katherine Giacoletti, Partner, SynoloStats LLC.

REGULATORY PROGRESS

in Global Advancement of Continuous Manufacturing for Pharmaceuticals

By Anita K. Lalloo, PhD


Anita K. Lalloo

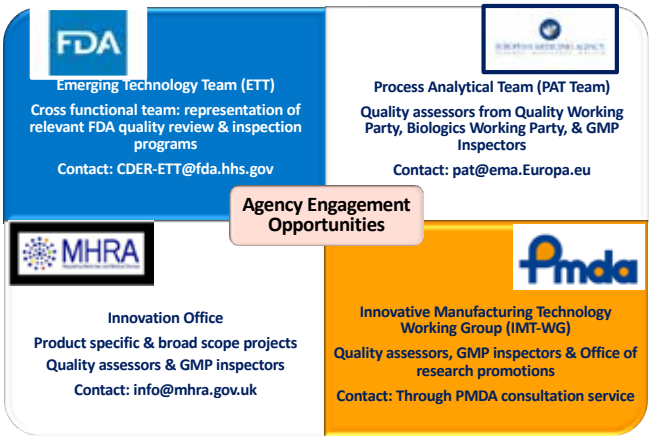
Continuous manufacturing (CM) is an advancement in pharmaceutical manufacturing technology that provides high assurance of product quality as well as enough flexibility and agility in production to respond to market demands. The decision to invest in CM can be challenging for a company given the cost of purchasing the continuous equipment, the resources and expertise required for additional in-process monitoring and testing, and the automation complexity of the integrated system. However, the economic benefits afforded by CM, specifically from optimizing supply chains by manufacturing according to variable product demand, provide a strong justification for this investment. Furthermore, several regulatory agencies have recently approved solid oral dosage forms for multiple new chemical entities as well as an already approved and marketed product, and these approvals have generated significant interest in and excitement about this novel approach to manufacturing pharmaceuticals.

To date, products manufactured by CM have been approved in at least seven markets, with several applications under review. The US FDA alone has approved five different applications for solid oral dosage forms produced by CM (Table 1) [1, 2]. It is

Table 1: Products manufactured by CM approved by the US FDA.

Products	Approval Date	Company	Application Type
Orkambi (lumacaftor/ivacaftor)	August 2015	Vertex	New chemical entity
Prezista (darunavir)	April 2016	Janssen	Marketed product
Verzenio (abemaciclib)	September 2017	Eli Lilly	New chemical entity
Symdeko (tezacaftor/ivacaftor and ivacaftor)	February 2018	Vertex	New chemical entity
Daurismo (glasdegib)	November 2018	Pfizer	New chemical entity

Figure 1: Teams within various agencies supporting innovation.



particularly encouraging to note that regulatory agencies have approved a range of equipment designs, differing degrees of equipment integration, and a wide variety of control strategies with varied extent of in-process monitoring and controls and use of real-time release testing. From presentations at conferences, it is clear that regulatory agencies are reviewing each CM application based on its individual merit, using a science- and risk-based approach to assess the manufacturing process and the product characteristics. This nonprescriptive approach drives innovative, creative thinking and supports the continued growth of CM for small- and large-molecule applications.

TEAM APPROACH

To support innovation in manufacturing and the adoption of novel technologies, several regulatory agencies have formed teams to advise sponsors seeking to implement new technologies such as CM. These regulatory teams include the Emerging Technology Team within the US FDA, the Process Analytical Technology Team within the European Medicines Agency, the Innovative Manufacturing Technology Working Group within Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and the Innovation Office within the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) (Figure 1).

These focused groups within each agency encourage companies to engage with agencies early and frequently as they work on new technology initiatives. The goal is to provide an opportunity to discuss novel strategies and approaches prior to the regulatory submission. This dialogue between industry and regulatory agency helps regulators understand the technology and alerts sponsors to potential regulatory concerns. Early engagement with regulators reduces regulatory uncertainty and lowers the number of questions during the review period. Each regulatory agency has a specific pathway to initiate interaction, and the opportunity to leverage these resources may be limited based on their availability and the agency's priorities at the time.

Although current regulatory guidance does not prevent the use of CM, final guidelines on the topic are not yet available. The lack of regulatory guidelines can hinder technology implementation, regulatory approval, and life-cycle management for CM-manufactured products, especially when those products are intended for international markets.

ICH Q13

To address these concerns, CM was selected as a topic for the recently initiated International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline, "ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products" [3].

The ICH Q13 guideline under development seeks to harmonize CM-related definitions and regulatory concepts, define key scientific approaches for CM, and clarify regulatory expectations. Some specific aspects of CM that the guideline is expected to address include state of control, system dynamics, material traceability, process models, and advanced process controls. The final document, which will likely be issued around 2021, will provide clarity on how drug manufacturers can use flexible approaches to develop, implement, and integrate CM for new and existing drug substances or drug products.

The ICH guideline process provides a unique opportunity to increase exposure to and knowledge of CM among regulators worldwide. ICH currently includes 10 regulatory agencies representing 37 countries and 13 regulatory observers, and it continues to grow steadily. Worldwide harmonization of regulatory concepts is especially important for CM because high levels of integrated measurements and controls are frequently used in CM processes. Alignment among all regulatory agencies on the different approaches for developing regulatory control strategies for CM is essential for the efficient deployment of these technologies.

As we wait for a finalized ICH guideline on CM, conferences and publications provide useful technical and regulatory information. Recently, conferences and workshops covering CM for both small and large molecules have proliferated; some of these events have been organized by ISPE as stand-alone conferences or as part of other regular conferences such as the ISPE Annual Meeting or the ISPE Facilities of the Future Conference. For additional regulatory insight into current approaches and expectations for CM, readers may refer to several recent publications on CM that are technical and regulatory/quality focused [4–8] as well as articles summarizing notable CM conferences [9, 10].

Acknowledgment

The author would like to thank Christine Moore, Global Head and Executive Director GRACS CMC-Policy at Merck & Co., Inc., Kenilworth, New Jersey, US, for reviewing the article.

About the author

Anita K. Lalloo, PhD, is Director, Global Regulatory Affairs, for Merck & Co., Inc., Kenilworth, New Jersey, US. She is responsible for developing a global CMC regulatory strategy, which is aligned

with major/regional regulatory requirements, authoring dossiers, and executing global submission plans. To promote innovation in regulatory sciences, Anita provides regulatory guidance for several novel initiatives including continuous manufacturing, 3D printing, APKS, and clinically relevant specifications. In her previous role in the Global Technical Operations at Merck (MSD), Singapore, Anita was responsible for ensuring reliable product supply, leading product/process investigations, identifying and driving manufacturing process improvements, and supporting postapproval changes and site inspections. Anita has more than 10 years of experience in drug development from early formulation development to commercial manufacturing site experience. Anita received her PhD in pharmaceutical sciences from Rutgers University.

References

1. Lee S. L. "Emerging Technology Program: A Key Enabler for Successful Adoption of Novel Pharmaceutical Technologies." Presentation at the ISPE Continuous Manufacturing Workshop, Arlington, VA, 6–7 June 2018.
2. Pfizer Inc. "U.S. FDA Approves Daurismo™ (Glasdegib) for Adult Patients with Newly-Diagnosed Acute Myeloid Leukemia (AML) for Whom Intensive Chemotherapy Is not an Option," press release, November 21, 2018. https://investors.pfizer.com/investor-news/press-release-details/2018/US-FDA-Approves-DAURISMO-glasdegib-for-Adult-Patients-with-Newly-Diagnosed-Acute-Myeloid-Leukemia-AML-for-Whom-Intensive-Chemotherapy-is-Not-an-Option/default.aspx
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "Final Concept Paper. ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products." 14 November 2018. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q13/Q13EWG_ConceptPaper_2018_1115.pdf
4. Allison G., Y. T. Cain, C. Cooney, T. Garcia, T. G. Bizjak, H. Oyvind, N. Jagota, et al. "Regulatory and Quality Considerations for Continuous Manufacturing May 20–21, 2014, Continuous Manufacturing Symposium." *Journal of Pharmaceutical Sciences* 104, no. 3 (March 2015): 803–12. doi:10.1002/jps.24324
5. Lee S. L., T. F. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, L. X. Yu, and J. Woodcock. "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Product." *Journal of Pharmaceutical Innovation* 10, no. 3 (September 2015): 191–9. doi:10.1007/s12247-015-9215-8
6. Nasr M. M., M. Krumme, Y. Matsuda, B. L. Trout, C. Badman, S. Mascia, C. L. Cooney, et al. "Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice: September 26–27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals." *Journal of Pharmaceutical Sciences* 106, no. 11 (November 2017): 3199–206. doi:10.1016/j.xphs.2017.06.015
7. Matsuda, Y. "Global Regulatory Landscape." *AAPS PharmSciTech* 20, no. 1 (December 2018): 2. doi:10.1208/s12249-018-1230-x
8. Hernán, D. "Continuous Manufacturing: Challenges and Opportunities. EMA Perspective." Slide presentation at the 3rd FDA/PQRI Conference on Advancing Product Quality 22–24 March 2017. http://pqri.org/wp-content/uploads/2017/02/3-DHernan.pdf
9. Hauser, D. B., C. M. V. Moore, International Society for Pharmaceutical Engineering. "ISPE 2018 Continuous Manufacturing Current Status." *Pharmaceutical Engineering* 38, no. 3 (May–June 2018). https://ispe.org/pharmaceutical-engineering/may-june-2018/continuous-manufacturing-current-status
10. International Society for Pharmaceutical Engineering. "ISPE 2016 Continuous Manufacturing Conference Highlights." *Pharmaceutical Engineering* 37, no. 3 (May–June 2017): 35–42.

TEN FREQUENTLY ASKED QUESTIONS ABOUT SERIALIZATION

By Laurent Arnould, Christophe Devins, Jean-Marc Libersa, Michel Raschas, CFPIM, Matthieu Thibaud, and Nathalie Wardé, PhD

To meet the EU serialization deadline on 9 February 2019, pharmaceutical companies and their contractors have had to reorganize their manufacturing lines and logistics to ensure compliance with the EU's Falsified Medicines Directive (FMD) of 2011 and the EU Commission Delegated Regulation 2016/161 of 2016. Worldwide, other anticounterfeiting regulations are already in place or coming soon in nations including the US, Saudi Arabia, Korea, and Russia. Thus, drug manufacturers that market products internationally must continue to reorganize their operations to comply with many different standards.

The European serialization scheme establishes specific safety features for prescribed medicines: an antitampering device and a unique identifier. The unique identifier is composed of a unique sequence of a product code, a serial number based on a randomized algorithm, a batch number, and expiry date, and, when required by the local authorities, a reimbursement number. It must be clearly printed on the packaging and encoded using a standardized data structure and syntax in a two-dimensional, machine-readable data matrix (i.e., barcode). Before the medicine is dispensed to the patient, the pharmacist at the dispensary or hospital ensures the medicine's authenticity in an end-to-end verification system by scanning the data matrix so the unique identifier can be compared with the information uploaded in a secured system of repositories. The repositories system for storing serialization data must be set up by the marketing authorization holders (MAHs) and/or the manufacturers (master data and unique identifier commissioning). The unique identifier is then decommissioned when the pack is dispensed within the EU or remarketed to a non-EU country.

To comply with EU serialization regulations, drug manufacturers have been working hard to modernize packaging lines in their production plants with the new printing devices, monitoring systems, and software necessary to serialize drugs subject to prescription and connect labeling information with data repositories at national and European hubs. For the last three years, the ISPE France Affiliate Serialization Workgroup has produced tools for serialization project stakeholders, which can be helpful for new or renewal projects, within the EU or overseas. Some of those tools are highlighted in the following frequently asked questions (FAQs).

WHY SERIALIZATION FAQS ARE TIMELY

Serialization is one of the biggest information technology (IT) challenges to affect the pharmaceutical sector in the last decade. In a global landscape of constantly evolving regulatory, market, and technical requirements, serialization is, and will likely remain, a complex topic for all industry actors. The Workgroup on Serialization was convened to capture the variety of insights gained by those who have implemented serialization. It has developed this easy-to-understand document to complement (but not replace) regulatory guidance from EMA, FDA, and others with information gathered from the industry. We hope serialization project stakeholders will find these FAQs useful.

QUESTION 1: WHAT ARE THE KEY COMPONENTS OF A SERIALIZATION USER REQUIREMENT SPECIFICATION?

A user requirement specification (URS) document is the first reference document built when a serialization project is initiated. URS documents are also needed when an existing system must be modified to comply with new regulations.

The URS document specifies all technical and functional requirements to be included in the request for quotation (RFQ) that is sent to all the vendors invited to bid during the sourcing phase of the seriali-


Leaders in Life Sciences
The leading provider in the Life Sciences Industry of technical, professional and construction services, including all aspects of architecture and engineering.
Everything is possible.
Consulting
Engineering
Architecture
Construction
Commissioning
Qualification
Verification
Find out more at www.jacobs.com
JACOBS®

zation solution. It includes requirements from all stakeholders of all areas in scope, and there are many stakeholders—serialization affects almost the entire supply chain, extending far beyond the packing hall and manufacturing lines.

When a preferred or preselected vendor is identified before the RFQ, the URS provided with the vendor's standard commercially available solution could be used. This approach is especially relevant for many of the Level 3 serialization solutions available on the market, which already include standard URS in their documentation. Even if standard URS are available, the user should perform their own risk assessment to ensure that they adequately understand the complexity and novelty of the scope of functionalities to be purchased.

The following list summarizes key components (i.e., chapters) of a serialization URS document. This list is not intended to be exhaustive. If information listed is already available elsewhere, it can be referenced instead of duplicated in the URS. FAQs 2–10 explore the items in this list in greater detail.

- Introduction
- Serialization project presentation and scope (in particular, which regulations must be covered and what kind of track and trace model is involved)
- Operational requirements
- Constraints on solution specification and operations
- Requirements for the serialization solution throughout its life cycle
- Approvals

QUESTION 2: WHAT SHOULD BE EMPHASIZED IN THE PRESENTATION OF THE SERIALIZATION PROJECT?

This project presentation section describes the overall purpose and scope of the serialization project—specifically, the objectives and deliverables that have been assigned to the project and the implementation strategy. For example, is the objective to meet only European regulatory requirements, or is the company looking for a solution that can accommodate more complex functionalities and/or the next wave of requirements to be published? Does the company hope to enhance its return on investment by implementing functionalities that will bring added value to its products and services?

Along with regulatory compliance (which is a must-have requirement), serialization projects may have additional benefits, such as the following:

- Tools to identify and help investigate problems: For example, the time stamp of the serial number operation on the packaging box can be useful when investigating complaints about products.
- Tools to help track and trace stock: The serial number can also be used to track stock in the supply chain from the manufacturer to the final patient, as well as to trace products returned to any part of the supply chain.

The presentation section should clearly identify the project scope by answering the following questions:

- Is the project limited to production site(s)? How many sites are in the scope? Does the project include sites other than manufacturing sites, such as general offices?
- How many packing lines are to be equipped with serialization?
- How many product families and SKUs are in the scope?
- What is the packaging configuration of the saleable unit?
- Does the management of serial numbers (creation, reporting, etc.) need to be included in the project?
- How many interfaces are in the scope? (For example, does the serialization solution need to interface with ERP (enterprise resource planning) or MES (manufacturing execution system) or support reporting to local or regional regulatory agencies?)
- Is there any need to connect the serialization solution to partners (e.g., joint ventures, alliances) or specific vendors?
- Which processes are in the scope? What are the applicable regulations for those processes?
- Is aggregation to be included if the company is supplying non-EU markets from Europe? If so, is aggregation to be done at just the case level, or will it be extended to pallets for the larger volumes and for efficiency purposes?

QUESTION 3: WHAT ARE THE OPERATIONAL REQUIREMENTS?

The following processes will have to be extensively specified to ensure generation and management of data in accordance with all regulatory requirements:

- Functions performed during the serialization process (see FAQ 5)
- Definition of data and data quality (see FAQs 6 and 7)
- Data management
- Technical requirements (see FAQ 8)
- Interfaces (see FAQ 9)
- Environment and corresponding installation prerequisites

Process descriptions and documentation (e.g., flowcharts) can be included as relevant in any of these sections of the URS.

All requirements specified should be pragmatically achievable and verifiable, although these objectives may be difficult to specifically define and subject to multiple interpretations. A good approach is to define criteria to measure how requirements are achieved. These criteria can be used to evaluate whether vendors that participate in the RFQ process provide proposals that reflect the business need as closely as possible. Additionally, these criteria could be used as benchmarks during the implementation phase.

QUESTION 4: WHICH FUNCTIONS ARE TYPICALLY PERFORMED DURING THE SERIALIZATION PROCESS?

The following functional requirements must be specified and documented in the URS:

- **Calculations:** All critical algorithms, such as those that ensure compliance with regulatory or key internal requirements, must be duly described. The supporting scientific sources and calculations for each algorithm must be documented, and the

relevance of these sources and calculations for each critical algorithm that has been adapted for the scope of the serialization project must be clearly articulated.

- **Performance of randomization algorithms:** Randomization shall be performed within a reasonable time frame. This performance level will need to be maintained across the life span of the project, in accordance with not only current but also future business needs of the company.
- **Volume represented by codes generated:** The number range that shall be dedicated to serial numbers will need to significantly exceed the number of serial numbers expected to be consumed across the life span of the serialization project (consider a minimum life span of 5 years according to Delegated Regulation 2016/161 Article 4 d). Each serial code generated will be controlled to ensure its unicity in the considered product code. If the number range for serial numbers is too short, it will become increasing difficult for the randomization algorithm to generate new serial numbers over time. Having an expansive range of serial numbers will prevent the randomization processing time from exponentially increasing, which could cause serialization systems to collapse.
- **Collision rate:** This is the risk that the same serial number will be generated twice. Best practices recommend that a system limit this risk to less than 1 chance out of 10 million. To guarantee an acceptable collision rate, the ratio of the number of all serial numbers generated to the serial number range must remain below 1:10 across the serialization project's life span.
- **Control of serial codes unicity before a batch of serial codes is released to manufacturing:** This activity is the responsibility of the function generating all serial codes. The process to perform this activity will need to be specified.
- **Reconciliation of serial codes generated at the end of manufacturing:** The process to perform this activity will need to be specified. For the EU market, only serial numbers of saleable products are communicated to the central database. Serial numbers of retention samples and stability samples are recorded for internal follow-up, but they are not communicated to the central database. For security reasons, it is crucial that all serial numbers that have been uploaded on the packaging line are not reused for any other production.
- **Security:** Measures to control access to serial codes and protect data must be specified.
- **Audit trails for all users and activities, including all changes performed:** Processes to support audits must be explained.
- **Electron signatures:** These must be defined and their usage specified for every critical activity that will be performed in the system, such as serial number generation or batch certification. For the EU market, batch certification is performed by the qualified person (QP) responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the member state where certification takes place, in accordance with the requirements of the marketing authorization (MA) and with Good Manufacturing Practice (GMP). After certification by the QP, the product is released for sale or supply to the market (according to Delegated Regulation 2016/161 Article 33 1, the MAH shall ensure that the unique identifier is uploaded to the repositories system before the release for sale or distribution by the manufacturer).
- **Reporting:** Every aspect of reporting (e.g., manufacturing reports, reconciliation, errors) must be covered in the URS document.
- **Error messages:** Specifications must ensure that error messages generated by the system will be clear and unambiguous.

QUESTION 5: WHAT DOES DATA QUALITY MEAN FOR SERIALIZATION DATA?

Data quality can be expressed through six principles:

- **Accuracy:** Data can be considered accurate and not altered by any event or whenever it is handled. Their definition remains consistent across the information processing chain and thus in all systems where they are handled. All modifications receive a time stamp (hence the importance of time-stamped audit trails).
- **Completeness:** Data are constantly available and comply with standards and controls in place. No data are lost after a transfer from one system to another.
- **Availability:** Data are readily available and can be handled directly without additional transformation. There is no need to manipulate data files; all systems use the same standard data format.
- **Integrity:** The data attributes are consistent in all systems where the data are handled. Each value has a fixed definition and is decoded and used consistently by all users.
- **Secured data sources:** Only authorized and validated data sources are used. All exchanges between systems are secured so that data integrity and availability can be ensured at all times.
- **Fit for use:** Data meet all needs of all stakeholders and allow the company to comply with all regulations enforced in the project scope.

QUESTION 6: WHAT DATA NEED TO BE SECURED AND ACCORDING TO WHICH PRINCIPLES?

The Delegated Regulation R2016/161 and European Medicines Verification Organisation (EMVO) guide identify 18 types of data that shall be managed and exchanged in a secured way. Protection of the data needs to be ensured throughout all data manipulation and transformation steps.

The following "ALCOA+" principles for the scope of data integrity can be used as well for data security. ALCOA+ data are:

- **Attributable:** The roles in the organization that are entitled to access and manipulate serialized data are clearly defined.
- **Legible:** Unauthorized recreation of serialized data without an audit trail is not allowed.
- **Contemporaneous:** Data are created and time stamped in real time, when the serialization takes place, not after the fact.
- **Original:** Original data, or a secured copy, can be accessed.
- **Accurate:** It is possible to confirm data accuracy against a known specification.

