PHARMACEUTICAL ENGINEERING®

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CONTINUOUS MANUFACTURING

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Global Acceptance of Continuous Manufacturing: Regulatory Aspects

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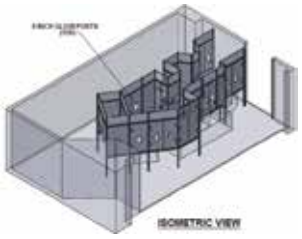

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CONTINUOUS MANUFACTURING

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By Joanne R. Barrick, RPh


Joanne R. Barrick, RPh

Remembering Pharma's "Why"

Remembering the "why" of our pharma industry is so important and, for me, also very personal. My sister Linda was 69 and her four grandchildren were the light of her life. In November 2017, she was diagnosed with appendix cancer (a rare cancer, closely related to colon cancer). After four months of nasty chemotherapy, Linda entered hospice care and died the next month. Previously, my mother passed due to colon cancer, a mere 18 days following her diagnosis. It is these tragic losses, and similar stories of so many others, that remind me just how much work is yet to be done.

The pharma industry has made significant progress toward stories that don't end like Linda's and my mom's, but so many still do. I felt, and in many ways still do, that I/we failed them, but there is now so much more hope and optimism, not only for treating cancer but also other rare, previously untreatable illnesses. Undoubtedly, we have all been touched by stories like mine and can utilize it as our "why" to fuel us when the path seems long and filled detours. I am excited about potential "quantum leaps" that potentially will occur soon. I hope that the newfound ways of working (an actual positive from the pandemic) will continue to facilitate solutions at a previously unprecedented pace, including accelerated commercial availability.

CONTINUOUS MANUFACTURING: A PATH FORWARD

One path toward accelerated commercialization is continuous manufacturing. While continuous manufacturing is most commonly utilized for dry products, there are also commercialized small molecule API manufacturing processes and commercialized continuous large molecule manufacturing steps. Continuous manufacturing can also accelerate manufacturing process development as the impact of varying many parameters can been studied in a single run. The equipment footprint is relatively small and often the commercial version is identical to the development equipment: alleviating scaleup and technology transfer concerns. These innovative approaches have challenged scientists to design new control strategies. In the case of dry products, this results in even greater quality assurance for individual dosage units, as well as the potential for real-time release.

ISPE has held numerous well-attended continuous manufacturing workshops over the years, with the last one held virtually in June 2020. Each one has highlighted advances in innovation and control strategy design. The ISPE Continuous Manufacturing Team, led by Co-chairs Gabriella Dahlgren, Senior Manager, Strategy Deployment and Excellence, PQM, Janssen Supply Group, and Wyatt J. Roth, Director, Small Molecule Development, Eli Lilly and Company, continues to be one of ISPE's most impactful Product Quality Lifecycle Implementation (PQLI®) groups. The team addresses both technical and regulatory related challenges. PQLI is led by Christine M.V. Moore, Executive Director, Organon, and also features project teams

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working on process validation, knowledge management, and ICH Q12 implementation. I view these as knowledge spaces where ISPE is leading the way.

RELIABLE SUPPLY

In addition to its roles in accelerated product development and enhanced quality assurance, continuous manufacturing may also have a role in assuring reliability of product supply. As evidenced by the COVID-19 pandemic, there are numerous vulnerabilities in our supply of essential medicines. While converting some older product processes to continuous manufacturing offers numerous advantages, there are numerous impediments such as development costs and enhanced regulatory expectations for conversion to new process. An in-depth look at advantages and disadvantages, other options, and potential areas of incentives are outlined in "DAF ACT Initiative to Support Domestic Manufacturing of Active Pharmaceutical Ingredients" [1], issued by ISPE in December 2020. The pandemic also unveiled another roadblock to reliable supply: process consumables such as protective equipment and filters, which also must be addressed.

Progress with treatment of Alzheimer's disease, cancer, and rare diseases awaits and continuous manufacturing is certainly not the only progressive manufacturing option we will utilize. This is an exciting time to be part of the pharma industry. Due to the response to COVID-19, I have never been prouder of our ISPE members and the industry as a whole. We have probably all experienced stories like those of my sister and mother. As we carry our learnings forward—with a focus on new technologies, enhanced supply reliability, and improved collaboration—please be energized by your "why."

BUILDING THE WORKFORCE OF THE FUTURE

Due to continued media coverage of efforts to combat COVID-19, there may never be a better time to attract emerging talent to our industry. I would like to challenge each of you to introduce just one student to the pharma industry, perhaps with an invitation to an ISPE Chapter or Affiliate event or a student membership.

If each of us does just a little, we can have a huge impact in addressing the anticipated talent shortage in our industry. We (ourselves and our families) will all be patients at one time or another. We can leave a lasting legacy by helping to develop our leaders of tomorrow. Thank you and stay safe.

REFERENCE

1. International Society for Pharmaceutical Engineering. "DAF ACT Initiative to Support Domestic Manufacturing of Active Pharmaceutical Ingredients." https://ispe.org/initiatives/regulatory/daf-act-initiative-support-domestic-manufacturing-active#

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By Alice Redmond, PhD


Alice Redmond, PhD

Making Mentoring and Recognition More Meaningful

Organizations wanting to ensure the well-being and growth of their employees need to invest in robust mentorship and recognition programs. Mentoring has played a key role in my career development. In the 1990s and early 2000s, I worked in Novartis and engineering services companies where I was part of informal mentoring groups with some senior directors and trusted collaborators across the industry. This was driven by my eagerness to do different things and gain knowledge.

As part of these programs, I had open discussions that guided me through difficult and complex business situations. Over the years, I have added other mentors, which isn't unusual—it's natural to have different mentors at different stages of your career. This process gave me substantial insights into knowledge leadership and business strategy and has helped me on my career journey.

SUCCESSFUL MENTORING

Respect, trust, and commitment are three integral, interdependent aspects of a successful mentoring relationship, which is a two-way process based on shared interests, areas of awareness, focus, challenges, and career objectives. The natural outcome of any relationship based on trust is a feeling of profound appreciation for each other's skill, knowledge, experience, abilities, qualities, and achievements.

For a mentoring relationship to drive success, it's critical that this respect be mutual. Mentees should realize that the mentor has their best interests in mind when providing guidance. Mentors should believe that their mentee has the utmost interest in skills development and is genuinely open to guidance and self-reflection. They must treat the information shared by the mentee with careful consideration and confidentiality. Where there is trust and respect, commitment comes naturally. When the mentor and mentee commit to making the most of each other's time and talent, their bond becomes stronger, bolstering the mentee's professional development.

The ISPE WIP Mentor Circles are a really good example of a successful mentoring program. The global circles are a phenomenon, growing all the time. They have helped the continued development of many careers in the pharma industry.

RECOGNITION PROGRAMS

Hand in hand with mentoring programs are recognition programs. In fact, mentoring can be looked at as an informal recognition program to recognize and encourage the potential talents of an individual. Employee recognition programs are critical to the ongoing success of companies and are key to employee satisfaction. If you want to keep your employees happy, engaged, and productive you need to let them know that their hard work is recognized and appreciated.

Public recognition ideas may include a "shout-out" on company communications or weekly newsletter, congratulatory emails, or giving kudos on LinkedIn. Private recognition can include feedback in a one-on-one meeting, handwritten notes, or home delivery of a token of appreciation. Promotion and recognition can be achieved via a new job title, ambassador opportunity, by asking for their help or opinion, or assigning them a special project beyond their regular responsibilities. Financial awards such as pay rises or bonuses are noteworthy, but it has been proven that the intangibles are often much more important to an individual. They definitely are to me!

Good mentorship is particularly important in today's challenging environment, where volatility, uncertainty, complexity, and ambiguity are increasing. During the pandemic, employees at all levels are filled with anxiety. This affects their ability to be effective in their job and personal well-being. Investing in employees under these difficult circumstances through mentoring and recognition programs is pivotal for employee well-being, engagement, and development. These provide a foundation for success.

Alice Redmond, PhD, is Women in Pharma™ Steering Committee Chair for Europe, a member of the ISPE International Board of Directors and the ISPE Foundation, and Chief Strategy Officer at CAI.

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John Clarke

CONNECTING
in the Virtual World

Optimism is in the air as we move through the summer months and the restrictions that have become second nature are slowly lifting. As I continue the second half of my year as the Emerging Leaders (EL) Chair and representative on the ISPE International Board of Directors, I realize that my experience has been and will be different from previous EL chairs, as it will likely remain fully virtual as we continue through 2021. Experiencing the workings and organization of the ISPE Board activities through the virtual format has been an insight into how leadership organizations across the industry have transformed and the virtual world they will continue to work in.

The restrictions over the past 18 months have accelerated the switch to fully virtual working for a lot of us. It's reasonable to assume that as ELs, our working lives will be predominantly spent in this virtual format. While it does not always have the benefits of face-to-face interaction and the opportunity to build relationships in informal environments, in other ways it provides an ease of interaction as the traveling and logistics around attending an event in person have been eliminated. EL Affiliates and Chapters have done an amazing job of building momentum on these events, with virtual career fairs, symposiums, seminars, and hackathons breaking records for attendance and engagement.

VIRTUAL BENEFITS

For me, the biggest benefit of being a member of the ISPE EL community has always been the opportunity to connect with peers, both within local Chapters and Affiliates and internationally. This international collaboration has increased exponentially over the past year and a half, as all events and task teams have been set up in fully virtual formats.

ISPE strives to give representation and a voice to members who may not have always felt included in the conversation.