- **Complete:** The completeness and consistency of combination of a global trade item number (GTIN) with serial numbers, including their attributes, must be maintained at all times. To ensure complete data, changes made to the data and deviations identified along with their resolution must be taken into account.
- **Enduring:** Data storage and access exist for the entire life cycle of all serialization data.
- **Available:** Data are available for review at any time throughout their entire life cycle.

QUESTION 7: WHAT TECHNICAL REQUIREMENTS MUST BE DEFINED?

All technical requirements of a serialization information system shall be defined, including the following:

- **Processes for managing changes to system operations:** How will changes that affect the way the system operates, such as start-up and shutdown sequences, test sequences, and cut-over phases, be managed?
- **The disaster recovery process:** The system must include a pragmatic process that can reconcile all materialized data (already printed on product packs) vs. all serial numbers that not yet been fully processed. The system must be able to generate disaster recovery reports, including how to take into account master data and variable data on hand. The disaster recovery process must also be capable of restoring a running production environment within a minimal time frame (the maximum allowed time to restore a live and functional production environment shall be part of the specifications documented).
- **The required level of performance and expectations for response times:** These must be expressed with clear values, and without any ambiguity. Level-of-performance specifications must cover what will be done to maintain data consistency in case of system breakdown, and the reconciliation processes. Response-time specifications can influence equipment choices, based on how the serialized solution will be operated. For example, if the check of unicity of the serial number will be done in real time during manufacturing or product picking, one will need response times of about a millisecond from the data server on each query. One way to handle this kind of requirement during packing could be to host the range of serial numbers manipulated on the server of the manufacturing line during production.
- **Data storage:** How will data be stored? What will be the maximum allowed amount of data stored?
- **Updates:** What will be the process for system updates and system patches?
- **Specific equipment/system requirements:** These can include requirements for onboard devices, especially for logistics-related activities on serialized products and requirements related to systems efficiency (loading times, screen refresh times, time to generate reports, etc.). The actual demonstrated performances of all user interfaces will be critical to ensure fluid operation of the serialization system and effective manipulation of serialized data, and, ultimately, to maintain trust and adherence to processes from the operations teams. When aggregation is implemented, a typical operation such as scanning serial numbers on product cartons or serial number of cartons on a pallet must be done with maximum fluidity to be integrated seamlessly into standard operating procedures of the warehouse operators.
- **Adaptability:** This is a major requirement. Because regulations and market requirements are constantly changing, the serialization system must have the critical capability to seamlessly adapt the database to accommodate new data elements or changes in data structure. The more markets are included in scope, the more critical it is that the system meet this technical requirement.
- **Security:** This is a critical function to be managed by any electronic or IT system. All security-related requirements about system access, networks, firewalls, VPN, and so on must be included.

QUESTION 8: WHAT INTERFACES MUST BE SPECIFIED?

Specifications for interfaces between systems should be classified as follows:

- **User interfaces:** These should be tailored to all authorized personnel who will have access to and play a role into the serialization process (e.g., operators, team managers, systems administrators).
- **Interfaces with other systems:** Having the capacity to connect the serialization solution to a variety of both internal and third-party systems is one of the key challenges of serialization.

Examples of interfaces to include in the URS might include:

- Interfaces between a marketing authorization holder (MAH) and its contract manufacturing organizations (CMOs)
- Interface between manufacturing and distribution centers
- Interface between Level 4 serialization solutions and ERP or MES
- Connections between all actors in a supply chain
- Connection to a warehouse management system
- Connection with regulatory hubs
- Connection with distributors

This list is only a partial one. It generally identifies interfaces that involve several actors, which may be using various, very different types of interface technology and information systems. Thus, the interface system may need to meet a variety of different needs and address many local constraints. There are also several ways to implement Electronic Data Interchange (EDI) and Electronic Product Code Information Services (EPCIS) standards.

It is important to keep in mind that following a standard does not necessary mean following a unique format for communications. There are many different ways to connect several systems, using several formats of data, and the appropriate approach can depend on local constraints. For example, requirements for the EU are not the same as those for the US, China, Brazil, or South Korea, and some EU-member states may have requirements that are more stringent than the EU Falsified Medicines Directive. Sometimes,

Make your life easier.

Get rid of paper with the zenon Software Platform.

Continuous improvement meets transparency and flexibility:

- *Record data electronically*
- *Control and optimize batch-based production*
- *Manage and visualize packaging lines*
- *Monitor utilities and buildings*

Gold Microsoft Partner

GAMP 5

FDA 21 CFR Part 11 Compliant

zenon by COPA-DATA

www.copadata.com/pharmaceutical

Figure 1: Serialization model: Standard CMO flow. Key: CMO, contracting manufacturing organization; EMVO, European Medicines Verification Organisation; HQ, headquarters; MAH, marketing authorization holder; NMVO, national medicines verification organization; S/N, serial number; 3PL, third-party logistics.

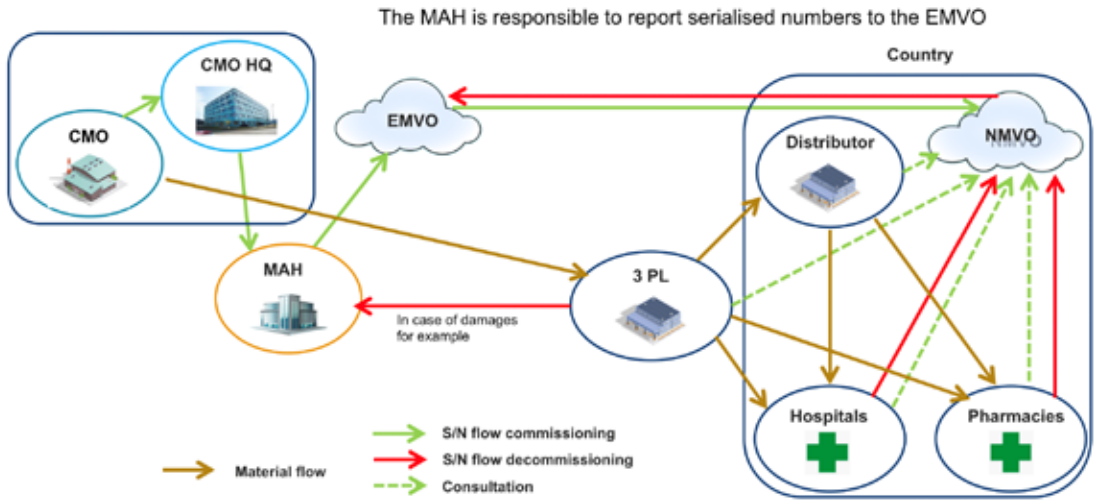
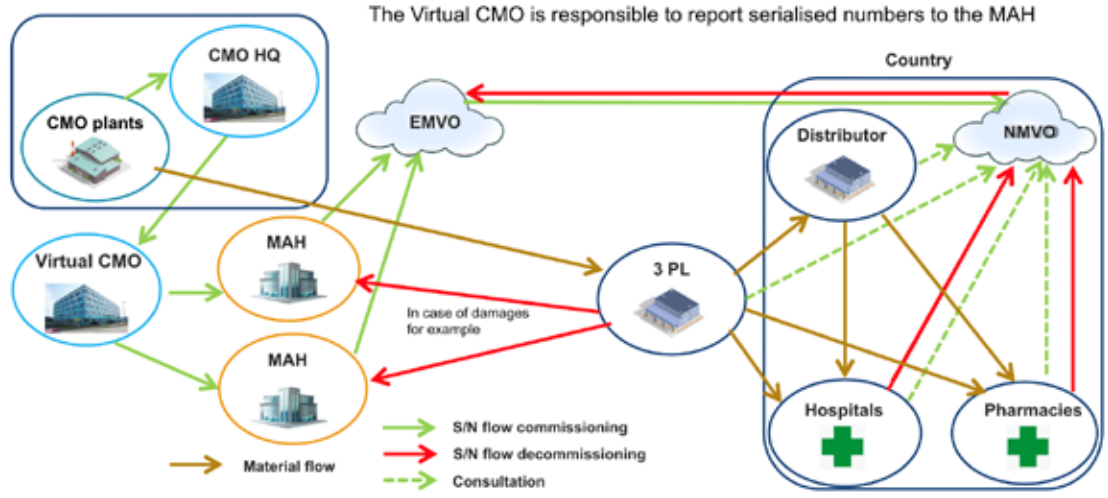


Figure 2: Serialization model: Virtual CMO flow.



market-driven requirements may be more stringent than regulatory ones (as in the case of the US market). Also, third-party logistics providers may use processes that are not yet covered by current regulations, such as aggregation for some markets.

The following are some of the distribution-related transactions that need to be supported by a serialization solution:

- Goods receipts (including batch, serialized, or aggregated data)
- Where-used and inventory reconciliation reports
- Proceeding to shipments
- Product returns and the batch recall process
- Support of investigations required by a customer or partner

The referent used by each actor is usually based on the GS1 standards such as main distribution-related standards or EDI/EPCIS communications. While EDI/EPCIS protocols use a common standard, communication formats may vary from one partner to another. These standards are complicated and have been in place in the supply chains for some time already; hence, it is preferable to consider adapting the serialization system to them vs. trying to

modify standards or protocols to fit the system. Other factors that may encourage users to adopt a flexible serialization solution are the many proprietary communication protocols on the market as well initiatives such as Open Serialization Communication Standard (OPEN-SCS), which aim to establish technical communication standard.

QUESTION 9: WHAT ARE THE ENVIRONMENT AND CORRESPONDING INSTALLATION PREREQUISITES?

The definition of the environment in which the serialization solution will operate should include the following items:

- **Footprint:** The location where the serialization solution is implemented or the configuration of that location can affect the solution's performance. Factors such as long-distance connections or a relatively small data center are examples of footprint-related concerns.
- **Environmental factors:** Considerations to specify could include temperature, moisture, interferences, presence of perturbating sources such as external high-frequency signals, ultraviolet sources, dirt, high-powered vibrating systems, electromagnetism sources, or the proximity of a sterile room.
- **Access control and all security procedures:** These prerequisites must be clearly defined.
- **Energy requirements:** It is important so specify voltage and frequency, waveform, protection against voltage drops, and other energy-related matters.

QUESTION 10: WHAT ARE THE POSSIBLE BUSINESS CASES WHERE CMOS ARE INVOLVED IN SERIALIZATION?

Two main business cases can be considered: between an MAH and its CMO (Figure 1) or between an MAH and a virtual CMO (a CMO that contracts manufacturing to other service providers) (Figure 2). Many variations in these business cases have been identified by the Workgroup and will be discussed in later versions of this document.

THE FUTURE OF THESE FAQS

The ISPE France Affiliate is hosting the Serialization Workgroup that has developed these FAQs, but the Affiliate cannot be held responsible for any statement or recommendation contained in this guide. We encourage the readers to contact the Workgroup with new questions, thoughts on points that seem unclear, and other feedback. Part of the Workgroup's mission statement (and what we also find exciting) is to respond to your feedback. This guide will be regularly updated to reflect the issues you raise. To contact the ISPE France Serialization Workgroup, email info@ispe-france.fr.

References

1. Official Journal of the European Union. Directive 2011/62/eu of the European Parliament and of the Council of 8 June 2011 (Falsified Medicine Directive). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011L0062
2. Official Journal of the European Union. Commission Delegated Regulation (EU) 2016/161 of 2 October 2015. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf
3. European Commission Directorate-General for Health and Food Safety. Safety features for medicinal products for human use questions and answers - version 13, January 2019. https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/qa_safetyfeature_en.pdf
4. Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme (PIC/S). Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments PI 041-1 (draft 3), 30 November 2018.
5. World Health Organization. WHO Technical Report Series No. 996 Annex 5 Guidance on Good Data and Record Management Practices, 2016. http://apps.who.int/medicinedocs/en/m/abstract/Js22402en/
6. European Medicines Verification System (EMVS). European Pack Coding Guidelines Version 4.0, July 2017.
7. SecurPharm. Regeln zur Codierung Verifizierungspflichtiger Arzneimittel im Deutschen Markt Version: 2.04a, 12 December 2018.
8. ISPE. GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems, February 2008.

About the authors

Laurent Arnould is a Senior Consultant with CTD Pharma and has more than 25 years of experience in pharmaceuticals supply chain operations, manufacturing, systems integration projects, and procurement. He has contributed to many transformational projects and initiatives related to supply chain management and SAP integration for companies including Procter and Gamble, Merck & Co, Bayer, and Abbott. Laurent has a master of science in mechanical engineering from ENSAM Paris Tech (France).

Christophe Devins is the cofounder and CEO of Adents, which creates software solutions for unit identification and traceability. In the 1980s, Christophe was actively involved in Gencod, which has since become the established GS1, and one of the key architects of the global standards for barcodes as well as a recognized expert in product identification and traceability. In the mid-1990s, Christophe designed one of the premiere software platforms for product traceability and created his first company, ADHOC. When ADHOC was subsequently integrated into Markem-Imaje, a global vendor of industrial coding and marking systems, Christophe became Head of Applications for that company and co-created with David Carpentier the first software platforms dedicated to unit identification and traceability. Christophe and David founded Adents in 2007. Christophe is regularly approached by international institutions for discussions around product identification standards and traceability issues.

Jean-Marc Libersa has worked for 37 years in the pharmaceutical industry (human and veterinarian) and is currently a consultant for GMP support. Previously, he served as Quality Director for a CMO, with overall responsibility for 15 plants manufacturing drug products and drug substances.

Michel Raschas, CFPIM, is Consulting Validation and Services Director of PROGMP, a consulting, engineering, and validation company for life sciences industries, where he oversees information systems services, including decision-making related to specification, design for implementation, system evolution, and regulatory compliance. He has an engineering degree and has been working for more than 30 years on information system topics. Michel is a member and Certified Fellow in Production and Inventory Management (CFPIM) of the American Production and Inventory Control Society (APICS) and is a member of the APICS Educational Society for Resource Management. Michel is Secretary of the ISPE France Affiliate. He initiated and is the cofounder of both the French Speaking GAMP® community of Practice, "GAMP Francophone," and the Serialization Workgroup. He provides training for professionals and lectures for major programs such as the pharmaceutical master's programs of the University Paris Sud and the University of Burgundy. Michel has been an ISPE member since 2003.

Matthieu Thibaud has been a Serialization Project Manager for Abbott Product Organization AG since 2011. He has a master's degree in business management from ESSCA and a background in of logistics operations for service providers, companies in the pharmaceuticals industry, and supply chain projects.

Nathalie Wardé, PhD, is Senior Consultant and Founder of Nad Pharma Consulting. After earning a PhD in pharmacy and a degree in human resources management, Nathalie started her career 29 years ago at Novartis in Switzerland, where she came to focus on sourcing strategy and technical support at an international level. In September 2005, Nathalie founded Nad Pharma Consulting, which is active in improving technical and supply chain operations efficiency and compliance of healthcare and fast-moving consumer goods companies in Europe and the Middle East. She has taught at several universities in Switzerland, France, and Lebanon, and is a regular speaker at seminars organized by professional associations. Since 2011, she has been working with GS1 France to promote the use of international standards in the healthcare supply chain.

ISPE | PHARMA 4.0

THE ISPE PHARMA 4.0 OPERATING MODEL'S

Pharma-Specific Maturity Index

By Hans Heesakkers, Sebastian Schmitz, Uli Kuchenbrod, Christian Wölbeling, and Thomas Zimmer

ISPE's initiative to transform industry-generic 4.0 models for pharma operations will help the industry benefit from digitalization.

In today's pharmaceutical industry, the landscape of operating models is heterogeneous, and the consequences of this heterogeneity can hinder progress. For example, the risk-based regulatory approach, in which regulators and companies proactively collaborate to prevent harm, is ready for use, but the industry lacks the tools and methodologies to demonstrate that there is a strong business case to adopt the approach.

Instead, the structural capabilities of pharmaceutical companies are mostly driven through regulatory requirements, and pharmaceutical regulation is narrowly focused on the current processes for marketing authorization approval, manufacturing, and postmarketing obligations through good practice (GxP) compliance activities.

Fortunately, digitalization opens new horizons for a holistic perspective on business. It can provide accurate information for decision-making that will allow the pharmaceutical industry to achieve new levels of connectivity, transparency, agility, and productivity. At present, digitalization in the pharmaceutical industry is immature. Adoption of global standards and concepts such as those coming from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is in progress. However, in some cases, the demands of the digitalized value network, stakeholders, and patients are still not being met. Specifically, current knowledge and tools to monitor the ICH control strategy throughout the global product life cycle do not completely allow for continuous improvement activities. In addition, the current environment is not allowing regulators to have a more digitalized overview of the pharma industry.

ISPE's Pharma 4.0 initiative aims to help the pharmaceutical industry overcome the obstacles to digitalization. Pharma 4.0 draws from an industry-generic Industry 4.0 Maturity Index from the German Academy of Science and Engineering (Acatech) to shape the environment of future pharmaceutical operations. The pharma-specific Pharma 4.0 Operating Model describes exemplary key enablers and elements of essential importance in the pharmaceutical operations processes, environment, and culture.

The various stakeholders in Pharma 4.0 have distinctive perspectives and motivations:

- Strategic point of view (e.g., from CEOs or business unit heads)
- Technical operations and quality risk management (QRM) point of view (e.g., from heads or experts of technical operations, production or engineering)
- Information technology (IT) point of view (e.g., from IT or engineering heads or experts)

Whichever perspective they hold, all stakeholders share a common expectation that digitalization will help their companies achieve business goals by operating faster, reducing costs, and being more competitive and agile

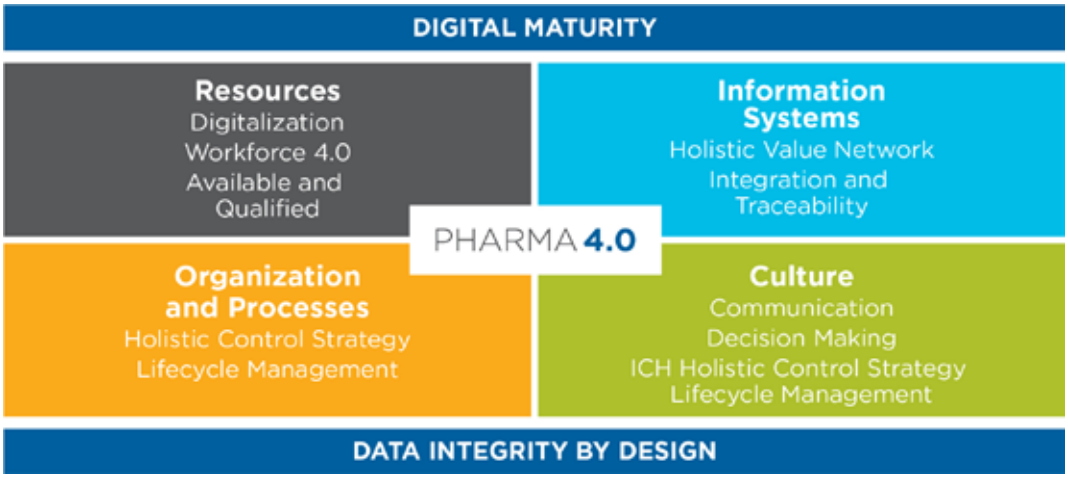
This article will focus on the technical operations/QRM and IT perspectives without neglecting the other perspectives. The Pharma 4.0 world is absolutely determined by a holistic view of the full value network and building digitalized end-to-end business processes. Connectivity and impact have never mattered more than now in the world of Pharma 4.0. Boundaries will become increasingly irrelevant in all dimensions.

VISION AND MISSION OF PHARMA 4.0

The following are the principle tenets of the Pharma 4.0 vision:

- Digitalization will open new horizons to achieve new levels of

Figure 1: The Pharma 4.0 Operating Model.



connectivity, transparency, agility, and productivity through the application of faster and more accurate information for decision-making.

- Functional silos will no longer exist after digitalization is successfully implemented.
- Globally harmonized GxP rules and technical standards will be in place. Mutual recognition of inspections will occur more frequently. In addition, enforcement of rules and standards will be driven equally by current industry practices and by digitalized and connected computerized systems.
- Regulatory authorities are essential partners in reaching this goal. Industry–regulatory agency partnerships are critical to design a win-win situation for all stakeholders in the pharmaceutical value network.
- In a Pharma 4.0 world, it will be feasible for stakeholders to be connected, while respecting and applying different cultures and management styles.

The ISPE Pharma 4.0 special interest group (SIG) created the following mission statement to pave the way for the regulatory Pharmaceutical Quality Initiative of the digitalized 21st century:

> *"Manufacture pharmaceutical products with maximum product and process understanding, data integrity by design, efficiency and optimal resource allocation on the basis of full digital data transparency—to the benefit of the patient."*

DEVELOPING A PHARMA-SPECIFIC MATURITY MODEL

The mission of the Maturity Index subgroup of the ISPE Pharma 4.0 SIG is to develop a *pharma-specific maturity model*, based on the four elements of the ISPE Pharma 4.0 Operating Model (Resources, Information Systems, Organization and Processes, and Culture) and two enablers, Digital Maturity and Data Integrity by Design (see Figure 1). The ISPE Pharma 4.0 Operating Model, including its enablers and elements, has been described in greater detail in past issues of *Pharmaceutical Engineering* [1, 2].