This fundamental change in organization has taught us many lessons and best practices that we will bring with us as the option to hold face-to-face events returns. By reducing the cost and time for ELs to attend, we are opening events to new audiences. Keeping these benefits while maximizing opportunities for networking and collaboration will be an exciting challenge for the rest of 2021 as we explore hybrid, face-to-face, and virtual events.

EXPANDING DIVERSITY

ISPE has always strived to ensure diversity and inclusion across our membership and initiatives. June was Pride Month across many of our EL regions, and it's a great time to recognize the diversity within our organization. By establishing communities such as the ELs and Women in Pharma®, ISPE strives to give representation and a voice to members who may not have always felt included in the conversation. I hope all our members used Pride Month as an opportunity to celebrate what makes them diverse and we continue to bring the spirit of inclusion to all our local and international initiatives.

There has never been a better time to volunteer with your local ISPE EL Affiliate or Chapter. Please get in touch by visiting ispe.org/membership/volunteer

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

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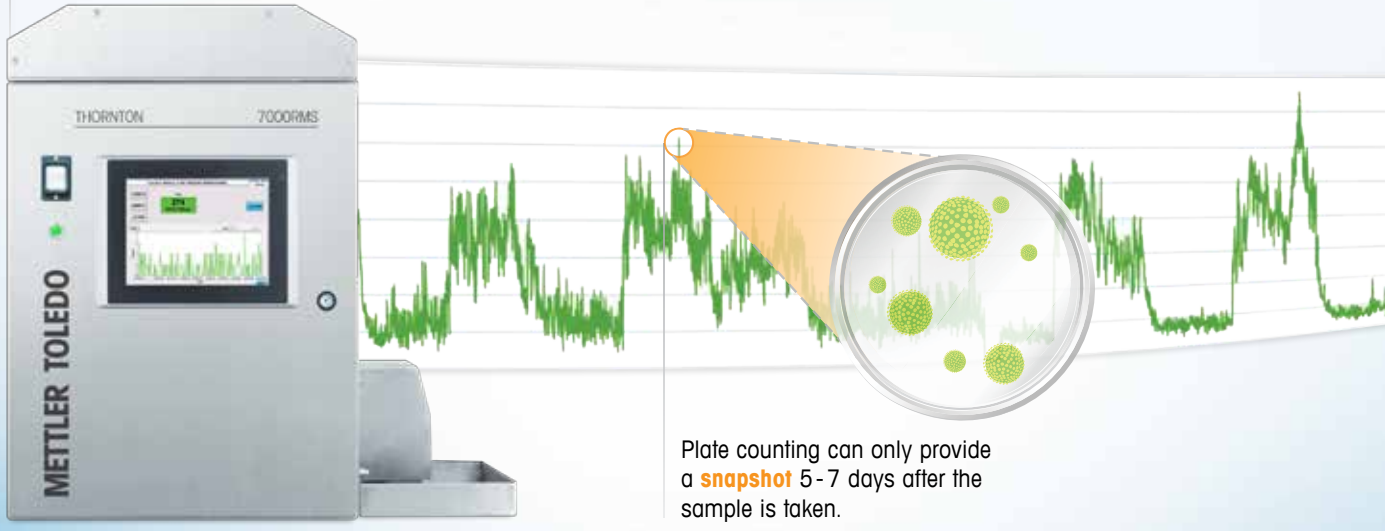

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OPPORTUNITIES IN CONTINUOUS MANUFACTURING of Large Molecules

By Robert Dream, PE, CPIP, Jeffery Odum, CPIP, José C. Menezes, and Antonio R. Moreira

Continuous manufacturing has attracted significant interest over the past decade for small molecules formulated as drug products. The case for adopting continuous manufacturing platforms for manufacturing biologics (i.e., large proteins or biologic products such as vaccines) would, in principle, be even more justified for both quality and business gains. This article briefly reviews continuous biomanufacturing (CBM) at a time of very high and global demand for vaccines as well as increased demand for cell and gene therapy products.

Biologics are very large molecules, complex to produce, with stringent aspects on interchangeability. Therefore, compared with small molecules, they present a considerably bigger challenge and have higher criticality in terms of manufacturing sciences and technologies, availability to patients, and the regulatory processes involved.

In June 2020, ISPE hosted the Continuous Manufacturing Virtual Workshop, a meeting where continuous manufacturing for both small and large molecules as drug substances and formulated drug products was addressed [1]. For a broader perspective on emerging continuous and integrated platforms for recombinant proteins, a review of novel technologies to enable continuous manufacturing of biologics, and specific analytics considerations for the reader is referred to the online presentations from that workshop [1], as well as to "Biotech Processes: Challenges for Implementation" (*Pharmaceutical Engineering*, November–December 2018) [2], which received PE's Roger F. Sherwood Article of the Year award in 2019.

There is a well-established business case for CBM, and it has significant support from the US FDA because it is seen as a very effective way to ensure product supply and mitigate drug shortages; more recently, its benefits for shoring up operations close to drug product demand with significantly shorter and more resilient supply chains have also been emphasized [3]. A recent report [4] indicates that the demand for continuous bioprocessing is increasing, and expenditures in both upstream and downstream continuous bioprocessing equipment are among the top three new expenditures by the companies surveyed. In this article, we focus on the drivers for moving to a CBM platform and on providing updates in a more compact view about technical aspects. Our aim is to provide insights into life-cycle and regulatory considerations and the potential for continuous manufacturing in emergency preparedness and rapid response efforts.

DESIGN AND OPERATION CONSIDERATIONS

Continuous manufacturing represents the highest level of integrated design and processing currently available in biomanufacturing (Figure 1). The different modalities that map out the boundaries of possible upstream process (USP) and downstream process (DSP) designs vary in terms of end-to-end (E2E) integration and the seamless operability integration of USP and DSP components. Several in-between modalities are defined, especially if USP or DSP is treated separately. Figure 1 defines CBM in terms of other designs and clarifies the distinction to modular or integrated designs.

Figure 1: CBM design and operation considerations.

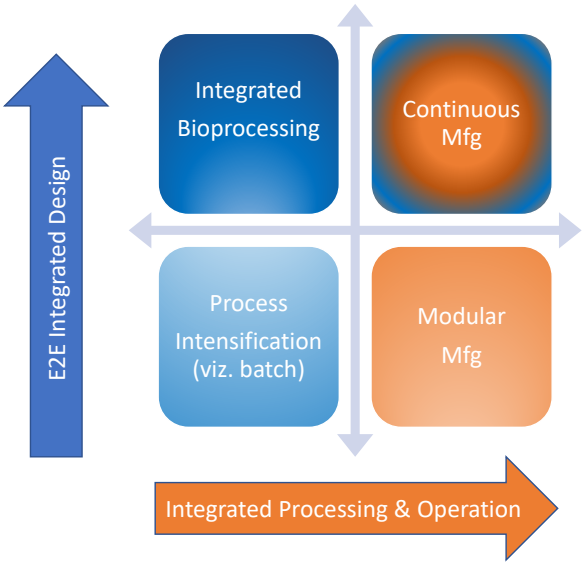


Table 1: Should you commit to CBM platforms?

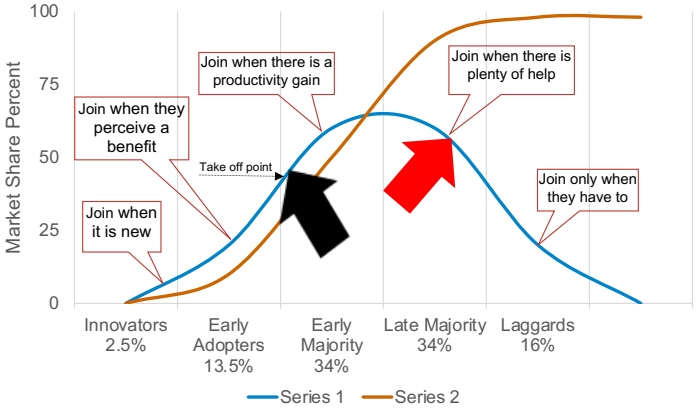
Positive Drivers	Reasons Why Change Is Resisted
• Improved productivity • Improved process intensification • Faster processing times • Reduced cost of goods • Yield improvement • Decrease in equipment size and space requirements • Effective use of single-use technology • Improved stability for labile products	• Increased capital costs to implement new technology within existing manufacturing assets • Technical challenges around existing operational capabilities • Regulatory concerns around introducing risk into the manufacturing process, real-time testing, and how to ensure "batch compatibility" around process control

Table 2: Upstream productivity increases impact process area: example from a flexible facility concept with 300 kg annual capacity.

Fed-Batch Manufacturing	CBM
Batch cycling time: 15 days Titer: 100% Output per bioreactor: 1×	Perfusion duration: 60 days Titer (1.5 RV/day): 33% Output per bioreactor: 30× (60 days × 1.5RV × 33%) Productivity increase: 7.5× (FB 4× in 60 days)
Titer: 3 g/L	Titer: 1 g/L
Process yield: 70%	Process yield: 70%
Runs per bioreactor: 18	Runs per bioreactor: 5
Capacity requirement: 4 × 2000 L SUB	Capacity requirement: 2 × 500 L SUB

Abbreviations: RV, reactor volume; FB, fed batch; SUB, single-use bioreactor.

Figure 2: The law of diffusion of innovations [5].



DRIVERS FOR MOVING TO A CBM PLATFORM

Continuous manufacturing of biologic products has a number of promising "paradigm shifts" that make the prospect attractive to many organizations. However, sources of resistance can also be identified. Table 1 summarizes some key factors to consider when evaluating whether CBM is a feasible platform for your specific application.