The ISPE Pharma 4.0 SIG offers a cross-functional working platform for relevant experts representing stakeholders to work on a volunteer basis in a formalized environment and at low-resource consumption to create new content and new best practices. When first developing Pharma 4.0, the SIG looked for resources on operations intelligence developed elsewhere, and used the methodology for an industry-generic maturity model developed by the Industry 4.0 Maturity Center at RWTH Aachen University in Germany as a starting point (see Figure 2).

An important asset of the industry-generic model is its Maturity Index, which clearly identifies objectives and building blocks for six maturity levels on the path from digitalization to industry transformation:

Level 1: *Computerization*—At this initial level of digitalization, the objective is to simplify repetitive tasks. Building blocks include introducing IT on the shop floor and elsewhere.

Level 2: *Connectivity*—At level 2, the objective is to streamline business and IT. Building blocks are the digital connection and integration of business practices.

Level 3: *Visibility*—The objective for level 3 is to make data-based decisions. The primary building block is the construction of a real-time digital shadow.

Level 4: *Transparency*—At this level, the objective is to grasp complex interactions through the building blocks of running data analytics and interpret the findings to understand effects.

Level 5: *Predictability*—At level 5, the objective is to prepare for upcoming situations. The key building block is the capacity to simulate possible future scenarios.

Table 1: ICH Q10 PQS and Pharma 4.0 elements and enablers applied to the Maturity Index.

	ICH Q10 PQS	Pharma 4.0
Elements	Corrective action and preventive action (CAPA) system Change management Management review	Resources: Digitalization, available and qualified workforce 4.0 Information systems: Holistic value network integration and traceability Organization and processes: Holistic control strategy, life-cycle management Culture: Communication and decision-making
Enablers	Knowledge management Quality risk management	Digital maturity Digital integrity by design

Level 6: *Adaptability*—Finally, the objective for level 6 is leave the control to the system. Wherever possible, the building blocks for this level should allow the system to adapt itself to new scenarios.

Pharma specificity was added to this generic maturity index by applying the principles of ICH Q10: Pharmaceutical Quality System (PQS), a model that defines the key enablers and elements as required from a pharmaceutical and regulatory perspective throughout the product life cycle and across the value network. Furthermore, additional elements and enablers were defined based on the Pharma 4.0 Operating Model (see Table 1). Figure 3 shows how the objectives for levels 1–6 of the industry-generic maturity model fit with the Pharma 4.0 Operating Model.

The method to characterize elements of Pharma 4.0 can be applied similarly to a description of a business process, a production process, or a computerized system or network. The term "enablers" in the ISPE Pharma 4.0 model is allotted to "Digital Maturity" and "Data Integrity by Design" because these enablers are considered most relevant for pharmaceutical operations and throughout the pharmaceutical life cycle. Readers should note that the usage of the term "data integrity" in pharma operations varies from its general meaning in IT. In pharma operations, it is a regulated term enforced in GxP inspections by regulatory authorities [3]. The addition of the phrase "by design" suggests that data integrity is embedded throughout the internal and external systems architecture.

MATURITY LEVELS FOR THE FOUR ISPE PHARMA 4.0 OPERATING MODEL ELEMENTS

The following sections review examples of how the Pharma 4.0 maturity index may apply within each of the four elements of the Operating Model: Resources, Information Systems, Organization and Processes, and Culture. The highlighted capabilities are key capabilities, but they are not an all-inclusive list.

Resources

Resources are tangible, physical assets. They include a company's workforce (human resources), machinery and equipment, tools, materials, and the final product.

Information Processing

In information processing, the maturation of resources may begin with a manual pull from different computerized systems, or even paper-based sources, to create databases that interact via sensors and actors (e.g., the "one data warehouse" concept). As information processing resources mature further, they can provide a digital "shadow" of processes to achieve high visibility in the connected shop floor.

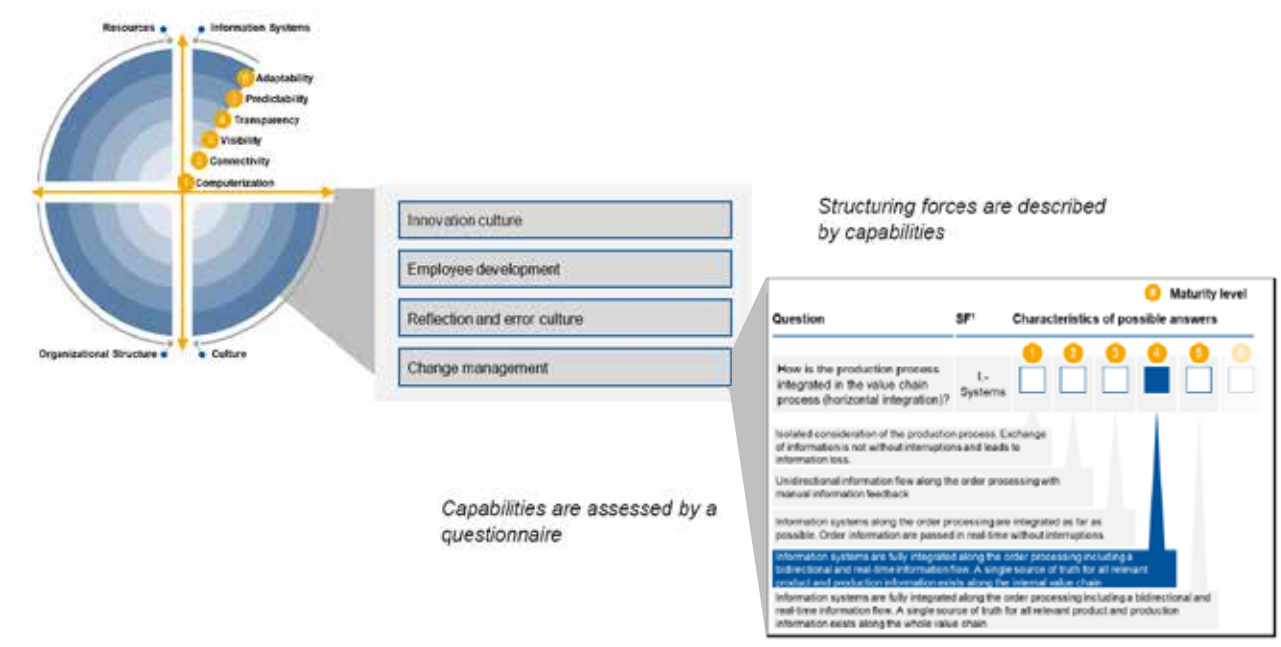
The next levels of information processing will connect all relevant functions in cross-functional business processes from along the complete supply chain, from drug substance/active pharmaceutical ingredient (API) development via drug product formulation and packaging and commercial manufacturing to the patient. A holistic view of these processes will allow for more transparency.

More mature levels of information processing are achieved when QRM is actively supported by digitized systems. For example, a corrective action and preventive action (CAPA) system available throughout a corporation could enable experts to obtain a global view of all events connected with their own process that occur at other places. The most mature level is achieved when a system is leading the process of its own adaptation (e.g., the corporate CAPA management system is linked to the decision-making process).

Communication Between Operator and Machine

Initially, communication between operator and machine requires a worker's physical presence at the machine. As communication matures, workers can make adjustments via a remote interaction mode. The next step is to make all digitalized information from the machine available to all employees concerned. Digitalized and standardized documents should be available for all relevant users. Also, critical information, such as reports, and warnings should be generated by the system and available 24/7 so that the responsible persons can intervene at the earliest possible moment. At the next level of maturity, all relevant functions around the machine (e.g., environmental control or preventive maintenance) are integrated. A fully mature system can lead quality-driven decisions in the manufacturing shop.

Figure 2: Structure of the Industry 4.0 Maturity Index with its elements, capabilities, and underlying questionnaire.



Information Systems

Information systems are sociotechnical systems in which information is provided based on economic criteria determined by people as well as by information and communication technology. Information systems prepare, process, store, and transfer data and information.

Master Data Management

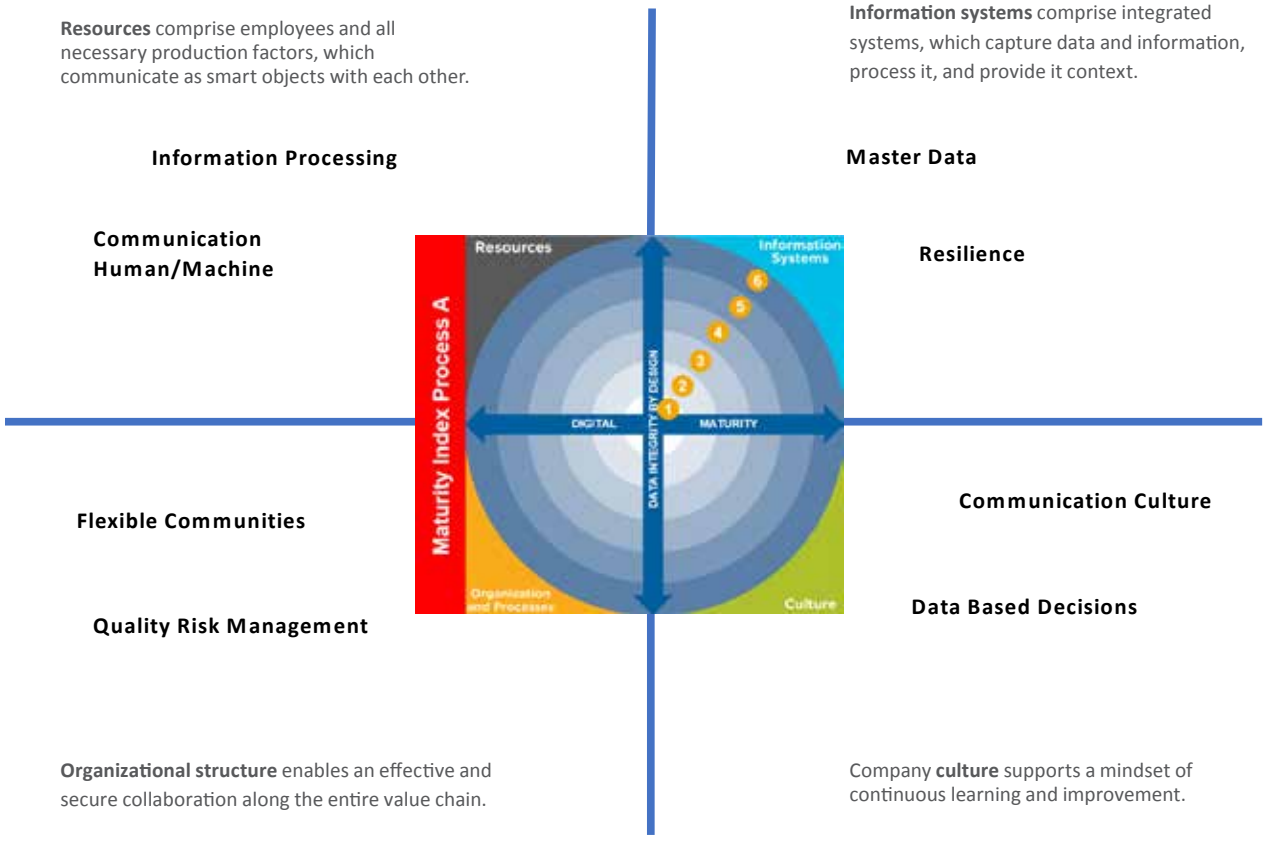
Starting from a situation where master data are created and maintained "in an island," the initial step toward maturation in master data management is likely driven by new regulatory requirements for data integrity (e.g., US FDA, World Health Organization, or Medicines and Healthcare Products Regulatory Agency requirements). Under these requirements, companies must create a companywide or value-chain-wide master data framework, and certain types of data (e.g., information about excipients and APIs) must also be globally and publicly available. Each substance must have a specific name and a quality-specific reference number. Master data management can then mature to capture and manage all pharmaceutical product-specific data, allowing for system-supported life-cycle management from product development to the transfer to production to the phase-out from all markets at the end of the life cycle. At the most mature level, the system could lead product life-cycle decisions in manufacturing, quality, supply chain, and business.

The process of maturation involves transitioning from a hierarchical organization, with separated functions, to an agile organization without silo-supporting structures.

Resilience of Information Systems

Companies may start from a situation where IT systems are manually configured and key systems do not have redundancies. These systems comply with US FDA Part 11 or EU Annex 11 requirements for validation of computerized systems in the sense that they work without any major deviations.

Figure 3: The four elements with exemplary capabilities to be considered in the Pharma 4.0 Maturity Model.



A maturing information system can isolate failures to avoid a cascade of failures to other systems. This is known as computerized system validation and compliance under control between systems, or data-flow control between systems.

The subsequent level of maturity is achieved when performance statistics are automatically generated and the integration of new servers can be easily reproduced and completed. The higher levels are described as the availability of a catalog of failures that supports a quick identification of failures and remediation. Finally, a mature system automatically generates operational reliability risk analyses and reports, thereby providing access to the digital world to inspectors.

Organization and Processes

"Organizational structure" refers to both a company's internal organization (structure and operational processes) and its position within the value network. The organizational structure establishes mandatory rules that organize collaboration both within the company and externally.

Flexible Communities

The process of maturation involves transitioning from a hierarchical organization, with separated functions, to an agile organization without silo-supporting structures. In a traditional organization, there are communication hurdles between the silos and between the hierarchical levels. The worker receives goals from the line manager, who also evaluates the employee's performance.

In theory, a fully agile organization can be established with self-organized teams, which have end-to-end accountability for their product. Squads, tribes, chapters, and guilds are the organizational elements. There is neither a classical hierarchical structure nor a single chain of command—just business goals. All organizational elements may be formed and disbanded spontaneously, or they may be established for the long term. Each employee can work in several squads and contribute to chapters and guilds. They are temporarily assigned to these units. Employees are responsible for finding assignments that interest them, and an assignment can last from several months to several years. Employees have a set of

goals for each of their assignments. Their performance is evaluated by the units they contribute to or by an owner of the total optimum/business goal.

Quality Risk Management

When considering the maturity of QRM, the key question is to what extent does the prevailing risk culture support compliance with the defined quality standards? On the immature end of the spectrum, there is limited or no risk communication among the different functions and organizations, and no training for risk management. In contrast, in a mature system, risk governance and information security enable trust in risk communication in the value network. Risk events are regularly detected and communicated in the value network to allow organizations to react in time to even weak signals of distress.

Culture

Culture is the value system within a company and thus describes the "soft" aspects of collaboration. The structural areas of organization and culture are mutually dependent and must be in agreement with each other.

Communication Culture

Starting from a situation where records are versioned, documented, approved, and simply accepted as facts, there is a long way to go to reach more mature levels of communication related to data. Generally, the path to transformation is the way from a "need to know" and "hierarchically controlled" culture to an "open" and "collaborative" mode of work.

Ultimately, an improved communication culture has a knowledge management system in place and an owner for the total optimum of the individual optima from individual process owners. Additionally, a dispute resolution process is installed and regulatory responsibilities are fully integrated in the decision-making system or process. Digitalization can play a key role in achieving such high levels of communication.

Data-Based Decisions

In contrast to situations where decisions are made based on the knowledge or intuition of individuals, a more mature communication culture allows expert teams to make decisions based on data, with historical data supporting their choices. A deep data analysis represents the next level of transformation. The highest-level decision-making processes are supported by automated data analysis and provide the possibility to run simulations and generate scenarios (Decision Making Automation). Digitalization can also play a key role in this aspect of communication culture.

OUTLOOK

The ISPE Pharma 4.0 SIG and its Maturity Index Working Group are continuing their work to create a Maturity Index to help pharmaceutical companies benchmark the level of digitization they have achieved and identify focus and development areas to fully transform into a digitalized organization. In its industry-generic model, Acatech considers structural areas and business processes and systems. For pharmaceutical operations, in general, the processes identified in that model exist; however, the pharma industry has certain distinctive priorities, including those shaped by regulatory requirements such as GxP inspection management and drug submission–approval processes. Additionally, driven by ICH, there are processes for life-cycle management of pharmaceutical products that are truly cross functional, as they include all functions and stakeholders from the value chain (i.e., the value network). These functions include development, product transfer units, production, quality control, quality assurance, engineering, supply chain management, marketing, and sales. In addition to pharmaceutical companies, they may involve third-party labs and manufacturers and all service providers.

References

1. Binggeli, Lorenz, Hans Heesakkers, Christian Wölbeling, and Thomas Zimmer. "Pharma 4.0: Hype or Reality?" *Pharmaceutical Engineering* 38, number 4 (July–August 2018): 40–4.
2. Herwig, Christoph, Christian Wölbeling, and Thomas Zimmer. "A Holistic Approach to Production Control—From Industry 4.0 to Pharma 4.0." *Pharmaceutical Engineering* 37, number 3 (May–June 2017): 44–9.
3. *ISPE GAMP Guide: Records and Data Integrity.* Tampa, FL: ISPE, 2017. *See also* US FDA. Data Integrity and Compliance with Drug cGMP: Questions and Answers Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf; MHRA. 'GXP' Data Integrity Guidance and Definitions. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

About the authors

Hans Heesakkers is Managing Director of Circuition Life Science Consultants, the Netherlands. He has worked in the life sciences industry for 29 years. Hans has 20 years of experience in business process reengineering and IT projects and 15 years of experience in clinical trials and clinical supply chain. He is an active member of ISPE's Community of Practice on investigational products, founder and core team member of the Dutch/Belgium Clinical Supplies Forum, and co-chair of ISPE's Pharma 4.0 Special Interest Group. He has been an ISPE member since 2001.

Sebastian Schmitz, Industrie 4.0 Maturity Center at RWTH Aachen Campus, Germany, is responsible for the practical application of the Industrie 4.0 Maturity Index and accompanying services for customers in the manufacturing sector. Over the last three years, he has significantly contributed to the Maturity Index development and led a number of Industrie 4.0 projects with manufacturing companies from different sectors. Sebastian has a degree in business administration and engineering: mechanical engineering from RWTH Aachen University, and a PhD from FIR at RWTH Aachen University with a focus on digital networking.

Uli Kuchenbrod, Vetter Pharma Ravensburg, Germany has worked in the pharmaceutical industry for over 20 years in various roles and positions. He holds a mechanical engineering dipl. ing. and an MBA. He is working for Vetter in the innovation field. Uli has been an ISPE member since 2017.

Christian Wölbeling is Senior Director Global Accounts at Werum IT Solutions based in Luneburg, Germany, part of the Körber Medipak Systems Group. He has a master's in mechanical engineering. With more than 27 years working in life sciences manufacturing IT, Christian has had great experience in all GMP-related processes. Within ISPE, he has served as Chairman of the Pharma 4.0 Special Interest Group, Co-Chair of the GAMP MES Special Interest Group, ISPE GAMP member-at-large of the European Steering Committee, Chair of the Knowledge Network Council, Steering Member of the PAT & Lifecycle Control Strategy Community of Practice, and Board Member of the ISPE D/A/CH Affiliate. He has been an ISPE member since 2001.

Thomas Zimmer, PhD, is ISPE Vice President, European Operations.

ISPE | PHARMA 4.0

DIGITAL REFERENCE ARCHITECTURE PRINCIPLES

for a Data-Driven Pharmaceutical Factory

By Wolfgang Dedden, Josef Trapl, Antonio Buendia, Anton Granget, and Christian Miguel-Langstrof

As members of the Architecture Team of the ISPE Pharma 4.0 Plug & Produce Initiative, we would like to share the principles we have developed with the broader life sciences community. Our aim is to foster further exchange and dialogue about these principles.

Currently, two dominant obstacles must be overcome to transform data collection, real-time bidirectional data transfer, and data analytics in life sciences manufacturing:

- There is a disconnect between shop-floor activities on the one hand, and decision-making on different enterprise levels on the other.
- Many types of locally run software do not conform to an Industrial Internet of Things (IIoT) standard for the pharmaceutical industry.

With connectivity protocols such as OPC Unified Architecture (UA) and MQ Telemetry Transport (MQTT) in place, many manufacturers in the life sciences sector are already implementing machine-to-information technology (IT) connectivity from the shop-floor level to the enterprise level on a limited basis. However, the broader rollout of connectivity is hindered by shortcomings in integration engineering and qualification. In this article, we propose that digital reference architecture is a simple and feasible solution to this challenge in both brownfield and greenfield scenarios.

DIGITAL REFERENCE ARCHITECTURE

Figure 1 maps the transition from the current (legacy) world with its closed systems—such as distributed control systems (DCS), supervisory control and data acquisition (SCADA) systems, manufacturing execution systems (MES), and process historian and analytics tools—into a future in which service-oriented data reference architecture is characterized by the following three main attributes:

- Supplier equipment (e.g., package units, supply units, sensors, portable appliance tester equipment) "speaks" the same language as IT services and functions.
- Message-based publication/subscription ("pub/sub") is used instead of tag-by-tag integration engineering.
- Enterprise-level pub/sub is used for service-to-service communication.

Unifying the Languages of Supplier Equipment and IT Services/Functions

The NAMUR Module Type Package (MTP) presents a possible standard for the formal representation of equipment capabili-

SAMSON

YOUR PARTNER FOR ADVANCED VALVE TECHNOLOGIES

FERMENTATION

Preventing the process medium from contamination is key to fermentation processes. Our diaphragm valves with CDSA-style seals make sure of that. On top, they control with high accuracy. Sterile bottom drain valves and sampling units guarantee that the fermented product stays safe while being processed further.

FILTRATION AND FILLING

Particularly in sterile filling processes, there must be absolutely no contamination after the product has been carefully filtrated. Our diaphragm valves with their minimized dead cavities and precise dosing capabilities support you in filling vials, syringes and bottles.

SUPPLY OF UTILITIES

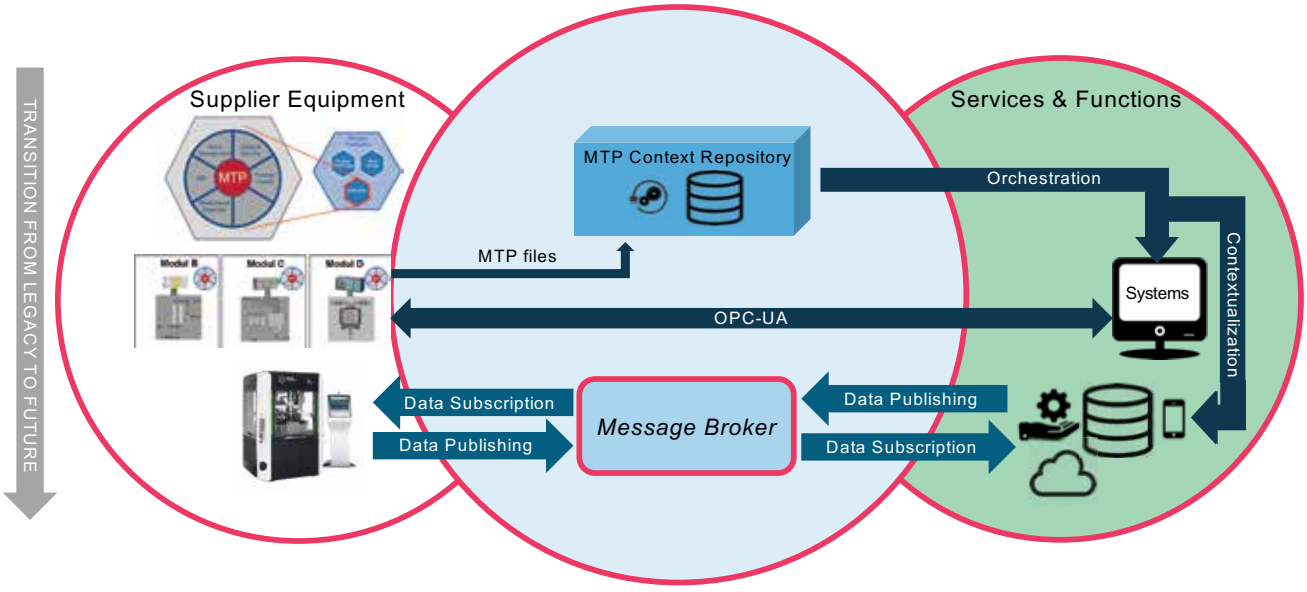
Our control valves make sure that production plants are supplied with the necessary process utilities, such as air, water, steam or refrigerants. Their high control accuracy optimizes processes and thus reduces the cost of operation.

HEADQUATERS
SAMSON AKTIENGESELLSCHAFT
Weismuellerstrasse 3
60314 Frankfurt am Main, Germany
Phone: +49 69 4009-0
E-mail: samson@samson.de
Internet: www.samson.de

SALES CONTACT
SED Flow Control GmbH
Am Schafbaum 2
74906 Bad Rappenau, Germany
Phone: +49 7264 921-0
E-mail: info@sed-flowcontrol.com
Internet: www.sed-flowcontrol.com

A01194

Figure 1: The transition from legacy systems to a future-oriented data reference architecture.



ties. Under this standard, the MTP file incorporates a full data interface specification to completely describe equipment data semantics. Bidirectional connectivity of process data (continuous and alarms/events), user data, and time sync allow for machine-to-machine interaction through process orchestration services. Equipment suppliers provide life-cycle management for the MTP file for the life of the delivered machines as part of a service-level agreement with the user, ensuring that the user receives all modifications or upgrades made to the MTP file. Thus, suppliers can systematically bring innovation (e.g., additional inline sensors, smart-equipment functions) to their established customer base. This paves the way for new business models such as software as a service (SaaS) or equipment as a service (EaaS) in the supplier market.

In this model, the MTP files are under strict version control; for example, they could be maintained in an MTP repository on the users' side. The various services subscribe to the MTP repository and are thus aware of the equipment capabilities currently present on the shop floor. These services can include:

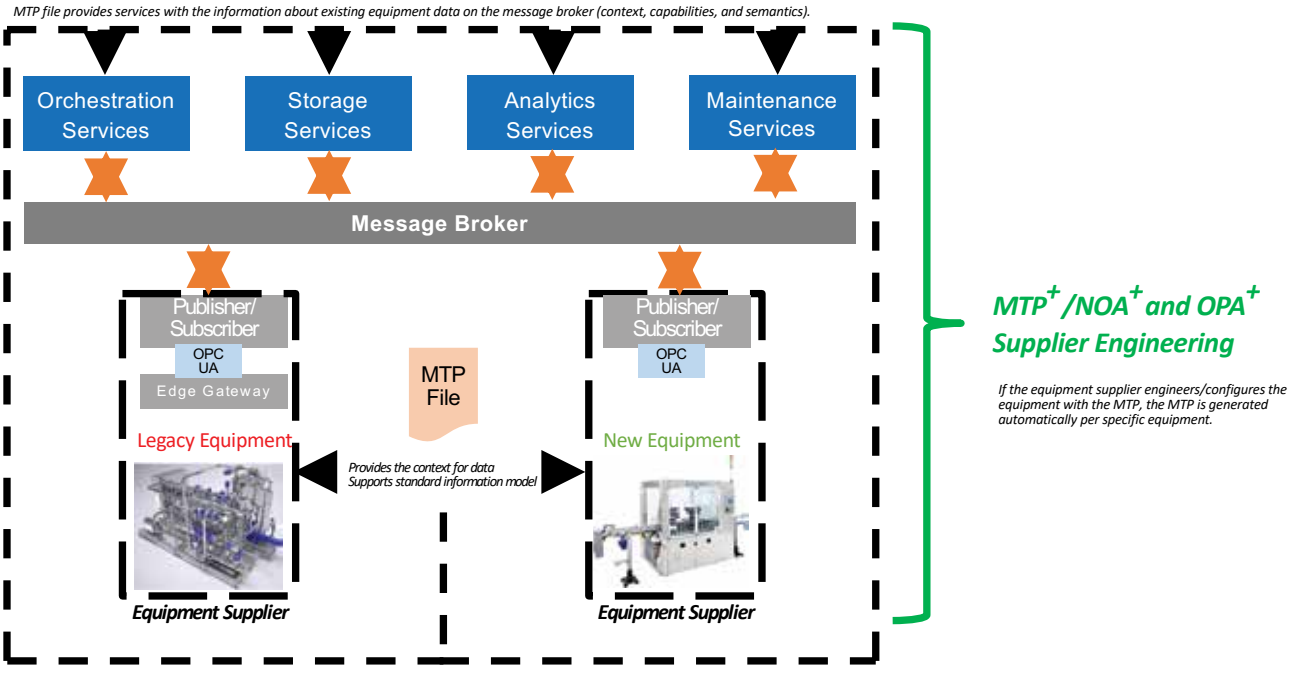
- Process orchestration
- Data storage/archiving
- Dashboards
- Decision aids and workforce support (e.g., remote operator guidance or operating guidance via smart devices)
- Predictions related to manufacturing operations (e.g., maintenance "sweet spots")
- Operations optimization (e.g., improvements in overall equipment effectiveness)
- External data exchanges (e.g., with regulators, partners, or suppliers)

Once a service's interface configuration complements a managed MTP file, connection consistency is ensured without any human interaction. There is no need to translate equipment data for a particular service (i.e., no need for integration engineering) because complete equipment data semantics are available with the MTP file.

Using Message-Based Pub/Sub Instead of Tag-by-Tag Integration Engineering

By default, if data reference architecture is used, equipment and services publish all of their data via the "message broker" in real time (see Figure 1). The message broker is a neutral component, unaware of the message structures and content. Its main functions are the distribution, buffering, and secure transfer of data. Data manipulation is constrained by policies and is subject to a full audit trail. Point-to-point and tag-by-tag engineering and qualification are not required. This saves precious time-to-production and integration engineering costs.

Figure 2: An alternate digital reference architecture model.



Using Enterprise-Level Pub/Sub for Service-to-Service Communication

Service-to-service communication is also achieved via a message broker, in the same manner as described previously. Services publish information and can subscribe to other services' data. The need for point-to-point connections between IT systems vanishes. The use of enterprise-level message brokerage (which is also referred to as "message-oriented middleware" or an "enterprise service bus") is a broadly accepted best practice for the flexible and maintainable integration of IT systems. Other regulated and data-integrity–sensitive sectors such as the financial industry are already using this type of message brokerage. Such solutions provide scalable, secure, and cost-efficient low-latency exchange of data.

Implementation Options

The three main attributes of data reference architecture described previously can be realized with today's connectivity and IT technologies. In addition to NAMUR's standardization work related to MTP and open architecture (NOA), the life sciences industry should consider the concepts and implementations developed around the Open Group's Open Process Automation (OPA). To create the message broker functionality, technical options range from a single "magic" product to a combination of multiple technologies, with the latter being a viable approach during the architectural transition phase.

Figure 2 provides a different perspective on the digital reference architecture presented previously. If MTP is considered the standard, it should become more than an instrument of core process control engineering. It should also be enriched with additional information (e.g., the full scope of the audit trail and system events) as well as a full set of equipment metadata, including unique identifiers, version information, and so on. The MTP should also include security mechanisms (e.g., checksums) and equipment life-cycle details.

The resulting "MTP plus" (MTP+) would offer cost-efficient standardized integration of legacy equipment to users. Furthermore, suppliers who use the MTP+ model for new equipment could streamline their engineering processes and ship the MTP+ file with the specific equipment. This would allow suppliers to provide plug-and-produce solutions in the shortest amount of time possible, and users could get equipment up and running much faster through a more unified qualification approach, while almost completely reducing the need for integration engineering.

Similarly, concepts like NOA and OPA could be extended to "NOA+" and "OPA+" to demonstrate that the message-based pub/sub is not just an instrument to transport field-device data to the cloud. These concepts will need to support high-volume, bidirectional data streaming.

SUMMARY AND OUTLOOK

The life sciences industry can build on existing best practices and solutions in IT and IIoT to establish digital reference architecture for data-driven pharmaceutical manufacturing.

The idea of an enterprisewide service bus, message broker, or data gateway and systems decoupling is well established. In fact, every smartphone user benefits from highly sophisticated IT/operational technology architecture. For example, your favorite app knows that it can subscribe to a contacts service and automatically asks for this permission upon initial launch. Your smart-home devices from various vendors automatically appear in your home surveillance dashboard once they connect to the wireless network.

In the pharma industry, challenges related to data resource architecture arise from the lingering automation-pyramid mindset, entrenched automation and IT silos, and the lack of consensus about principles and standards. The NAMUR activities around MTP and NOA, the Open Group's OPA, and the latest version of the International Society of Automation's Enterprise-Control System Integration (ISA-95) Standard provide the perfect foundation to start real-world projects. These projects will rely heavily on new collaborations between innovative equipment suppliers, cutting-edge IT partners, and open-minded users.

This article and related activities of the Pharma 4.0 Plug & Produce Initiative are an open call for engagement. The initiative is actively engaging a community of users and suppliers, and it is excited to see a growing number of contributors, proofs of concepts, and projects across the industry.

Additional Resources

Automatisierung modularer Anlagen
https://www.namur.net/fokusthemen/automatisierung-modularer-anlagen

Industry Standards Groups to Converge Their Work
https://www.arcweb.com/blog/industry-standards-groups-converge-their-work

Open Process Automation Update
http://wps1705.international-bc-online.org/wp-content/uploads/2017/09/1.-Forbes-ENG.pdf

ISA-95 evolves to support smart manufacturing and IIoT
https://www.isa.org/intech-plus/2018/feb/isa-95-evolves-to-support-smart-manufacturing-and-iiot/

Patterns and Best Practices for Enterprise Integration
https://www.enterpriseintegrationpatterns.com/index.html

About the authors

Wolfgang Dedden is Principal Expert and Senior Project Manager for MES in pharmaceutical production at Bayer AG corporate function in Engineering and Technologies in Leverkusen. He is responsible for the conceptual approach on process automation over the entire manufacturing chain in regulated pharmaceutical production. He is accountable for realizing complex functions with digitized production data and Pharma 4.0 initiatives, which meets his passion for starting and running a smart factory. Wolfgang has been an ISPE member since 2017.

Josef Trapl is Global Head of Technology within the Global Engineering Organization in Takeda, based in Zürich, Switzerland. He has been with Takeda since 2015. He has long-term professional project experience serving the pharma industry in engineering, IT/automation, and GMP consulting. He is a chartered Chemical Engineer with extensive global design and has project execution experience across quality and other business areas in the biopharmaceutical industry including bio-API, fill and finish, and oral solid dosage production. Josef has an MBA from the Mannheim Business School, Germany. In his current role, he supports the UPI project (track and trace) globally and is also responsible for industry trends, new technologies, and automation (Pharma/Industry 4.0/IoT), technology transfer, and operational excellence. He has been an ISPE member since 2011.

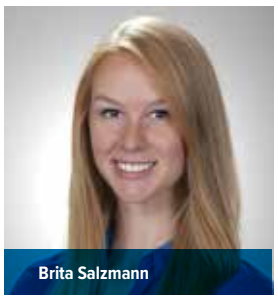
Antonio Buendia is Senior Principal Automation at Novartis, responsible for automation of the 32 plants of solids platform. Previously, as Global Head of Automation, Pharma division (25 sites), he articulated a "factory of the future" strategy based on a datacentric approach, including the definition of the vertical integration concept to connect SAP-MES-Historian-equipment with a best-in-class integration. Before that, at Eli Lilly, he was instrumental in the transformation of the Madrid site from a local market to a worldwide launching facility. Antonio has more than 20 years of experience in automation and digital, project management, facilities master planning, and qualification of facilities, utilities, and equipment. Antonio holds a master's in industrial engineering from the University of Comillas in Madrid. He is a founding member of the ISPE Spain Affiliate, which he chaired from 2007 to 2009, and was a member of the ISPE International Board of Directors 2009–2011.

Anton Granget is the founder of TechPivot, a technology advisory firm specializing in innovation projects and PoCs in convergence of IT and automation in biopharma. He holds a diploma in aerospace engineering and has worked on technology projects in the aerospace, automotive, and process industries. Anton collaborates with innovation leaders in the life science industry to conceptualize and introduce IIoT solutions by the successful transfer of cutting-edge technologies and best practices from forward-leaning sectors. He has been an ISPE member since 2017.

Christian Miguel-Langstrof, Diplom-Ingenieur (FH), is Team Lead of the automation and IT department at NNE in Germany. He has been with NNE since 2013. His passion is developing concepts, working with and leading automation teams through all phases of a pharma project (CD/BD/DD/CQ). Career highlights include developing a global equipment integration strategy and rollout; being automation project manager of a complex fill-and-finish project; and strategic automation consulting to develop an enterprise architecture. He has been an ISPE member since 2017.

Member Profile

HIKING BOOTS AND MOLECULES



Young Professional Brita Salzmann, a Process Engineer with CRB and member of the ISPE Greater Los Angeles Chapter, loves the challenge of backpacking. She continues to add to her hiking resume, which includes treks across segments of the John Muir Trail in the Sierra Nevada Mountains of California, 14,000-foot-high peaks in Colorado, and national parks throughout the West. For Salzmann, the allure of the outdoors is multifaceted: "You must be present to enjoy the beautiful experience. You rely on what you can carry and work as a team, which makes you self-sufficient and collaborative."

The winding paths and changing conditions that hikers face provide a fitting metaphor for Salzmann's professional journey. The steps on Salzmann's path have been varied, and this diversity of experience equips her with dynamic perspectives on the constantly evolving landscape of the biopharma industry. Good planning, effective preparation, and reliable mentors have helped her tackle

> "You cannot expect to be an expert on day one, but you can jump feet first into new challenges and not be afraid to ask questions."

challenging terrain with measured confidence, which she has coupled with an enthusiastic drive to discover what lies around the next switchback.

CHOOSING ENGINEERING

Salzmann's academic experience has been an evolving journey. "High school teachers encouraged me to apply to an engineering school because I was good in math and science. I didn't know what engineering entailed, but I applied and happily got accepted. I was eager to start figuring it out at the University of Colorado at Boulder as open option engineering. Initially I had a closed mind on chemical engineering because it sounded really hard." But Salzmann ended up changing her mind. "I discovered in my freshman engineering chemistry and biology classes that I am fascinated with molecular-level thinking—with how the world is built." She was a founding member of the ISPE Student Chapter at the University of Colorado during her junior year, and she took a leadership role as Chapter President one year later. "ISPE fostered my networking skills and technical growth. I was fortunate to attend the 2014 ISPE Annual Meeting & Expo, where I met people passionate about pharmaceuticals who enjoyed sharing that with the community."

Salzmann's fascination with "how the world is built" is evident in both her enjoyment of the outdoors and her career as a process engineer. The beauty and wonders of landscapes, and the interplay of their inhabitants, inspire her excitement to understand the architecture of natural ecosystems. In a similar way, Salzmann's job also entails the exploration of complex environments. In a recent project, for example, she worked on establishing a basis of design for a clinical-stage cell therapy biopharmaceutical company. This entailed evaluating, expanding, and relocating operations to a new facility, along with defining the process and developing a manufacturing layout. Design needs included flexible manufacturing capability for clinical and commercial production. The project required a detailed coordination effort—the development, in a sense, of a small ecosystem.

Salzmann credits her internship experiences for significantly influencing her professional growth. "I found great value in two diversified internships. One was in a lab at a small oligonucleotide start-up. It was a great hands-on experience with downstream equipment, including packing chromatography columns and operating the ultrafiltration/diafiltration unit. The other was at a large food production facility, where I worked in quality and collaborated with disciplines across the factory floor. These two experiences helped me define what I wanted to do when I graduated."

INDUSTRY EVOLUTION

A true growth mindset requires an openness to change, and Salzmann brings this outlook as she considers the evolution of the biopharma industry. "When I was an undergrad, the focus of the chemical and biological engineering senior projects was monoclonal antibodies (mAbs). Since then, I have seen a shift in the industry focus toward advanced therapy medicinal products (ATMPs)," she stated. "I am seeing an increased demand to understand the growing cell and gene therapy markets. In 2016 the ISPE Biopharmaceutical Manufacturing Conference was promoting continuous mAb production, and in 2018 the emphasis was on ATMPs. I am excited to be part of the future of biotech." She mentioned a few elements of this future: closing the process for autologous therapies, increasing automation to replace operator-centric design, and detecting virus or viral vector presence. These are a few key factors, Salzmann explained, to minimize operational costs and meet patient demand.

Like any wise hiker, Salzmann knows that the right traveling companions can enrich the journey. When asked what advice she would share with fellow Young Professionals, Salzmann emphasized how much she appreciates influential mentors and effective networking. "Find a mentor you can learn from technically and who will guide you professionally. I am fortunate to have an awesome mentor at CRB, but I also have a large support group outside of my official mentorship. I started to reach out to experienced process engineers across the company for a one-on-one chat about success. A common theme was being open and speaking up. You cannot expect to be an expert on day one, but you can jump feet first into new challenges and not be afraid to ask questions."

ISPE continues to play an important role in Salzmann's professional development. "Almost four years out of school, I still run into people that I met during my Student Chapter years. I'm now involved in the Los Angeles Chapter and recently attended the ISPE Biopharmaceutical Manufacturing Conference, where I met inspiring Young Professionals. I cannot wait to see what ISPE and Women in Pharma® have in store for the future."

California seems like an ideal place for Salzmann and other Young Professionals. She described it as a biotech hotspot. "In Los Angeles specifically, I'm seeing an increase in start-up companies and new initiatives to promote life sciences locally. There are a handful of exciting new cell and gene therapy companies in California that prove the area will be a destination in biotech for years to come."

Of course, proximity to phenomenal hiking doesn't hurt, either.

—Paul J. Cumbo, M.S., M.Litt.

The Foundations for Single-Use Manufacturing. Redefined from A–Z.