Table 2 provides one real-world example of the benefits of moving to a continuous manufacturing platform. Improvements in facility area reduction, increase in upstream productivity, downstream column size reduction, and reduced buffer usage are just some of the benefits that can be realized when CBM is implemented.

IMPLEMENTING NEW TECHNOLOGIES

How organizations choose to implement a new technology is based on their business, operational, risk, and market strategies. Generally, all industries fall into one of the five categories shown on the x-axis of Figure 2 [5]. A company's decision to implement a CBM process will be somewhat influenced by which category it belongs to. The black arrow represents where the current movement to continuous manufacturing seems to be for both pharmaceutical and biological products. The red arrow represents where disruptive technologies, single-use systems, and digital sensors, are perceived to be in today's manufacturing environment. Although a specific organization may not be totally aligned with these advances, the point of implementation can be seen (Table 3).

If continuous manufacturing is implemented, the impact on any new facility assets should also be factored into the decision-making process. When continuous manufacturing requires smaller equipment or less equipment, the facility footprint may be reduced, which can result in facility cost savings. The business case will also discuss the scale of operations and whether the process can be "right sized" in critical unit operations, such as chromatography, to produce the desired outputs while controlling aspects such as column sizing, resin selection, and resin

Table 3: Key questions for organizations considering CBM implementation.

Area of Focus	Key Questions
A Is CBM technically feasible?	When deciding whether to implement CBM, organizations must first ask: • Is CBM technically feasible for our protein/product? • How complex is the system (product and process attributes) and can it be adapted to this platform? • From an equipment perspective, do the manufacturing process attributes align with available equipment technology? • Does the existing technology allow the control of the process while also providing the right level of analytics to ensure that batch-to-batch consistency is maintained?
B Is the business case acceptable?	The next questions should focus on the business case for CBM: • What is the impact on development time? • How extensive will the changes to the facility asset be, and will these changes introduce any risks to ongoing operations? • What will be the return on investment if CBM is implemented? (This will be a factor of both time and investment.)
C Is the product risk acceptable?	Is the risk to the product an acceptable one given the organization's business and operational strategy? Product knowledge around critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs) is a must. If moving to a CBM platform impacts product CQAs, the decision should be a no-go. Cell viability must be well understood, going back to the development effort. If the process is not going to be a 100% single-use process, what cleaning impacts will need to be addressed?
D Are the process risks acceptable?	Are the process risks resulting from implementation acceptable? • Because process efficiency and optimization will be critical to any go/no-go decision on implementation, what are acceptable failure rates (if any)? • Can the current operations staff be trained to perform a new set of tasks, which will likely be more complex than their current tasks? • How user-friendly will the process be to adjustments that need to be made, going back to a valid process analytic technology (PAT) implementation?.
E Is the process control strategy acceptable?	Does the organization have the ability to develop the robust control strategy needed? Continuous manufacturing requires a robust process control strategy. The organization must not only have the ability to manage and control variations, as well as implement tools such as real-time release testing, but also have the ability to collect and analyze the data in a manner that supports the process validation effort (and continued process verification) that will now become critical to ensuring process viability and robustness.
F Is the implementation strategy acceptable?	Life-cycle management considerations: Is the organization able to address these? • In the transfer of the process from development to manufacturing, have all of the technology transfer aspects of this handoff been identified and addressed? • Have all of the possible regulatory questions been identified and their mitigation strategies developed? • Will internal quality and regulatory groups be on board with this paradigm change/shift?
G Is the logistic control strategy acceptable?	Operations management and scheduling need to be considered in CBM. • Will your supply chain be able to address new needs and demands? Will there be the level of reliability of the supply chain needed to minimize risk? • How will the development-manufacturing "handoff" identify campaign lengths, and how does that impact current manufacturing asset operations? • Does the organization have the physical resources to operate in a 24/7 run mode? • What is the anticipated long-term impact to facility maintenance and the logistical sequencing of shutdowns and start-ups?

utilization. Resin storage and inventory can be reduced, which further improves the business case. A change of this magnitude will disrupt significantly the current cadence of day-to-day manufacturing. This cadence has a number of elements that must be addressed. USP and DSP unit operations require advanced scheduling and robust production planning to ensure long-term operational integrity and allow leaner start-up and shutdown sequences in terms of volumetric productivity, product quality, and contamination safeguards.

Many manufacturing processes are initially developed in a batch-driven mode of operations and subsequently transferred to a CBM platform. When implementing a new manufacturing strategy, there must be a plan that includes key elements that address questions that will be asked both internally and during the external regulatory review.

A key driver of continuous manufacturing implementation is the opportunity to reduce the cost of goods. CBM allows organizations to make more product faster with lower capital costs and less operator intervention. For example, a company could make more material by using N-1 bioreactors in perfusion mode rather than N bioreactors in batch mode. A new capital facility could be less expensive to build if only an N-1 perfusion mode bioreactor configuration were installed. Continuous manufacturing also has positive impacts in reducing the risk of contamination over successive campaigns because DSP resin lifetime could be consumed during a single campaign, allowing for timing of new campaigns and resin replacements.