In the past, biopharma companies were struggling with various risk factors which kept them from implementing single-use solutions.

With our solid single-use foundation for biomanufacturing processes we are solving all of these challenges simultaneously. Our fully integrated single-use platform connects an exclusive approach in biocompatibility, state-of-the-art integrity control and testing as well as a unique automation platform and supply network.

This strategy provides flexibility and acceleration which leads to a cost-effective process that ensures the quality of your biologics and enhances patient safety.

www.sartorius.com/single-use-redefined

sartorius stedim biotech

ISPE Briefs

Another Success for ISPE CaSA Chapter with Life Sciences Tech Conference

Left to right: Mike Putnam, CaSA President; Wes Robbins, CaSA Past Board Member; Chris Combs, Founder of Team Chris Combs; Christopher Small, Conference Chair.

Andy Stober, keynote speaker.

The ISPE Carolina-South Atlantic (CaSA) Chapter's 26th Annual Life Sciences Technology Conference was a highly successful event that took place on 12 March 2019 at the Raleigh Convention Center. The conference featured 209 exhibiting companies and organizations and attracted over 1,200 attendees.

Keynote speaker Andy Stober, Chief Technology Officer at AveXis, addressed a standing-room only audience, and education sessions were well attended. Over 27% of attendees were employees of owner/manufacturing companies. During lunch, manufacturing companies' leaders gathered for the Industry Advisory Council. This group of executives, site heads, and manufacturing directors discussed industry trends and how the ISPE community can better work with their companies.

Women in Pharma® hosted an evening reception at the Stockroom to benefit Team Chris Combs, a local charity affiliated with Project ALS, a national organization devoted to funding research to find a cure for amyotrophic lateral sclerosis. Throughout the day, fundraising and a 50/50 raffle raised $17,300 for these organizations.

The conference continues to be the marquee event of the CaSA Chapter and has grown to become one of the largest industry events on the East Coast. For more information, please visit www.ispe-casa.org.

—Christopher Small, Life Sciences Technology Conference Chair

Rocky Mountain Chapter 2019 Vendor Show

Jim Breen addresses the Rocky Mountain Chapter event.

The ISPE Rocky Mountain Chapter had a successful 24th Annual Vendor Show on 7 March 2019. This year's event featured two keynote speeches. The first was provided by Jim Breen, 2019 ISPE International Board of Directors Chair; Vice President, Lead Biologic Expansion, Janssen Pharmaceutical; and Adjunct Professor at Drexel University. The second was given by Mike Freeman, CEO of Innosphere.

The event had 625 attendees, and featured 110 paid booths and four trade partner booths. A range of sponsors participated this year, including 11 platinum sponsors, five gold sponsors, five presentation sponsors, one lanyard sponsor, and one beer sponsor.

The Annual Ski Day took place the next day at Copper Mountain Resort with more than 80 attendees.

We'd like to feature your group in an upcoming ISPE Briefs! Share the highlights of training programs, conferences, social events, or other activities with ISPE members. Article length is 250–400 words; photos should be 300 dpi or greater than 1 MB. Send your briefs to Susan Sandler, Editorial Director, at ssandler@ISPE.org.

SAMPLING CONSIDERATIONS

in Continuous Manufacturing

By Plinio A. De los Santos, Jeffrey Hofer, MS, Eric Jayjock, PhD, Timothy T. Kramer, Kevin R. Lief, and Martin Otava

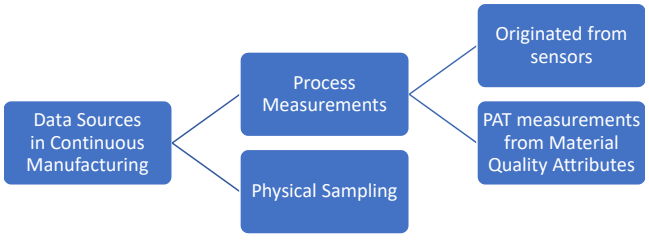
Sampling is the selection of a representative portion of the population to make inferences about the entire population. In pharmaceutical manufacturing, samples are drawn from different stages of the process for both controlling process parameters and assessing drug product quality. In the case of a traditional batch process, a fixed amount of material is processed and the batch quality is established after it has been fully manufactured. In contrast, in a continuous manufacturing (CM) process, material is continuously flowing through the process from one unit operation to the next, being converted from raw materials to finished product, and the control strategy focuses on maintaining a state of control of the process (after its start-up and before its shutdown) as raw materials continuously enter the process, so that good quality product is produced. This article describes aspects of sampling within a continuous process during both development and commercial manufacturing of solid oral dosages and draws comparisons to sampling in the traditional batch process.

SAMPLING DATA SOURCES FOR CONTINUOUS MANUFACTURING

Data sources represent mechanisms for extracting sampling information from the CM process for inferential purposes. As summarized in Figure 1, these mechanisms can be generally separated into two categories: physical sampling and process measurements. Sampling by physical removal of material for off-line or at-line analytical testing is employed in both traditional batch processes and CM. In this article, the term "physical sample" will be used when referring to removal of material from the line.

Two types of process measurements could be considered for CM, both originating from process analytical technology (PAT) [1]. The first originates from sensors measuring the performance attributes of the process itself. The second encompasses PAT measuring raw or in-process material quality attributes and translating these raw measurements into the attributes in question; the translation is frequently based on multivariate models applied to near-infrared (NIR) spectroscopy signals. Note that the models must be developed and calibrated against laboratory-analyzed physical samples.

Figure 1: Categories of data sources.



All these information sources (physical samples, online material measurements, and process measurements) play a role in the development of process understanding. And, as process knowledge matures, strategic decisions can be made as to which elements are required to ensure material quality as well as appropriate limits for the respective measurements.

As is the case with batch processes, the objectives for physical sampling and especially PAT measurements change substantially as the product moves through development toward commercial

production. The use of NIR methods requires model development that translates spectroscopic signals into a response of interest (e.g., concentration of active pharmaceutical ingredient). Hence, during early product and process development, measurements must be gathered from both NIR and traditional at-line or off-line analytical methods to define and refine the prediction model. In this early stage, final quality statements should be based on the results of physical samples. Before such a model is formally validated, the data collected from PAT cannot be used for *absolute* quality statements about the final product for purpose of release. However, nonvalidated PAT measurements may still provide an indication of quality and potentially be used as supportive information. Nevertheless, until PAT models are fully developed, PAT data collection and physical material sampling should be aligned so that collected data can be used for PAT model development and for quantifying the model's accuracy and precision.

As the process approaches validation, both physical sampling and PAT should continue to be used. Physical sampling and validated PAT measurements allow quality statements to be made of the final product, with PAT enabling the monitoring of the quality attributes throughout the continuous run. Real-time release testing (RTRT) strategies may be employed to further replace certain physical sampling–based testing with validated PAT measurements. In general, both data sources should be leveraged to confirm process quality and enhance process understanding until all processes and methods are appropriately validated.

Both the physical sizes of the sample and the physical sample representation of all manufactured items play a role in determining the representativeness of inline PAT measurements about the entire process [2]. The material flowing through a continuous line is not truly observed continuously; instead, the measurements are taken at a certain frequency, and each measurement represents some fractional amount of material out of the total. The minimum frequency is determined by the residence time distribution (RTD)—a distribution of the time it takes for a distortion to propagate throughout the line (or part of the line, depending on the presence/location of diversion points within the process). Variability in feed rates is attenuated by the blenders and mixing in a tablet press feed frame or encapsulator bowl, and the resulting blend uniformity may be quite insensitive to short-time feeder flow distortion. The combination of RTD studies with quality requirements allows determination of the minimum required measurement frequency. Generally, the maximum frequency of PAT measurements is bounded by the device capabilities. Once the PAT measurement frequency is determined, a quantitative estimate of the variability of the "unseen" material is established to provide confirmatory statements of the acceptability of the sampling frequency.

The precise location of the PAT sensor is especially important in relation to the point of physical sampling. Because of the dynamic nature of a continuous line and material transport, blend uniformity measured between two-unit operations may change. For example, because additional blending of material occurs during transportation, a sensor installed at the output of the mixer may provide different blend uniformity results when compared with a sensor on the feed frame of a tablet press.

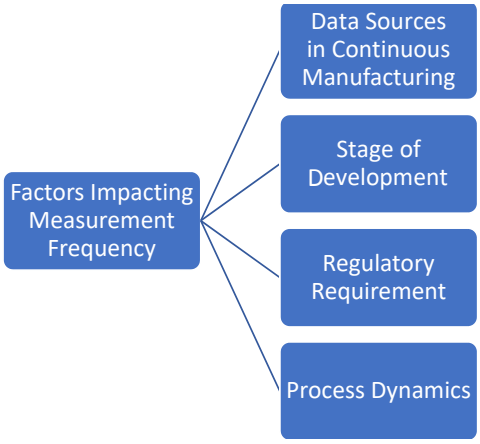
During process validation, it is vital to collect sufficient evidence to confirm that process performance is satisfactory when the process is run as designed and to ensure that physical sample measurements confirm performance as indicated by online measurements. Commercial production is considered satisfactory unless confirmatory measurements suggest otherwise. Once validated, the role of the physical sample measurements changes from being the primary indicator of quality to solely confirming quality, because quality is ensured by the process parameters staying within acceptable ranges. Indeed, for many processes, the PAT measurements become confirmatory as well, providing evidence that the process is performing acceptably. The difference between the confirmatory physical samples and confirmatory PAT measurements is that the PAT measurements provide a high-frequency signal of process quality that depends on a predictive calibration model, whereas the physical samples provide a low-frequency quality signal using reference methods. PAT measurements generally provide a low-cost input to a statistical control check against special-cause process upsets [3].

In addition to PAT measurements being used to monitor process quality, they may also be incorporated into a feedback loop to further reduce variability about a desired quality target. Upstream process settings may be adjusted based on the downstream PAT measurement. If the PAT is intended to be used in a feedback capacity or as part of the control strategy of a validated process, the PAT measurement becomes a required process element and should not be eliminated (unless there is another suitable analytical method available). This is true even if historical performance shows that the process is well behaved without the collection of PAT measures during process quality monitoring. In contrast, when not operated in a feedback loop, certain PAT measurements of material quality attributes may be unnecessary if a strong relationship between these material quality measurements and other associated process measurements is sufficiently demonstrated.

SAMPLING FREQUENCY ASSESSMENT STRATEGIES

Within the traditional batch manufacturing approach, quality is typically ensured by maintaining process parameters within certain predefined boundaries and then confirming the quality of the product produced through postproduction testing. A key aspect of this batch manufacturing approach hinges on establishing the quality of the batch after it has been fully manufactured. This is in juxtaposition to the CM process, where material moves through the process from one unit operation to the next, being converted from raw materials to finished product. Best practices involve a continuous control strategy that focuses on establishing the process is in a state of control at the time that good product is being produced. In other words, batch manufacturing focuses on demonstrating the quality of the product within space, whereas CM focuses on demonstrating the quality of the product in time.

Figure 2: Factors affecting measurement frequency.



To determine the frequency of obtaining the product- or process-related quality attributes, one must consider the data source, the stage of development (as discussed in the previous section), and the purpose of the data. Figure 2 lists some of the factors that affect the measurement frequency. The collection of process and product data can be generally organized into two categories: data that are used for active control of the process and data that are used for confirmation that the process is operating as designed.

If the data are being collected to make control decisions within the process, the collection frequency should be driven by the dynamics of the process. Process dynamics is the understanding of how a process changes in time. When a disturbance happens within a process, the time it takes for the disturbance to propagate through the process is known as the process's characteristic time (i.e., the RTD). If data are being used for control, the collection frequency must be fast enough to provide a measurement of the process attributes that has adequate statistical power to determine the appropriate control output. If the data are being used for confirmation, the collection frequency should be driven by the time it takes to produce the batch (this is much like the batch manufacturing approach).

As noted previously, data sources can be generally separated into two categories: process measurements and physical sampling. Process measurements are typically high-frequency measurements, which typically repeat on the scale from milliseconds to tens of seconds. They are normally nondestructive, and they can be performed either online (a sensor looking at part of a stream) or inline (the entire process stream passing through a sensor) or come from sensors integrated within the process equipment (e.g., compression force measurement within a tablet press). Process measurements are usually automated and require minimal or no operator interaction. Physical sampling involves collecting material samples from the process stream and submitting them to testing away from the line. The collected samples can be analyzed at the line, where the analysis is carried out near the process, or taken to a lab for traditional wet chemical analysis. Physical sampling approaches are often at least somewhat operator-driven activities. They are frequently, but not always, destructive and results can take minutes to weeks to receive.

There is a natural synergy between the high-frequency demands of the data needed for control and the high-frequency capabilities of process measurement. Likewise, the low-frequency capability of physical sampling makes it an appropriate option for confirmatory testing. While this heuristic is generally reliable, special cases do apply. For example, the high-frequency nature of a process measurement would not preclude its use as a confirmation test. Likewise, if a physical sampling approach can be used to provide feedback information more quickly than the characteristic time, it would be suitable for control. The key concept is that the frequency of each test must be defined with respect to the purpose for conducting the test.

As defined in ICH Q10, state of control is "a condition in which the set of controls consistently provides assurance of continued process performance and product quality" [4, p.15]. Consequently, a process can be said to be in control when the critical quality attributes are demonstrated to be within predefined levels by the data collected from the process via process measurement, physical sampling, previously established process capability, or some combination of these. Several common examples of quality attributes and control strategies will be offered to provide context to the discussion.

The simplest way to demonstrate a particular quality attribute is within range is to directly measure it (assuming that is possible). For example, encapsulators are often paired with check-weighers to individually assess the weight of each capsule in the product stream.

While direct measurement is ideal, it is not possible for most quality attributes. For example, consider the weight of a tablet. While tablet presses use a force control loop to monitor and adjust the amount of volume to fill in the die, the force loop does not directly measure the tablet weight; instead, it is a process measurement that correlates with the weight. The force measurement can be used to make an individual quality statement about each tablet compressed, predict the variability of the product stream, and segregate individual tablets from the stream. However, the force loop by itself cannot predict the actual tablet weight. The latter is enabled by externally assessing the tablet weight and adjusting the press to keep the tablet weight on target. This well-known feedback loop is an excellent example of combining a high-frequency process measurement with a low-frequency sampling-based measurement to ensure a process stays in a state of control and assures product quality.

Of course, the actual final critical quality attribute of a tablet or capsule is not its weight; it is the dose, which is the product of the concentration of the API within the drug form and the aforementioned weight. Within the CM paradigm, there are two common options for assessing the concentration of the blend: (a) prediction

of the concentration using loss-in-weight feeder data combined with a dynamic process model, or (b) prediction of the concentration using a spectrometer (e.g., NIR or Raman) and an associated multivariate model to assess the concentration. In both cases, it is typical for the predictions of the concentration to be capable of capturing the average concentration of the process stream, but not necessarily the variation in the process stream. The multivariate spectrometer variation is often driven by noise associated with the instrument and the way the sample is presented to the sensor. The feeder data approach is typically based on a perfect mixing model, which does not account for the level of micromixing within the process. The most common approach for addressing the variability of the stream is to use development trials to demonstrate the extent of natural variation within the process stream. If the variation is found to be small compared to the specification limit, targeting and adjusting ensure that the mean concentration is tightly controlled within a specified control limit; this is a perfectly acceptable control strategy.

For batch release of a final product, the physical sampling frequency will need to be aligned with regulatory requirements. For traditional batch testing, the number of representative physical samples for release will be smaller than the number of measurements when using PAT. However, in both instances, the number of samples and associated acceptance criteria should provide acceptable assurance of the product's ability to meet the specifications.

Results of high-frequency data streams should be interpreted within the context of the capability of the method and the known behavior of the process, including the extent to which the measurements could be considered independent and identically distributed. High-frequency data streams will lead to occasional outlying observations. For example, consider a multivariate spectroscopic process measurement such as an NIR method. Assume that this method is developed to monitor the average concentration of the process, and the probe frequency is orders of magnitude higher than the characteristic time. A few outlying measurements can be safely ignored because it has been previously established that the stream does not vary appreciably in such a short time frame. Therefore, these variations are likely caused by variation of the method and not the process. Similarly, a single missing observation in the case of multivariate spectroscopic (or other) method does not necessarily raise immediate concerns about product quality.

Next, consider an extreme compression force measurement within the tablet compression scenario discussed previously. This is a measurement of an individual tablet being created and is indicative of a single out-of-specification unit. The proper response would be to reject that unit because under- or overfill events can occur.

Establishing that a process is operating in a controlled state is key to the successful implementation of CM. The need to demonstrate the control within a time frame that is relevant to the process (e.g., the characteristic time) calls for a more nuanced discussion of what data are collected from the process and how they are used. For most continuous processes, the resulting control strategies will be a combination of many of the tools used within the traditional batch paradigm (e.g., in-process controls and stratified sampling), but they will be built around advanced high-frequency data streams that can help demonstrate and maintain a state of control.

CONTROL TECHNIQUES AND DIVERSION AND REDUNDANCY DECISIONS

Physical samples may be gathered throughout a batch to confirm that the process is producing or has produced products or intermediates (e.g., blends or uncoated tablets) with quality characteristics within the prespecified attribute ranges. These confirmatory samples provide some assurance that the process is operating or has operated as desired. Generally, these physical samples are low frequency and are used to augment other process or inline measurements that generally provide a higher-frequency assessment of process performance. For example, feeder rates and spectroscopic signals of the blend at the feed rate ensure consistent blend proportions, torques on the mixer ensure consistent flow of powders, and compression forces ensure consistent tablet weights. These high-frequency product and process measurements could be collected as often as every few fractions of a second and could thus provide thousands of measurements per hour of a batch.

From a volume perspective, the high-frequency process sensors and inline measures overwhelm the low-frequency sample measurements, and the value of the physical sample measurements is limited. However, the physical sample measurements have two potential advantages. First, they are generally collected from final or near-final products (e.g., uncoated tablets) and thus reflect the totality of the process, including any atypical behavior that may affect quality. Second, they use reference methods for measurement. On the other hand, the critical disadvantage of physical samples is that because of their low sample frequency, they may miss short-term changes in the process.

Inline measurements near the end of the process combined with well-developed predictive calibration models allow accurate and precise estimation of reference method measurements and can match the two advantages of physical sample measurements. For example, a well-characterized spectroscopic model that translates measurements of the blend at the feed frame into concentration measurements can be used in combination with a compression force gage at the tableting station that provides indirect tablet weight measurements, and this combination can provide tablet potency estimates that accurately reflect the behavior upstream of the feed frame. These potency estimates are thus valid surrogates for reference potency measurements. In such a situation, the confirmatory aspect of physical sample potency measurements is redundant and can potentially be replaced by this indirect method, if it is appropriately validated. Also, relative to infrequently gathered physical measurements, the high-frequency measurements can be configured to have a high probability of detecting short-term aberrations in the process [3].

Well-designed control systems incorporate combinations of sensors and inline measures that span the process and either

prevent quality aberrations or detect their existence. For example, mass flow sensors can ensure that the correct proportions of powders are fed to a mixer. However, if two excipients were inadvertently loaded into the wrong hoppers, the individual feeders may lead to normal mass flows (of the switched materials); the mass flow sensors would not detect this error, but an NIR signal at the feed frame could provide evidence of the mistake (e.g., through extreme Q residuals, which measure the difference between a sample and its projection into the principal components from a model [5]).

Equipment design may also minimize the likelihood of potential failure modes. For example, the path of powder movement may be designed to eliminate ledges that allow powder aggregation and to be as short as feasible.

Typically, the control system design incorporates failure modes and effects analysis combined with verification testing during development to prove that untoward changes are detected. The control algorithms generally incorporate warning and alarm limits that signal or stop the process when atypical readings are obtained. When the control system design has been proven to effectively prevent or detect product quality issues, the need for confirmatory samples is obviated.

Both univariate statistical process control (SPC) and multivariate statistical process control (MSPC) may be used to evaluate current performance relative to past performance and could provide assurance that the process is performing within historical norms. Signals (atypical measurements or patterns of nonrandom behavior) may trigger process stoppages to allow investigation or diversion of material to prevent questionable product from being forward-processed. In cases where measurements are affected by autocorrelation, the use of SPC and MSPC techniques could result in an increased number of false alarms [6] and the use of time-series techniques should be considered [7].

When an end- or near-end-of-process measurement of a quality attribute is unavailable, the process should be evaluated to determine whether upstream and correlated downstream measures provide acceptable assurance of quality without confirmatory physical sample measurements. Past process behavior and equipment design will influence this assessment. For example, content uniformity in a continuous direct compression tablet process is largely determined by feeding powders at the targeted rate, providing adequate mixing, and compressing the desired amount of blend into tablets. As mentioned previously, sensors on each feeder, the mixer, and the compression station can provide acceptable evidence of consistent potency.