Table 3 includes a series of questions to answer when considering CBM implementation. If the answers to all the questions posed by activities A through G are positive responses, the decision to implement a continuous manufacturing platform should be seriously investigated and strong consideration given to its implementation.

CBM PLATFORM AND REGULATORY REQUIREMENTS

Current regulations and guidelines are supportive of innovative biopharmaceutical development and manufacturing approaches. Although continuous manufacturing is not specifically addressed in guidelines, it fits well into the "enhanced approach." Some of the following points that are intertwined and integrated into continuous manufacturing may improve regulatory compliance:

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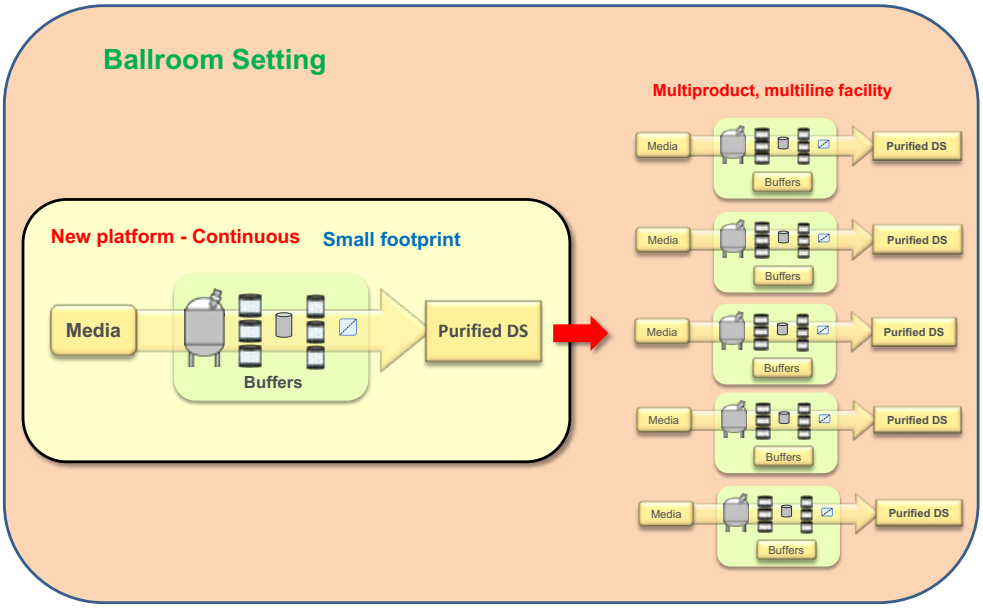
Figure 3: The future use of CBM platforms in multiproduct facilities.



- Optimized and stable buffers
- Universal, standardized platform (various proteins)
- Steady state (metabolism)
- Closed system (minimized microbial issues)
- No scale-up (same scale from pilot to commercial manufacturing—scale-out)
- Compatible with disposable technology
- Minimized hold time (eliminate hold tanks and nonessential equipment—improved stability for labile products)
- Continuous flow (minimized residence time)
- High volumetric productivity
- Integrated, modular, simplified operation
- Flexible capacity increase/decrease (within the operating range and then scale-out, if desired)

CBM platforms have a small footprint (as illustrated in Figure 3) with feedback/feed-forward control that allows for collecting data on the operation/manufacturing process continuously [2, 6]. The importance of process analytical technology (PAT) as the main enabler of a robust monitoring and control strategy for continuous manufacturing has been delineated in recent publications [2, 7]. PAT can support the implementation of continuous manufacturing throughout the entire life cycle. This will provide a state of control of the manufacturing process at all times [2], with benefits including:

- Productivity (cell growth and apoptosis, and all CMAs and CPPs)
- Quality (CQAs)
- Flexibility
- Cost savings (due to reduced equipment and equipment size, footprint, operational services)
- Simplicity
- Mobility (operate at any site near patients)
- Standardization (a technology platform, minimized design and validation)

When capacity demand increases, manufacturing requirements will be accomplished via scale-out (i.e., by repeating the same line). Building an additional production line with the same specifications allows for a quicker design and build, and it simplifies the commissioning, qualification, and validation activities. One can utilize existing protocols and know-how (from baseline) to document and execute all needed requirements. The regulatory approvals process may go faster because no drastic changes have been made.

ICH has initiated the development of a new guidance (ICH Q13) on the topic of continuous manufacturing of drug substances and drug products. Currently projected to reach adoption as a final guideline in November 2022, ICH Q13 guidance will:

- capture key technical and regulatory considerations that promote harmonization, including certain cGMP elements specific to continuous manufacturing;
- allow drug manufacturers to employ flexible approaches to develop, implement, or integrate continuous manufacturing for the manufacture—drug substances and drug products—of small molecules and therapeutic proteins for new and existing products; and
- provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of continuous manufacturing technologies used in the manufacture of drug substances and drug products.

Table 4: Regulatory considerations [9–12] and future continuous manufacturing opportunities for large molecules.

	Regulatory Considerations
Batch[a]	• In-process testing • Specifications • Process validation • GMP compliance • Batch basis identification (time elapsed, etc.) • QA batch release plan/protocol • Batch record data collection and archiving • CMA and CPP associated with each batch
Raw material[b]	• Raw material properties (functionality, safety, impurities) • Batch-to-batch/lot-to-lot variability and sources of variability • Impact on process and control strategy (IPC) measurements • Continuous drip feeding/hybrid approach • Stability and traceability of raw materials within the CBM process
Process description[c]	• Time-related parameters as a result of dynamic process • Flow rates (e.g., volume over time), mean residence times • Scalability aspects (e.g., running time, equipment design) • Procedures for start-up/shutdown and interruption • Design spaces (address potential interactions between steps)
Control strategy[d]	• Product- and process-specific strategies • Product knowledge (structural and functional relationship (e.g., monoclonal antibodies [mAbs]), platform knowledge/prior knowledge) • Control systems (automated valves, feedback and feed-forward controls, feeder controls) • IPCs and sampling potentially different from batch processes • Online measurement (e.g., multiattribute method: relevant readout/degradation products) • In perfusion culture: end-of-production cell characterization • Procedures for handling deviations, nonconforming material • Real-time release testing or hybrid approach realistic
Equipment[e]	• Design considerations • Larger contact surface area (temperature control, leaching) • Single-use equipment • Location of segregation points • Potential for microbial growth/contamination • Indicators of equipment failure • Strategy for cleaning validation
ICH Guidance	• Product and process understanding and process control (ICH Q8R2) • Quality risk management (ICH Q9) • Quality systems (ICH Q10) • Development and manufacture of drug substances (ICH Q11) • Quality by Design (QbD) • Life-cycle approach to process control/validation (ICH Q12) • Cell banking; characterization and testing of cell banks; end-of-production cell characterization (genetic stability) (ICH Q5D)

[a]Definition of batch size should be stated prior to manufacture as a specific quantity of material produced in a process or series of processes, so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.
[b]Raw material is a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or drug substance-drug product.
[c]Refer to "EudraLex Volume 2B: Notice to Applicants and Regulatory Guidelines for Medicinal Products for Human Use. Presentation and Format of the Dossier Common Technical Document (CTD); Differences to a Batch Process" [10].
[d]Manufacturing process produces the product of intended quality in a reproducible way (batch process).
[e]Discussed during a preapproval inspection (GMP).

The ICH Q13 position paper [8] states:

> *There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would facilitate international harmonization and could reduce barriers to the adoption of CM technology.*

Table 4 [9–12] captures from a regulatory perspective the future opportunities for impacting the scientific understanding of the use of continuous manufacturing technologies for the production of biologic molecules.

A number of issues in the regulatory domain require resolution to make CBM a viable technology platform for the manufacture of large molecules. These include:

- Differences from batch manufacture: Many CBM-related definitions and terminologies require further clarification and explanation in the regulatory context.
- Definitions of continuous manufacturing concepts: Examples of key concepts include start-up/shutdown, state of control, process qualification and validation, and continued process verification.
- Harmonizing regulatory common understanding and consistent usage of terminology across different regions: This will lead to improved communication among stakeholders.
- Establishing key scientific approaches for continuous manufacturing: Fundamental scientific approaches for continuous manufacturing may differ from those encountered in batch processes (e.g., concepts of system dynamics, monitoring frequency, detection and removal of nonconforming material, material traceability, process models, and advanced process controls).
- A common understanding of scientific approaches: This will facilitate consistent science, risk-based implementation, and regulatory assessment of continuous manufacturing across different regions.

- Identifying regulatory expectations related to continuous manufacturing: Harmonized regulatory expectations for approval and aspects of life-cycle management that are pertinent to continuous manufacturing can facilitate the adoption of continuous manufacturing and result in consistent regulatory assessment and oversight.

Given the technology and manufacturing of drug substances and drug products for therapeutic proteins, new and existing products need to be addressed. The regulatory expectations with respect to marketing applications and postapproval changes, site implementation, and biopharmaceutical quality systems must also be addressed.

CONCLUSION

Continuous manufacturing represents the highest level of integrated design and processing currently available. These qualities enable unique functionality and platforms that are potentially capable of rapid deployment and of delivering agile and accelerated timelines from development to on-demand manufacturing. The drivers for adoption of CBM relate to improved productivity, reduced plant footprint, and overall capital and operational expenditures, many of which are favorable life-cycle considerations. All of these come with more sophistication (i.e., supervisory controls) to enable consistent quality and in-process continued verification. Regulatory considerations for biologics have a higher level of complexity than for small molecules. Therefore, companies considering CBM platforms must be ready to support their applications with robust control strategies with sound evidence-based considerations as well as risk-based justifications.