In some cases, physical sampling will be deemed necessary to verify that the process has not experienced a special-cause event. During development, experiments can be conducted to quantify the impact of certain special causes. For example, drug substance feed rates of various magnitudes and durations can be enacted, monitored, and modeled to provide an understanding of the powder flow dynamics [8] and quantify changes necessary to effect a meaningful potency impact. These powder flow dynamics can be used to guide the collection of confirmatory physical samples—the frequency determined by the size and duration of a special-cause disturbance required to appreciably affect quality and the probability that such a disturbance occurs. For special causes related to refilling operations, one might choose to collect a physical sample after every refill operation (appropriately delayed to allow for the residence time within the system) to confirm that the correct proportions and powders were being used. Alternatively, one may implement a spectroscopic identification verification whenever refilling powders and thus obviate the need for confirmatory physical downstream samples. The collection of the physical samples should reflect the likelihood of special causes that might be missed by other process sensors and the ability to detect them.

Three factors influence the determination of the frequency of physical samples: (a) the powder flow dynamics, (b) the extent of process experience, and (c) the degree of assurance provided by in-process measures of quality attribute acceptability. At the one extreme, where there is little process experience and no guarantee that the inline sensors adequately monitor blend concentration, additional representative sampling may be appropriate. At the other extreme, extensive process experience may justify not using physical sampling. This is especially true when inline measurements provide definitive signals of changes in key quality

attributes. There is also a middle ground, where some physical sampling is conducted to provide confirmation that the process has run as expected. This is akin to content uniformity testing in batch processes where, for example, meeting USP<905> requirements provides weak confirmation that the process has produced products near the desired label claim.

Inline sensors and online monitoring may signal that a quality attribute is deviating too far from the desired target. For example, NIR spectroscopy of blend powders prior to the feed frame may signal that the drug substance concentration is too high. If this powder (or the related tablets) is diverted from forward processing, downstream concentration can be assured without confirmatory physical samples when the PAT method is validated. The criteria of "too far from target" requires justification as well as limits to the amount of time that material is diverted; this latter aspect is both a business risk and a potential signal that the process is running neither as designed nor as previously experienced.

When a process has multiple sensors and/or possible controls, a likely outcome is that discrepant and/or inconsistent signals are occasionally obtained. Postproduction (or, potentially, online) multivariate analysis may identify the signal(s) that are most likely the source of the discrepancy, and this analysis can trigger an investigation to uncover the problems. When product quality is questionable because of inconsistent signals, a material use decision must be made. The simplest solution is to divert or dispose of that material, but this option may be the costliest strategy. An alternative approach is to make a probabilistic assessment of the acceptability of the material and to use the material if that probability reaches an established threshold. A formal description of such a probabilistic assessment of the acceptability of material that was produced during a period of inconsistent signals should include the development and communication of rules (through standard operating procedures) for handling inconsistent signals and the testing and potential use of the related material.

The control strategy should address the possibility that the model for predicting drug substance concentration could malfunction during the batch or that it might be unavailable for an entire batch. In this scenario, the feeder controls could still provide confidence that the material was of acceptable quality at that point in the process, but the material quality near the end of the process could not be confirmed. In these situations, it may be helpful or deemed necessary to have backup physical samples of the drug product (e.g., core tablets) to confirm that the process performed as expected. These samples should be gathered in a systematic manner, similar to how they would be obtained for a batch process, to ensure that they are representative of the remainder of the batch. To demonstrate the acceptability of the material, the sampled dosage units could then be tested in line, using criteria similar to those used for a batch process, with the registered detail of the approved process. These data would be supplementary to the feeder information, which would provide high-density information about the performance of the process in between the physical sample information.

PROCESS CAPABILITY

Process capability analysis is an assessment of the product performance relative to its specifications [9]. This section explores differences between the CM and batch manufacturing processes that could have a critical effect on process capability.

CM processes allow for the collection of a large amount of in-process data, which can provide great insight into the ability of the process to produce material that meets the requirements. This information enables the manufacturer to understand and observe process dynamics and potentially react as needed to ensure acceptable production. In contrast, a batch process generates a more limited quantity of data, and one therefore has less insight into the overall process performance and is more dependent on simplifying assumptions about the expected process behavior.

In a batch process, materials are fed into the process during a discrete manufacturing step involving the entire quantity of material. The materials are blended as an entire quantity without opportunity for blend adjustment. This blended material is then held until it is compressed into tablets or used to fill capsules. In this scenario, there is material source separation between batches and the overall process variability could be impacted in two ways related to the blend: (a) by the inherent variability of the lot blend, or (b) by the lot-to-lot differences resulting from differences in the incoming raw material lots. In a CM process, new material is constantly fed into the system [10]. In this type of manufacturing, data from partial blends (or microblends) are analyzed and suboptimal blends can be removed via diverting equipment using appropriate controls. In other words, by diverting suboptimal blends, the CM process avoids potential manufacturing issues in critical quality attributes downstream. Also, if controls are implemented to remove potentially unacceptable material, the distribution of critical quality attributes is expected to be truncated at predefined values, which should result in improved process capability as compared with that of a batch process. To establish the necessary controls for material diversion during CM, one must have a sound mechanistic understanding of how the different raw material components contribute to the blend. Some of the key powder attributes include the material density, particle shape, particle size, flowability, compressibility, and compactability [11].

In a batch process, the theoretical amount of drug product mass in a lot from tends to be fixed, whereas a CM process can manufacture lots with flexible sizes. With a batch process, batch sizes are subject to the size of equipment used (which is available in only a few sizes), whereas batch size in a CM process is a function of how fast materials are fed from the various feeders and how long the process is run. Therefore, the CM process has increased flexibility to deliver specific quantities of materials. This flexibility is ideal for clinical trials, which may require varying material needs, and for meeting market demand. A batch process is less flexible, and the process settings must be modified as equipment of varying sizes is used.

In a CM process, a successive material flow between unit operations may be implemented. This reduces the likelihood of material segregation and degradation during in-process storage, and it should

Figure 3a: Normal distribution density example.

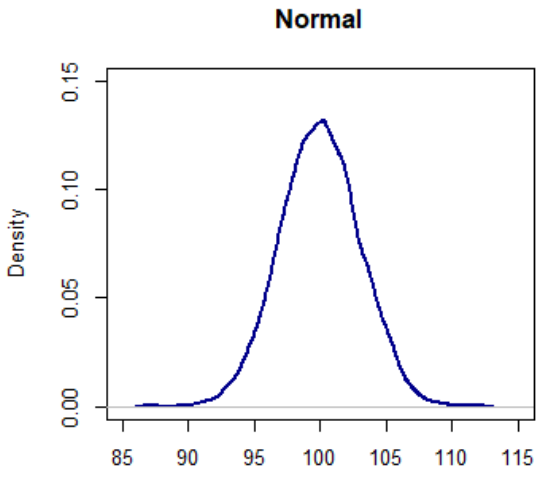


Figure 3b: Log-normal distribution density example.

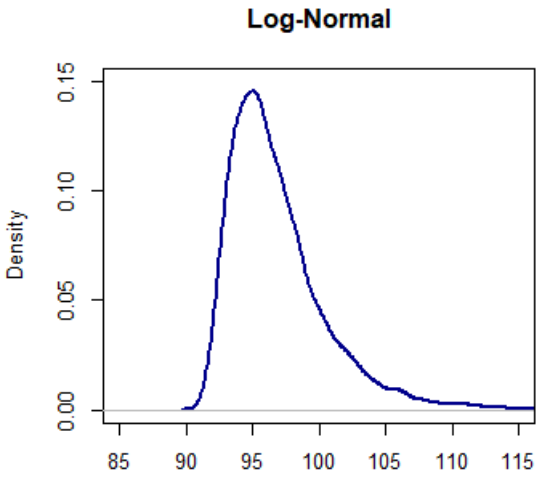


Figure 3c: Weibull distribution density example.

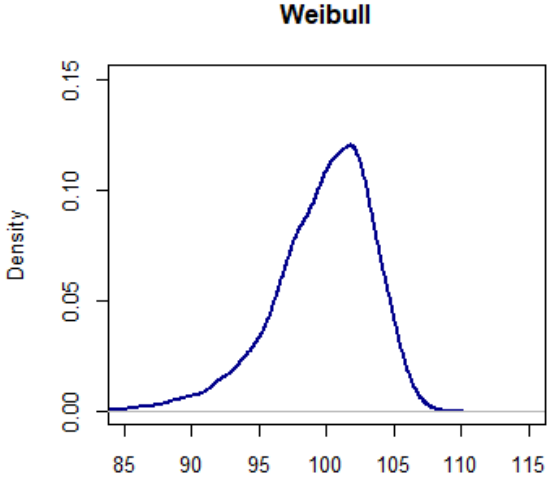
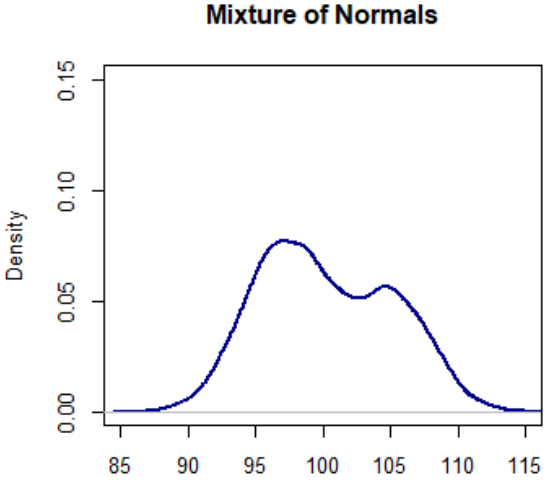


Figure 3d: Density of mixture of two normal distributions example.

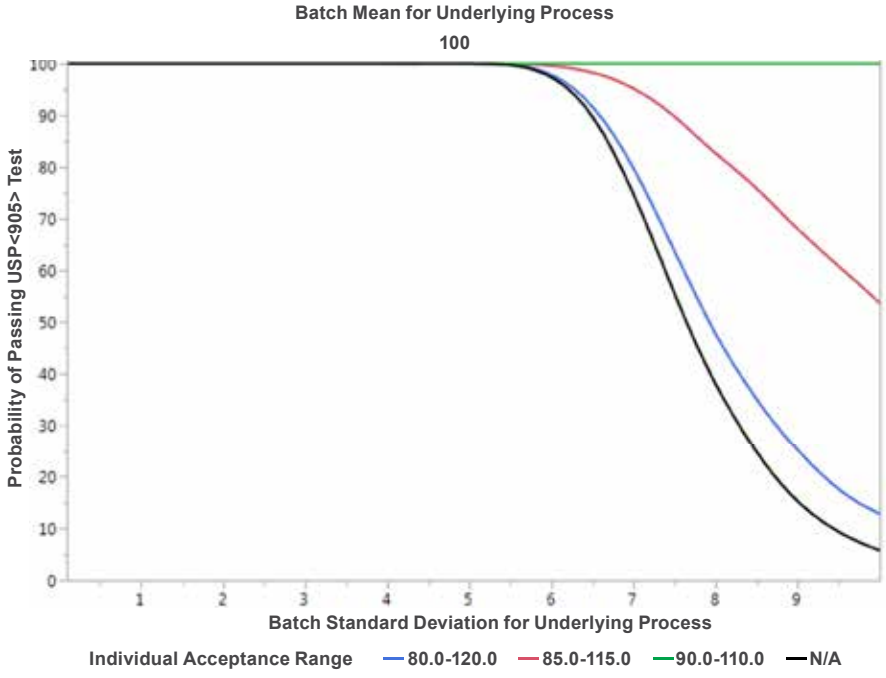


have a positive effect on the quality attributes capability, as compared to a batch process. Because specifications are typically numerical ranges within which test results are expected to comply, process and/or performance capability indices are commonly employed [9, 12–14]. The application of process capability indices requires that the process is at a state of near statistical control, and it also relies on an estimate of the process inherent or common cause variability. On the other hand, the capability analysis is sometimes still required when the process is not strictly in a state of statistical control; in that case, process performance indices could be employed [9]. Differing from process capability indices, process performance indices employ an estimate of the overall process variability.

Notably, the application of either process capability or performance indices has the following shortcomings:

- Standard process capability or performance indices assume that the data come from a normal distribution; therefore, measurements are assumed to be independent of one another (otherwise, a time-series approach should be considered). Although this assumption is, in many instances, a reasonable one, the standard indices are not robust to departures from

Figure 4: OC curves for the USP<905> test when considering different levels of diversion controls.



normality [15]. Figures 3a to 3d depict some distributions from quality attributes that may be observed in manufacturing process: skewed distributions (e.g., log-normal and Weibull distributions), multimodal distributions (e.g., mixture of two normal distributions), and unimodal with central tendency (e.g., normal distribution).

- Although nonparametric approaches for estimating capability indices exist, these have some limitations [15]:
  - The application of robust capability indices is essentially suitable for two-sided specification cases.
  - Capability indices based on the percentiles of the fitted distribution rely on the appropriate identification and fitting of the distribution.
  - Data-normalizing transformations are not always feasible and, in some instances, may not have a natural interpretation for practitioners.
  - Capability indices based on resampling methods (such as bootstrap) have been shown to yield relatively poor results when distributions are highly skewed.
- Compendial test requirements are more complicated than the single-range specification used in process capability or performance indices. Compendial tests (e.g., the USP<905> test for uniformity of dosage, the USP<711> test for dissolution, and the USP<701> test for disintegration) can require multiple-stage testing and may include simultaneous constraints.

Given the preceding limitations, capability comparisons should be focused on assessing the probability of passing the test using either parametric or nonparametric assumptions. The use of nonparametric estimation techniques is suitable for CM because of the large density of data collected over time.

As a parametric example, Figure 4 provides a comparison of operating characteristics (OC) curves developed for the USP<905> test under the following assumptions: (a) One curve is based on normally distributed results with a fixed mean of 100, and variable standard deviations ranging from 0 to 10; (b) the other three curves reflect the existence of blending controls that divert material from the process to satisfy various target allowable ranges for individual uniformity of dosage units. The OC curves show that the narrower the window of allowable individual range due to more stringent controls is, the higher the probability of passing the USP<905> test is for the same expected level of underlying process variability prior to diversion. Therefore, conceptually, the appropriate level controls at the blending would tend to increase the capability of the process. Because these levels of controls can be implemented within a CM process and there are no hold times, product quality (and hence capability) can be improved relative to a traditional batch process. However, in some continuous processes with high natural variability, there could a trade-off: the increase in the capability could come at the cost of a reduction in yield (due to an increased waste of diverted material).

CONCLUSION

In a CM process, data from partial blends can be analyzed and suboptimal blends or tablets can be removed using the appropriate controls to avoid manufacturing issues downstream or out-of-specification final products. If these controls are implemented, a CM process could remove potentially unacceptable material, and the distribution of the critical quality attributes could result in improved process capability as compared to that of a batch process.

Data sources for CM controls include feeder controls and related models, chemical tests from physical samples, model-based predictions based on NIR spectroscopy or other similar technology, and indirect measures of the quality of the material obtained through physical sensors. Well-designed control systems will incorporate combinations of sensors and inline measures that span the process and either prevent quality aberrations or detect their existence. In some cases, physical sampling will be deemed necessary (and complementary) to verify that the process has not experienced any special-cause events. To determine the sampling frequency, one must consider the source of the measurements (e.g., physical samples vs. samples obtained using PAT tools), the development stage, and the measurement purpose (making local process-stage vs. batch-level quality statements).

References

1. US Food and Drug Administration. "Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." September 2004. https://www.fda.gov/downloads/drugs/guidances/ucm070305.pdf
2. US Food and Drug Administration. "Development and Submission of Near Infrared Analytical Procedures: Draft Guidance." March 2015. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM440247.pdf
3. Box, G. E. P., and A. Luceño. *Statistical Control by Monitoring and Feedback Adjustment.* Hoboken, NJ: Wiley & Sons, 1997.
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System Q10." Published June 4, 2008. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf
5. Mujica, L. E., J. Rodellar, A. Fernandez, and A. Güemes. "Q-statistic and T2-statistic PCA-based Measures for Damage Assessment in Structures." *Structural Health Monitoring* 10, no. 5 (2010): 539–53. doi:10.1177/1475921710388972
6. Mastrangelo, C. M., and D. C. Montgomery. "SPC with Correlated Observations for the Chemical and Process Industries." *Quality and Reliability Engineering International* 11, no. 2 (1995): 79–89. doi:10.1002/qre.4680110203
7. Harris, T. J., and W. H. Ross. "Statistical Procedures for Correlated Observations." *Canadian Journal of Chemical Engineering* 69, no. 1 (January 1991): 48–57. doi:10.1002/cjce.5450690106
8. Engisch, W., and F. Muzzio. "Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing." *Journal of Pharmaceutical Innovation* 11 (2016): 64–81. doi:10.1007/s12247-015-9238-1
9. Murphy, T. D., S. K. Singh, and M. L. Utter. "Statistical Process Control and Process Capability." In *Encyclopedia of Pharmaceutical Technology,* 3rd ed., edited by James Swarbick, 3499–512. Boca Raton, FL: CRC Press, 2006.
10. Lee, S. L., T. F. O'Connor, X. Yang, C. N. Cruz, S. Chatterjee, R. D. Madurawe, C. M. V. Moore, L. X. Yu, and J. Woodcock. "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production." *Journal of Pharmaceutical Innovation* 10 (2015): 191–9. doi:10.1007/s12247-015-9215-8
11. Schiano, S. "Dry Granulation Using Roll Compaction Process: Powder Characterization and Process Understanding." Doctoral diss., University of Surrey (UK), 2017.
12. Czarski, A. "Assessment of Long-Term and Short-Term Process Capability in the Approach of Analysis of Variance (ANOVA)." *Metallurgy and Foundry Engineering* 35, no. 2 (2009): 111–8. http://journals.bg.agh.edu.pl/METALLURGY/2009-02/metalur03.pdf
13. Juran, J. M. *Quality Control Handbook*, 3rd ed. New York: McGraw-Hill, 1974.
14. Wu, C. W., W. L. Pearn, and S. Kotz. "An Overview of Theory and Practice on Process Capability Indices for Quality Assurance." *International Journal of Production Economics* 17 (February 2009): 338–59. doi:10.1016/j.ijpe.2008.11.008
15. Ryan, T. "Confidence Intervals for Process Capability Indices." In *Statistical Methods for Quality Improvement*, 2nd ed., 195–201. New York: Wiley & Sons, 2000.

About the authors

Plinio A. De los Santos is a Principal Scientist at the Center for Mathematical Science in the Merck Manufacturing Division at Merck & Co., Inc., Kenilworth, New Jersey, US. He provides statistical and mathematical support to development, manufacturing, packaging, laboratory, and supply operations of small-molecule products. His interest areas include process validation, design of experiments, statistical process control, and manufacturing systems optimization. Plinio holds a doctorate in decision sciences and engineering systems and a MS in industrial management and engineering, both from Rensselaer Polytechnic Institute, an MBA from the University of Puerto Rico, and a BS in industrial engineering from the Technological Institute of Santo Domingo.

Jeffrey Hofer, MS, is a Senior Advisor, Statistics, at Pearl Pathways. He provides statistical consulting on CMC projects for a variety of pharmaceutical companies. Previously, Jeff worked as a CMC statistician at Eli Lilly and Company from 1990 to 2017. During this time, Jeff supported product development and manufacturing and worked on several submissions. He also worked on a team developing a continuous drug product. Jeff also was an active member of the PhRMA CMC Statistics Expert Team from 1994 to 2005 and chaired the team from 1997 to 2005. Jeff's main areas of statistical interest are stability analyses, content uniformity and dissolution, and continuous manufacturing.

Eric Jayjock, PhD, is Director of Continuous Manufacturing at Patheon, a Thermo Fisher Scientific company. His graduate studies were at Rutgers University, where he was a part of the NSF Center for Structured Organic Particulate Systems (C-SOPS). At Rutgers, Eric worked on developing scalable manufacturing processes for oral solids dosages. He designed and coordinated the construction of the C-SOPS continuous direct compression line in collaboration with Janssen, a Johnson & Johnson company. Eric joined the Janssen team and worked to bring the continuous manufacturing approach to the industry. At Pantheon, Eric is focused on developing highly flexible, highly capable continuous manufacturing frameworks to serve the diverse needs of the pharmaceutical industry.

Timothy T. Kramer is Senior Research Advisor at Eli Lilly and Company. He joined Lilly in 2007 and has supported the development of many small molecules. Tim is particularly interested in experimental designs and has spearheaded development and use of nearly orthogonal screening designs through custom programs, development of a web interface, and promotion within and outside of Lilly. Tim advises peers on advanced statistical techniques as well as routine techniques to support submissions. He received his doctorate in statistics from the University of Wisconsin-Madison, and worked for 18 years at Hewlett-Packard as a statistical consultant, customer satisfaction representative, and warranty modeler. While at HP, he developed an integrated, worldwide forecasting tool.

Kevin R. Lief is a Statistics Director at GlaxoSmithKline, which he joined in 2003. With over 20 years in the pharmaceutical industry, Kevin has worked across the discovery area through to commercial product manufacture. Most of his work has been in pharmaceutical development, where he has contributed to many GSK submissions, successfully leading the chemistry, manufacturing, and control statistical effort to regulatory approval in a number of major markets.

Martin Otava, is a Principal Statistician in Quantitative Sciences of Janssen Pharmaceutical Companies of Johnson & Johnson. He provides statistical support to research and development activities in pharmaceutical manufacturing, mainly for small molecules products, from early process characterization to process validation and early commercial production. Major areas of interest are statistical challenges in implementation of continuous manufacturing. From a methodology perspective, he is interested in design of experiments, Bayesian approach toward hierarchical modelling, and inference on equivalence. Martin received a doctorate in statistics and master of science in biostatistics from Hasselt University, Belgium. He also has a master of science in mathematical statistics from Charles University, Czech Republic.

INLINE DILUTION:

An Agile Capability for Downstream Manufacturing

By Lindsey Daniel, PE, and Avril Vermunt

Lindsey Daniel

Avril Vermunt

As the global population demands faster and more affordable drugs, biopharmaceutical companies are continually trying to find ways to produce their drug products more economically and efficiently. Today, the competition and need for drugs are greater than ever before. Companies have been considering operational alternatives to reduce production costs and increase manufacturing rates [1, 2]. Inline dilution provides an agile solution by reducing long-term costs and increasing process flexibility.

Automated inline dilution has been a growing solution for downstream bioprocessing since the 1980s. Because upstream productivity increases titers, downstream processes have been targeted as potential bottlenecks that require more efficient and flexible solutions [3]. To address the increased need for a responsive capability in downstream processing, manufacturing facilities are implementing inline dilution for optimum throughput in their facilities [4].

Inline dilution is an added capability to chromatography systems that brings multiple process streams together to dilute or blend a solution at the point of use. Buffer and process solutions are mixed with water to meet the targeted final buffer composition. There are several advantages to inline dilution, but like any process, there are also challenges. Inline dilution systems can increase process efficiency and flexibility, but they require a design that reflects the individual process and the company's manufacturing philosophies. Every process has unique buffer profiles and chemistry requirements. Therefore, the key to successful processing using inline dilution is choosing a design option that best fits the specific process needs. Exploring different design options and understanding the pros and cons of each are critical aspects of inline dilution. This article offers an overview of inline dilution basics, the benefits and challenges of implementing an inline dilution system, and the types of designs implemented in today's manufacturing environments.

BUFFERS OR PROCESS SOLUTIONS?

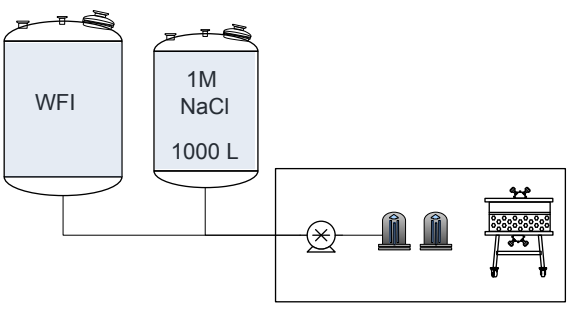
Chromatography is a powerful separation tool that takes advantage of different molecular attributes to separate target molecules and impurities. To optimize these techniques, conditions that promote specific chemical interactions must be controlled. These conditions include pH, conductivity, and other attributes [5]. For this reason, chromatography conditions are thoroughly screened and selected during development work [6]. Buffers are solutions containing a conjugate acid and base designed to maintain a specific pH during component additions, such as a small addition of a strong titrant [7]. Throughout the industry, chromatography process solutions are inappropriately called "buffers" even though they have no buffering capacity. For example, the sodium chloride (NaCl) solution from Figure 1 does not have capacity to resist the pH change because of a titrant addition. Nevertheless, all chromatography process solution compositions, buffers or not, are important to the unit's operation performance and product quality [8]. Therefore, dilution of process solutions and buffers is essential to secure the expected chromatography results.

MAJOR BENEFITS OF INLINE DILUTION

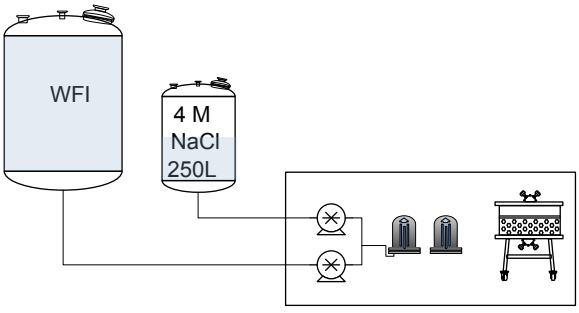
Inline dilution allows for more efficient and flexible design by blending or diluting multiple buffers to required concentrations at the point of use, resulting in smaller buffer batch sizes and thus a smaller facility footprint. Furthermore, if the hold times can be validated, concentrated buffers can also be used for multiple batches, which then results in reduced utility and equipment costs. Although long-term inline dilution usually results in cost savings, the up-front capital costs can be greater.

One of the greatest drivers for inline dilution is long-term cost savings. Implementing inline dilution usually results in a smaller facility footprint; materials usage optimization; waste reduction;

Figure 1: Inline dilution concept for a chromatography example.



Concept 1: Solutions delivered at use-strength to chromatography system.



Concept 2: Concentrate delivered at 4x strength and diluted at chromatography system.

and validation, labor, and utility savings [9]. The design utilizes buffer concentrates that supply the same amount of buffer as use-strength solutions with a fraction of the volume. If a company requires a 1000 liter (L) 1 molar (M) NaCl solution, it can implement a 250 L 4 M NaCl concentrate solution and dilute it at the point of use, as shown in Figure 1. That not only reduces the tank size but also allows companies to use disposable systems, which further cuts the costs of utilities and cleaning validation [10]. Even if disposables are not implemented, this process still results in utility savings because cleaning a 250 L tank requires less water, steam, and cleaning solutions than cleaning a 1000 L tank. Reduction of classified space for buffer preparation and storage operations saves in up-front capital as well as maintenance costs over time. Facilities that have space limitations will also benefit from the smaller footprint of concentrate vessels.

Reduced buffer volumes require fewer raw materials and consumables—such as preparation filters and samples—per manufacturing lot, and the savings accumulate over a manufacturing campaign. By cutting buffer preparation volumes, the filter area is also decreased because buffer filters are typically sized volumetrically for aqueous solutions. For volumes that span multiple preparations, using a concentrate that reduces the volume to a single preparation eliminates an equal number of samples. In cases where concentrates can be used for multiple operations or production lots, release testing is also reduced. Although it is easy to overlook these simple reductions, they collectively add up to long-term savings.

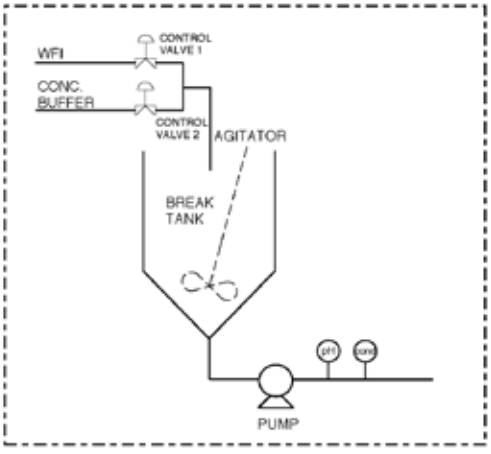
If buffer concentrates are used for multiple batches, companies also benefit from labor and utility savings because they do not need to make batches as often and systems require fewer cleaning cycles. For higher titer processes, cell culture media preparations may require a similar number and similar volumes of buffer preparations as lower titer processes. However, the trade-off for more productivity is an increased need for chromatographic cycles, and therefore more buffer volume and preparations [11]. In some cases, this burden requires that existing facilities make multiple buffer batches for multiple cycles in one product lot. If concentrates are used for multiple lots and require fewer preparations, a company can redirect the resources and labor that would have been required for preparation—that is, the setup and teardown time of buffer equipment, the sampling and testing of buffers, etc.—to more critical unit operations. That could represent a significant potential reallocation. Furthermore, utilities are also reduced when employing a multiple-lot buffer concentrate strategy because clean-in-place and sterilize-in-place processing of vessels is not required between process runs. Fewer cleaning cycles also can lead to a faster and more flexible manufacturing schedule.

The flexibility of inline dilution is another factor that appeals to many companies. Different concentrations of the same solution may be required throughout the process. This is especially common for companies that use a process platform to develop, scale-up, and deploy for multiproduct facilities [12]. With the implementation of inline dilution, companies that use a process platform create maximum flexibility for future products by validating and proving the makeup of multiple buffer concentrates. Buffer concentrates allow for one concentration to be made and then diluted to various use-strength concentrations. The concepts that allow for appropriate inline dilution are also applicable in a chromatography gradient elution where the dilution rate will change over time to achieve the product elution.

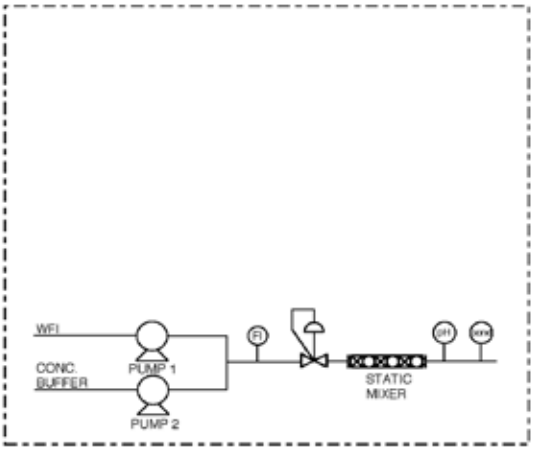
CHALLENGES

Inline dilution provides benefits but also presents challenges. One of the greatest challenges to inline dilution is maintaining and confirming the quality of the buffers. Inline blending/mixing, flow control, and inline feedback and monitoring must be robust

Figure 2: Inline dilution design examples.



Example 1: Break tank with control valves



Example 2: Inlet pumps in parallel with static mixer

Inline dilution provides an agile solution by reducing long-term costs and increasing process flexibility.

for inline dilution to be successful. Demonstrating and maintaining good mixing, whether in a vessel or inline, is a challenge in itself. However, mixing a solution in a vessel over a period of time with an agitator is often better understood than mixing inline, as fluid flows through in one pass. A robust design for inline mixing and confirmation of mixing is a major component to be considered in the design. A chromatography system can be validated for mixing by inline feedback control or through commissioning and validation data. Although good mixing and maintaining a controlled solution composition are important, many companies have found that slight variations in the concentration have no impact on the product [13]. To ensure inline dilution is feasible for the process, the allowed variation must first be determined in process development. Inline dilution usually requires pump turndown with lower flow rates because multiple streams are utilized. Depending on the type of pump implemented, greater turndowns can be harder to control and maintain across the full flow rate range.

The other major challenge with inline dilution is the up-front costs. Although the long-term costs of inline dilution will likely result in cost savings for some companies, companies, especially startups, may not have the up-front cash to implement such a solution. An existing facility requires greater modifications if inline dilution is implemented. The design usually requires at least two pumps, or at least three pumps if performing dilution and gradients, and will likely involve more inline instrumentation for control and monitoring. The startup time required for inline dilution is generally greater because inline dilution requires additional system characterization, including flow ratio capability, instrumentation accuracy, and system mixing.

Because the buffer chemistry is critical to unit operations, successful chromatography and product quality also depend on a firm understanding of the chemistry of buffer concentrates [14]. The concentrate recipe must account for common ion effects to ensure that the use-strength composition has the correct pH and conductivity for the process [15].

Although inline dilution may increase the number of process batches that can be made with one preparation of concentrate process solutions, multiple-lot buffers introduce additional challenges related to stability and the risk of contamination. Before multiple-lot buffer systems are implemented, extended hold-time validation and growth-promoting studies are required. Traditional quality programs may need to adapt to the testing and release of concentrates and may have to consider new approaches for the release of real-time use-strength solutions.

A final challenge involves material compatibility evaluation of the preparation and hold vessels or facility and system piping. Materials of construction for tanks, piping, and associated

components such as instruments, valving, and seals must be selected to withstand the conditions posed by concentrates, including pH levels and temperatures. Process concentrates should be assessed for extractables and leachables in single-use vessels and evaluated for corrosivity in stainless steel vessels [16, 17].

FUNDAMENTAL DESIGN CONSIDERATIONS

When designing an inline dilution system, stakeholders need to ask questions up front to determine the design best suited for their process. Here are a few examples of points to consider prior to implementing inline dilution:

- How many buffers does the process require?
- How many different concentrations of a single buffer are there?
- Are there varying flow rates? What are the flow rate ranges?
- How critical is the buffer composition to the process? Is gradient or step elution used?
- How accurate are the monitoring and control instruments?
- Are the use-strength buffer and concentrate recipes well understood? Will concentrates pose solubility or viscosity issues? Are there shifts in pH after dilution? Is the dilution exothermic?
- Do any buffers or concentrates require specialty construction materials? Are there corrosive buffers that need additional safety assessments, such as double-contained piping? Do any require a higher alloy metal for vessels, piping, and components?

These questions will drive the design as well as the monitoring and control strategy.

ENGINEERING DESIGN

Design options for inline dilution systems include a variety of system components, control options, and inlet supply flow paths. Some systems use multiple pumps to blend concentrated buffer with water, whereas others use blending tanks and inlet control valves, as shown in Figure 2.

When designing a system with inline dilution, five key design components need to be explored:

- Mixing, including piping and optional static mixer and/or break tank
- Pumps, including types, accuracy, and turndown
- Flow measurement for monitoring and/or control
- pH and/or conductivity for measurement and/or control
- Control valves

Example 1 in Figure 2 shows a break tank that provides hydrostatic decoupling of the upstream inlet supplies and combined process stream through the chromatography system. This type of break tank uses an agitator and sometimes baffles, which help with mixing solutions but result in a costlier design. The residence time in the tank helps balance the dilution but can increase buffer losses [18]. A 100 liters-per-minute (LPM) system that has a 5- to 10-second residence time will result in an approximately 30 L break tank. If it is assumed that piping volume is approximately 20 L, a 5 system-volume flush would result in 250 L of buffer use rather than 100 L of buffer use without the break tank. Over multiple uses, that additional 150 L of buffer can be costly. This is another example of why a company needs to discuss the points to consider at the beginning of their design and business strategy implementation.

Table 1: Pros and cons of pumps used for inline dilution.

Type of Pump	Pros	Cons
Diaphragm	• Easy maintenance • Prevents backflow • Can be self-priming • Low shear	• Pulsing/lack of precise flow control • Flow control can be improved by multiple pump heads, but that adds cost
Peristaltic	• Disposable/easy to clean • Feed rate is less affected by varying pressures	• Pulsing/lack of precise flow control • Can trap air • Pressure limitations (back pressure from column)
Rotary lobe	• Flow control is more precise and efficient • Low shear	• Hard to clean/maintain • Less efficient when operated at high pressure • Prone to slip

Achieving a homogenous solution is a critical performance requirement for inline dilution and can be further challenging based on the miscibility of process solutions, especially at higher concentrations. Processes that have greater viscosity may benefit from a break tank that can use baffles or an agitator, but an inline mixer is sufficient for most systems.

Simple things that can have a long-term impact, such as pipe hold-up volume, are frequently overlooked [19]. Designing a system that assesses dead legs is critical. Several options for valves minimize dead legs, but best practices include minimizing system hold-up volumes and reducing dead-leg distances. An example of a design component able to achieve this is block body valves. The design, performance, and cost should be balanced to achieve the appropriate system for the intended use. Systems that use pumps require robust flow accuracy, and the type of pump selected is therefore key to the system design [20]. Positive displacement pumps are generally preferred for chromatography systems because they pose low shear risk to the product. The main types of pumps used for large-scale chromatography are diaphragm, peristaltic, and rotary lobe [21]. The pros and cons of various pump types are highlighted in Table 1.

When utilizing pumps for flow control, the varying inlet pressures from the upstream fluid pose a challenge. Example 2 in Figure 2 shows that a back pressure regulator can be installed to prevent slippage through pumps and to help control flow. Rotary lobe pumps provide great flow control; however, if there is a high pressure differential across the pump, there is likely to be some

Table 2: Control modes used for inline dilution.

Type of Control Mode	Pros	Cons
Open-loop ratio control	• Simplest design • Simple speed set point automation	• No reaction to actual conditions • Actual flow dependent on back pressure
Total-flow feedback with ratio control	• Ensures total flow-rate range is achieved	• Actual flow dependent on back pressure observed by each pump
Flow feedback control	• Ensures flow parameters for each channel as well as total flow are achieved	• Requires more instrumentation and control components • May require fine-tuning depending on turndown
Conductivity feedback with ratio or flow control	• Achieves process stream condition specifically required by unit operation	• Requires precise conductivity instrumentation • Temperature compensation needs to be considered
pH feedback with ratio or flow control	• Achieves process stream condition specifically required by unit operation	• Requires precise pH instrumentation • May require special handling as pH probes may be susceptible to process solutions (especially at extreme pH) • Concentrates must account for dilution and salt effects on pH • Standardization practices and managing drift should be considered

slip. Peristaltic pumps are a great option because they require no cleaning, but the tubing usually has a low pressure rating. Diaphragm pumps are easy to maintain, but they offer less-efficient flow control due to pulsing. Flow control can be improved by using multiple pumps, but this strategy adds cost. As more applications look to disposable flow paths, understanding pump technology and performance becomes more time-sensitive because the technology is rapidly changing in this area.

The three key operating parameters to control and/or monitor for inline dilution are flow, pH, and conductivity. Flow control may be sufficient to create a process stream with the desired pH and conductivity and can be controlled through pumps or control valves, as shown in Figure 2. Confirming good mixing and proper flow control can be achieved by monitoring pH and conductivity. When instrumentation is selected, the design should consider the chromatography solutions' attributes. For instance, pH may need to be within ±0.2 units and conductivity may need to be within ±10% of the process target for most applications. For cases where parameters for pH and conductivity need to be more precise, measurement tolerances of ±0.05 pH units and ±2% conductivity target may be implemented.

Buffer concentrates require lower inlet flow rates because there are multiple streams. For example, a 4x buffer of NaCl that has an outlet flow rate of 100 LPM will use an inlet flow rate of 25 LPM of 4x NaCl and 75 LPM of purified water. This lower flow rate of 25 LPM could be affected by flow-through of the higher flow pump, making it harder to achieve precise flow control and, therefore, dilution ratios. A back pressure regulator can be used downstream of the pump to prevent flow through the pumps, but it does not always resolve the lack of flow accuracy. A flow meter is usually placed downstream of the pumps to monitor the flow and can tie into the pumps or control valves to provide closed-loop feedback control. Flow-meter accuracy should ensure that typical flow rate operating ranges are ±5%–10%, but acceptable operating ranges may be tightened depending on process needs.

Finally, more advanced designs address the use of more than two or three inlet supply streams being blended and controlled to deliver use-strength solutions to chromatography unit operations. These systems incorporate multiple pumps of various sizes, which add cost but meet performance and quality expectations and provide flexibility to address a large range of buffer recipes [22].

AUTOMATION, MONITORING, AND CONTROLS

One of the biggest challenges with utilizing multiple pumps is balancing the flow to minimize overshoot and provide a continuous flow of concentrate and water within a specified range. If the flow rate varies, a slower-acting proportional–integral–derivative control loop may be required so that the system keeps the process solutions in a steadier range rather than oscillating significantly. An acceptable oscillation must be within the operating range of key operating parameters, such as ±0.2 pH units or ±10% for conductivity. The controller response time should be balanced with the overall ramp to ensure concentrate and water are not wasted. A typical ramp should be less than a few minutes, but the duration depends on the flow-rate set point relative to the overall range.

The control of inline dilution generally comes with two options: inline feedback control and ratio control. Both options involve monitoring of pH, conductivity, or flow to confirm the buffers are in range. The pros and cons of these options are highlighted in Table 2.

The type of control is generally based on how much risk is acceptable. Control modes for inline dilution should consider the distance of the normal operating range from the critical design range, and they may include pH and conductivity monitoring as an additional engineering control to verify that process stream composition is as expected.

Open-loop ratio control does not include any feedback control and is based on commissioned or standardized ratios. If a 4x concentrate were used, the pumps would run at a flow ratio of 3:1 to achieve the required use-strength buffer concentration. Open-loop ratio control is a cheaper option, especially when a system is running at high flow rates relative to design range, which are easier to control. The main concern with ratio control is that if the buffer pH or conductivity goes out of specification, the ratio will not automatically adjust. The system may be programmed to activate an alarm, and manual intervention may be required. Being out of specification could pose a risk to the product if the deviation substantially affects the quality or yield. However, some processes may accept varying buffer concentrations without product impact [23]. For example, for many chromatography cleaning steps, the cleaning solution has a design range that is much wider than the operating range, allowing for more variability to be accepted by the process. The acceptable degree of variability should be considered for each process step.

Total-flow feedback with ratio control has enhanced automation and therefore generates a lower risk of the buffer concentrate being out of specification, as long as concentrates are well characterized and have accounted for any pH shifts upon dilution [24]. Total-flow feedback with ratio control is likely the best option for risk-adverse companies and in situations when processes require tight process stream composition. It is impossible to completely guarantee that a process will never go out of range; however, with inline controls and proper tuning, the system can adjust accordingly and have good control over the process. Alarms can be used to alert operators when the process deviates from its specific range. This design is generally more expensive and requires automation and control tuning, which results in greater startup and commissioning investment. Not all systems require feedback control. When considering whether to use it, companies should evaluate the amount of risk they are willing to take, how confident they are in commissioning the system, and their requirements for concentration.

Regardless of the control strategy adopted, automated inline dilution provides benefits such as [25]:

- Eliminating risk of release sample contamination or failure
- Generating trends to support validation and continuous improvement
- Supporting ongoing buffer preparation and downstream process monitoring
- Enabling online, real-time release

TESTING AND PERFORMANCE

When implementing inline dilution, several areas should be addressed before engineering and operational decisions are finalized. Objectives for the system that will meet expected performance should be based on process definitions. Once the objectives are clear to decision makers and stakeholders, further details can be evaluated for proper selection. The criteria for performance should drive design and be revisited periodically through the design and execution milestones.

Once a system has been engineered and assembled, it should be tested to ensure the performance meets expected requirements [25]. Commissioning and qualification tests should be developed in accordance with the system requirements and risk assessment. These tests could include simple checks of the system components such as pump curves and flow control that cover the full range of the respective operating parameters. If needed, a more complex set of tests could include blending and dilution of concentrates with analysis of the subsequent resulting output response—for instance, conductivity, pH, or ultraviolet absorbance. Output trends can be analyzed using linear least squares and normalized to provide a percent error. Finally, when specific operational conditions are considered to be high risk, a process qualification can include tests for those conditions. For example, it may be prudent to run tests to verify that the system accounts for pKa changes from concentrates or heat of dissolution when diluted [23]. Another test might evaluate whether the system demonstrates the critical control needed to create a gradient for a chromatographic elution.

These tests may not be relevant for every system, especially when mathematical models inform design, or when duplicating systems already utilized in a facility [26]. A family approach to commissioning and qualification may be taken for functional performance, or a design qualification may be all that is necessary once system designs have been previously implemented and fully characterized. To understand what to test and the performance needed, it is helpful to conduct a risk assessment that includes experience with the design and the criticality of buffer composition to the process. This assessment can also help feed into defense-in-depth activities that inform deviation investigations undertaken during manufacturing.

CONCLUSION

The bioprocessing industry is becoming more agile with increased design and technology solutions. As manufacturers find ways to increase titers, the bottleneck is shifting to downstream operations such as buffer preparation and chromatography. As long as biopharmaceutical processes continue to intensify, scale-up, and scale-out, inline dilution will be a useful tool for avoiding bottlenecks in solution preparation and decreasing buffer hold capacity. Although there are many questions to address when implementing inline dilution, careful consideration of system design, components, instrumentation, and control strategies can ensure successful integration. The use of inline dilution in chromatography unit operations optimizes manufacturing throughput by providing an agile capability in downstream manufacturing.

References

1. Kelley, Brian. "Very Large Scale Monoclonal Antibody Purification: The Case for Conventional Unit Operations." *Biotechnology Progress* 23, no. 5 (September–October 2007): 995–1008. https://doi.org/10.1021/bp070117s
2. Noble, John. "The Capacity Challenge—Shifting Paradigms in Biopharmaceutical Facility Development: Point of View." *Pharmaceutical Engineering* 37, no. 6 (November 2017): 50–1.

3. Langer, Eric. "Trends in Downstream Bioprocessing. Special Coverage: Purification and Separation." *BioPharm International* 26, no. 9 (September 2013). http://www.biopharminternational.com/trends-downstream-bioprocessing?pageID=2

4. Brooks, Bob, Jonathan Dakin, Clare Simpson, and Linda Wilson. "BioPhorum Operations Group Technology Roadmapping, Part 3: Enabling Technologies and Capabilities." BioProcess International, April 17, 2017. https://bioprocessintl.com/manufacturing/single-use/biophorum-operations-group-technology-roadmapping-part-3-enabling-technologies-capabilities

5. Karow, Anne R., Sven Bahrenburg, and Patrick Garidel. "Buffer Capacity of Biologics—From Buffer Salts to Buffering by Antibodies." *Biotechnology Progress* 29, no. 2 (March–April 2013): 480–92. https://doi.org/10.1002/btpr.1682

6. Faraji, Naeimeh, Yan Zhang, and Ajay K. Ray. "Impact of Operating Conditions on Chromatographic Column Performance: Experimental Studies on Adsorption of High-Value Minor Whey Proteins." *AIMS Bioengineering* 4, no. 2 (2017): 223–38. https://doi.org/10.3934/bioeng.2017.2.223

7. Tindall, G. William. "Mobile-Phase Buffers, Part II—Buffer Selection and Capacity." *LCGC North America*, December 2002, 1114–8.

8. Borg, Niklas, Yan Brodsky, John Moscariello, Suresh Vunuum, and Ganesh Vedantham. "Modeling and Robust Pooling Design of a Preparative Cation-Exchange Chromatography Step for Purification of Monoclonal Antibody Monomer from Aggregates." *Journal of Chromatography* A 1359 (September 2014): 170–81. https://doi.org/10.1016/j.chroma.2014.07.041

9. Patterson, Brandon J. "A Closer Look at Automated In-Line Dilution." *BioPharm International* 22, no. 10 (October 2009). http://www.biopharminternational.com/closer-look-automated-line-dilution

10. Frank, Gregory T. "Transformation of Biomanufacturing by Single-Use Systems and Technology." *Current Opinion in Chemical Engineering* 22 (2018): 62–70. https://doi.org/10.1016/j.coche.2018.09.006

11. Challener, Cynthia A. "Behind the Scenes with Buffers." *BioPharm International* 28, no. 2 (February 2015). http://www.biopharminternational.com/behind-scenes-buffers

12. Shukla, Abhinav A., Brian Hubbard, Tim Tressel, Sam Guhan, and Duncan Low. "Downstream Processing of Monoclonal Antibodies—Application of Platform Approaches." *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences* 848, no. 1 (March 2007): 28–39. https://doi.org/10.1016/j.jchromb.2006.09.026

13. Lee, So-Hee, Jung-Soo Kim, and Chan-Wha Kim. "Optimization of Buffer Conditions for the Removal of Endotoxins Using Q-Sepharose." *Process Biochemistry* 38, no. 7 (2003): 1091–8. https://doi.org/10.1016/S0032-9592(02)00243-1

14. Tindall, G. William. "Mobile-Phase Buffers, Part III—Preparation of Buffers." *LCGC North America*, January 2003, 28–32.

15. Challener, Cynthia A. "Improving Process-Scale Chromatography." *BioPharm International* 29, no. 11 (November 2016): 14–7. http://www.biopharminternational.com/improving-process-scale-chromatography

16. Ding, Weibing, Gary Madsen, Ekta Mahajan, Seamus O'Connor, and Ken Wong. "Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing." *Pharmaceutical Engineering* 34, no. 6 (November–December 2014): 74–85.

17. Lopolito, Paul, Dijana Hadziselimovic, Amanda Deal, and Amy Thanavaro. "Cleaning Buffer Preparation Tank Air–Liquid Interface Rings." *Pharmaceutical Engineering* 36, no. 1 (January–February 2016): 66–72.

18. Faanes, Audun, and Sigurd Skogestad. "Buffer Tank Design for Acceptable Control Performance." *Industrial & Engineering Chemistry Research* 42, no. 10 (May 2003): 2198–208. https://doi.org/10.1021/ie020525v

19. Dolan, John W. "Reducing Column Diameter in Gradient Elution—A Case Study." *LCGC North America*, December 2000, 1228–32.

20. Majors, Ronald E., Howard G. Barth, and Charles H. Lochmueller. "Column Liquid Chromatography." *Analytical Chemistry* 54, no. 5 (1982): 323–63. https://doi.org/10.1021/ac00242a028

21. Markarian, Jennifer. "Pumping Fluids in Biopharmaceutical Processing." *Biopharm International 30*, no. 2 (February 2017): 26–9. http://www.biopharminternational.com/pumping-fluids-biopharmaceutical-processing-2

22. Fabbrini, Davide, Carlo Simonini, Joakim Lundkvist, Enrique Carredano, and Debora Otero. "Addressing the Challenge of Complex Buffer Management: An In-Line Conditioning Collaboration." *BioProcess International*. December 13, 2017. https://bioprocessintl.com/downstream-processing/separation-purification/addressing-the-challenge-of-complex-buffer-management-an-in-line-conditioning-collaboration

23. Tindall, G. William. "Mobile-Phase Buffers, Part I—The Interpretation of pH in Partially Aqueous Mobile Phases." *LCGC North America*, November 2002, 1028–32.

24. Carredano, Enrique N., Roger Nordberg, Susanne Westin, Karolina Busson, Tomas M. Karlsson, Torbjörn S. Blank, Henrik Sandegren, and Günter Jagschies. "Simplification of Buffer Formulation and Improvement of Buffer Control with In-Line Conditioning (IC)." In *Biopharmaceutical Processing: Development Design and Implementation of Manufacturing Processes*, edited by Günter Jagschies, Eva Lindskog, Karol Lacki, and Parrish M. Galliher, 513–525. Amsterdam: Elsevier, 2018. https://doi.org/10.1016/B978-0-08-100623-8.00027-X

25. Castillo, Francisco C., Brendan Cooney, and Howard L. Levine. "Biopharmaceutical Manufacturing Process Validation and Quality Risk Management." *Pharmaceutical Engineering* 36 no. 2 (May–June 2016): 82–92.

26. Kaltenbrunner, Oliver, and Jungbauer Alois. "Simple Model for Blending Aqueous Salt Buffers—Application to Preparative Chromatography." *Journal of Chromatography* A 769, no. 1 (May 1997): 37–48. https://doi.org/10.1016/S0021-9673(97)00161-1

Additional Resources

Baek, Youngbin, Deyu Yang, Nripen Singh, Abhiram Arunkumar, Sanchayita Ghose, Zheng Jian Li, and Andrew L. Zydney. "pH Variations During Diafiltration due to Buffer Nonidealities." *Biotechnology Progress* 33, no. 6 (November 2017): 1555–60. https://doi.org/10.1002/btpr.2544

Min, Byeong Jo, Seong Woo Kang, Yoon Seok Song, Jong Ho Lee, Seung Heon Lee, Chulhwan Park, Seung Wook Kim, and Chan-Wha Kim. "Verification of the Final Anion Exchange Chromatography in the r-hGH Manufacturing Process." *Biotechnology and Bioprocess Engineering* 15, no. 3 (June 2010): 488–96. https://doi.org/10.1007/s12257-009-3053-9

Thömmes, Jörg, and Mark Etzel. "Alternatives to Chromatographic Separations." *Biotechnology Progress* 23, no. 1 (2007): 42–45. https://doi.org/10.1021/bp0603661

Van Beijeren, Peter, Peter Kreis, and Tim Zeiner. "Ion Exchange Membrane Adsorption of Bovine Serum Albumin: Impact of Operating and Buffer Conditions on Breakthrough Curves." *Journal of Membrane Science* 415–416 (October 2012): 568–76. https://doi.org/10.1016/j.memsci.2012.05.051

Acknowledgments

The authors would like to thank Madhu Raghunathan, Enrique Carredano, Chris Krein, and the *Pharmaceutical Engineering* Editorial Review Board for their thoughtful review of this article. A special thanks to Josh Van Kirk for his review and support, and for introducing the authors to each other.

About the authors

Lindsey Daniel, PE, is a Senior Process Engineer at the Takeda Pharmaceuticals Brooklyn Park, Minnesota, facility, where she focuses on the downstream operations. She has been involved with ISPE since she was a student at Virginia Polytechnic Institute and State University, where she graduated in 2012 with a degree in chemical engineering. Lindsey currently sits on the ISPE Midwest Chapter Board and serves on the Young Professionals Committee (which she chaired in 2013–2014) and the Biotech Steering Committee. She has been an ISPE member since 2012.

Avril Vermunt is a Program Manager for Connected Biomanufacturing at GE Healthcare. She loves lending her large-scale bioprocess expertise to help colleagues industrialize process solutions that optimize efficiency and productivity. Her contributions have led to several successful tech transfers globally, including Amgen Singapore's Next-Generation Biomanufacturing facility. Prior to her time with Amgen's process development organization, Avril worked in manufacturing and process engineering at Diosynth. She currently serves as an ISPE Rocky Mountain Chapter Board Director and the Facility of the Year Award (FOYA) Committee Cochair. Avril has been an ISPE member since joining the student chapter at North Carolina State University, where she received her degree in chemical engineering. She has been an ISPE member since 1998.

INDEX

CLASSIFIEDS

ARCHITECTS, ENGINEERS, CONSTRUCTION

CRB
1251 N.W. Briarcliff Parkway
Suite 500
Kansas City, MO 64116 US
+1 816-880-9800

EI Associates
8 Ridgedale Avenue
Cedar Knolls, NJ 07927 US
+1 973-775-7777

Jacobs
Three Tower Bridge
2 Ash Street
Conshohocken, PA 19428
US
+1 610 238 1000

Pharmadule Morimatsu AB
DanvikCenter 28
SE-13130 Nacka Sweden
+46 (0)8 587 42 000

ASEPTIC PROCESSING

TSI
500 Cardigan Road
Saint Paul, MN 55126-3903
US
+1 800-680-1220

CONSTRUCTION

Fluor Corporation
100 Fluor Daniel Drive
Greenville, SC 29607 US
+1 864-281-4400

CONTRACT SERVICES

Ultraclean Electropolish Inc
1814 Sunny Dr.
Houston, TX 77093 US
+1 281-442-2208

ENGINEERING AND DESIGN SERVICES

BPE Biopharma Engineering
Cork office (HQ):
NSC Campus, Mahon, Cork
Ireland
Dublin Office: Unit D,
Westland Business Park
Willow Road
Dublin 12 Ireland
+353 212307120

INFORMATION TECHNOLOGY

COPA-DATA
Karolingerstrasse 7b
Salzburg Austria 5020
+43 662 43 10 02-0

Kneat Solutions
Unit 7, Castletroy Business
Park,
Plassey Park Rd, Limerick,
Limerick V94 KW28
Ireland
+353 61-203826

INSTRUMENTATION

Endress + Hauser AG
Kaegenstrasse 2
4153 Reinach BL
Switzerland
+41 61 715 7700

MACHINERY DESIGN AND CONSTRUCTION

Gericke AG
Althardstrasse 120
CH-8105 Regensdorf
Switzerland
+41 44 871 36 36

PROCESSING AND MANUFACTURING

Sartorius Stedim Biotech
GmbH
August-Spindler-Straße 11
37079 Göttingen Germany
Phone: +0049-551-3080

PURE WATER AND PROCESS ANALYTICS

Mettler-Toledo, LLC
900 Middlesex Turnpike,
Building 8
Billerica, MA 01821 US
+1 800-352-8763

PUMPS

Fristam Pumps USA
2410 Parview Road
Middleton, WI 53562 US
+1 800-841-5001

SIZE REDUCTION

Sturtevant Inc.
348 Circuit Street
Hanover, MA 02339 US
+1 800-992-0209

SOFTWARE SIMULATION AND PROCESSING SYSTEMS

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076 US
+1 908-654-0088

VALIDATION SERVICES

CAI
652 N. Girls School Road
Indianapolis, IN 46214 US
+1 317-271-6082

Ellab Inc.
303 E. 17th Ave.
Suite 10
Denver, CO 80203 US
303-425-3370

VALVES

SAMSON CONTROLS Inc.
USA
5 Earl Court, Suite 180
Woodridge, IL 60517 US
Tel +1 (0) 815 609 3844
Fax: +1 (0) 815 609 3836

WATER/STEAM SYSTEMS

BWT Pharma & Biotech Inc.
417-5 South Street
Marlborough, MA 01752 US
+1 508-485-4291

SPIRAX SARCO
Charlton House
Cheltenham
Gloucestershire
GL53 8ER
United Kingdom
Tel +44 (0)1242 521361

Stilmas SpA
Viale delle Industrie, 14
Settala (MI) 20090 Italy
+39 02 9508061

WATER TREATMENT AND PURIFICATION

Elettracqua Srl
Via Adamoli 513
16165 Genoa Italy
+39 010 8300014

PLEASE SEE THE ADS FOR EACH OF OUR ADVERTISERS IN THIS ISSUE

BACKING BIOSIMILARS

By Stephanie Sutton

Initially, the American College of Rheumatology urged caution around the use of biosimilars. Information about the manufacturing process for a branded biologic is proprietary; a biosimilar manufacturer will not have access to the details of the process, so how could they guarantee their product would be the same? It is now well accepted by the scientific community that biosimilars are safe, and in February 2018 ACR published a white paper, "The Science Behind Biosimilars: Entering a New Era of Biologic Therapy," [1] which aims to educate ACR members about and support the use of biosimilars.

"Increased real-world experience with biosimilars in Europe, new data including a prospective switching study (NOR-SWITCH), and increasing clarity around FDA policies (naming, switching) have all served to increase confidence in biosimilars," explains Doug White, one of the authors of the paper and ACR Board of Directors member at large.

The paper explains that a biosimilar and its reference product must have identical amino acid sequences and must be "highly similar… notwithstanding minor differences in clinically inactive components" in many analytical assays. "The biosimilar must be equivalent to its reference product in clinical trials assessing pharmacokinetics/pharmacodynamics and clinical efficacy and must have comparable safety and immunogenicity to its reference product," says Jonathan Kay, Professor of Medicine and Timothy S. and Elaine L. Peterson Chair in Rheumatology at the University of Massachusetts Medical School in Worcester, and another author of the paper. "Thus, any differences in manufacturing processes between an approved biosimilar and its reference product do not result in 'clinically meaningful differences.' Patients receiving treatment with an approved biosimilar should not experience any difference in response than that which would be expected when using another lot of the branded reference product."

Despite the fact that biosimilars are safe and effective, uptake in the US has been slow. According to Angus Worthing, a doctor with Arthritis and Rheumatism Associates and Chairman of the American College of Rheumatology's Government Affairs Committee, "Only two of the six FDA-approved biosimilars for rheumatologic diseases are available; the biggest obstacle is patent disputes and manufacturer decisions that prevent their use. One important long-term barrier is insurance coverage. Ironically, despite being priced 15% to 30% lower than reference products, we're seeing some biosimilars kept off formularies."

This appears to be a result of the US drug distribution system in which medication formularies are dictated by interactions between pharmacy benefits managers (PBMs) and manufacturers. The larger the rebate or price concession paid by manufacturers to PBMs, the more likely a drug will be on formulary, and a lower-priced drug may result in a lower rebate payment. "Biosimilars may be kept off formularies precisely because they are less expensive! This is paradoxical and may prevent biosimilars from realizing their promise of lower prices and increased access to treatment," says Worthing.

To help patients get better access to biosimilars, Worthing would like to see the FDA quickly finalize its interchangeability approval pathway so that manufacturers can perform clinical trials to demonstrate safety and efficacy of alternating back and forth between reference products and biosimilars. In addition, he believes it would be beneficial for Congress to reform the drug distribution system to create more transparency in the rebate system. Boosting the supply of biosimilars—including interchangeable biosimilars—and improving incentives to bring them onto formularies should improve access to biosimilars and help lower biologic drug prices.

This article was originally published as "A New Supporter" in the May 2018 issue of *Medicine Maker*.

About the author

Stephanie Sutton says, "Making great scientific magazines isn't just about delivering knowledge and high-quality content; it's also about packaging these in the right words to ensure that someone is truly inspired by a topic. My passion is ensuring that our authors' expertise is presented as a seamless and enjoyable reading experience, whether in print, in digital, or on social media. I've spent seven years writing and editing features for scientific and manufacturing publications, and in making this content engaging and accessible without sacrificing its scientific integrity. There is nothing better than a magazine with great content that feels great to read."

Reference

1. Bridges, S. Louis Jr., et al. "The Science Behind Biosimilars: Entering a New Era of Biologic Therapy." *Arthritis and Rheumatology* 70, no. 3 (March 2018): 334–44. https://www.rheumatology.org/Portals/0/Files/ACR-White-Paper-Science-Behind-Biosimilars.pdf

E-Val Pro

Smart Thermocouple System

Validation Solutions

RETIRING YOUR OLD THERMOCOUPLE SYSTEM?

- Lightweight and Compact, 6 lbs.
- Plug and Play USB thermocouples
- RH - CO_2 - Pressure
- Onboard battery
- Up to 40 channels per module
- Network or stand-alone usage
- Touch Screen Graphical Display
- NIST traceable thermocouples

Sensor Flexibility *with the new E-Val Pro interface to easily combine with TrackSense® Pro wireless sensors*

Customizable feed-throughs for thermocouple applications

For more information contact:
usa@ellab.com | 303.425.3370

ellab.com

OLSA
MASCO GROUP

OLSA: advanced processing solutions for biopharmaceutical and cosmetic industry.

Almost 7.000 units installed on liquid, semisolid and solid applications in 5 continents to more than 1.500 customers.

WWW.OLSA.COM