Though CBM is not suited for all companies and may only be advantageous to specific products in a portfolio, the future seems quite promising for those organizations committing to enable faster response times to global emergencies and to improved drug product availability (i.e., supply reliability and patient access). As demonstrated in the 2020 ISPE Continuous Manufacturing Virtual Workshop [1], continuous manufacturing and CBM will contribute to shaping pharma and biopharma as true bioindustry 4.0 technologies, given the level of science, technology, automation, and knowledge management involved and required for their effective deployment. It will be fascinating to witness what the future holds in this regard!

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CONTINUOUS MANUFACTURING as a Tool for Accelerated Development

By Katherine E. D. Giacoletti and Wyatt J. Roth, PhD

Continuous manufacturing (CM) offers one way the pharmaceutical industry can accelerate development of the drug product control strategy to ensure a robust and reliable supply of medicine to the clinic and/or market. This article explores the promise of CM in enhancing accelerated development, as evidenced by experience in solid oral products.

It has been inspiring to see what our industry has accomplished in an unprecedented time frame in response to the COVID-19 pandemic: development and emergency use authorization for vaccines, neutralizing antibodies, and expansion of previously approved therapeutics for the treatment of COVID-19, to name a few. The industry's ability to respond to the challenges that the pandemic presented demonstrates the significant value and impact that pharmaceuticals bring to the world, but it also raises the question: How can we apply learnings from our industry's response to the pandemic to routine development activities to accelerate delivery of medicines to the patients we serve?

The answer to this question is multifaceted, and it will require each function within an organization to assess what role it can play to deliver the solution. As pharmaceutical scientists and engineers, one of our primary responsibilities is developing the drug product control strategy to ensure a robust and reliable supply of medicine to the clinic and/or market. There are myriad ways to accelerate development of the control strategy, but one of the more promising technologies that can facilitate acceleration is CM.

CM ON THE RISE

Since the first US FDA approval of a CM application in 2015, there has been a steady increase in CM's implementation across the industry. In fact, the 2019 and 2020 Annual Reports from the Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, indicate that at least seven applications using CM have been approved [1, 2]. Although these approvals span small molecule drug product, small molecule active pharmaceutical ingredient (API), and biomanufacturing processes, the majority of the approvals are related to CM of small molecule drug products. Because this area of CM is the most mature within the pharmaceutical industry, this article focuses on some advantages and strategies that companies employing continuous drug product manufacturing have used to help accelerate development of solid oral products.

CONTINUOUS DIRECT COMPRESSION

The three primary manufacturing platforms (direct compression/encapsulation, dry granulation, and wet granulation) used for batch manufacturing of solid oral dosage forms are also used in CM. Analysis of 435 regulatory filings between 1996 and 2017 revealed that wet granulation is the most common manufacturing platform, with 38% of products using that process, followed by direct compression at 18% and dry granulation at 12% [3]. Because the first application of a continuously manufactured drug product was not approved until 2015, these data overwhelmingly represent the manufacturing platforms that were selected for batch processes. However, a comparison of manufacturing platforms used for products publicly known to be made with CM shows a much different distribution: direct compression is the most common at 50%, followed by dry granulation at 33%, and wet granulation at 17% (see Table 1) [4–9]. Although the pharmaceutical industry is still early in its journey with CM, it is interesting to note that early adopters of the technology tend to favor direct compression over the two primary granulation platforms.

Determining which manufacturing platform to select for the development of a new molecular entity usually starts with a risk assessment or decision tree based on the unique requirements for the molecule being developed. Examples of items typically included in the risk assessment are (a) considerations related to the highest or lowest expected dose, (b) API powder physical properties (e.g., flowability, cohesiveness, compressibility), (c) API moisture sensitivity, and (d) API segregation potential. For

Table 1: Publicly known drug products produced using CM and the associated manufacturing processes.

Product	Company	Manufacturing Process	Reference
Orkambi	Vertex	Continuous wet granulation	4
Prezista	Janssen	Continuous direct compression	5
Verzenio	Eli Lilly	Continuous direct compression	6
Daurismo	Pfizer	Continuous direct compression	7
Symdeko	Vertex	Continuous dry granulation	8
Trikafta	Vertex	Continuous dry granulation	9

example, the two primary reasons pharmaceutical engineers often select granulation platforms for batch processes are to minimize segregation potential and to improve the flowability of the blend due to high API concentrations in the formulation. However, when developing these risk assessments, it is important to note that the risk profiles may be quite different between batch and continuous processes due to the differences in the equipment operating principles. To illustrate, studies performed at Eli Lilly compared critical quality attributes (CQAs) of identical formulations, which were manufactured using both batch and continuous processes [10]. The results demonstrated that the continuous direct compression process had equivalent or superior performance compared to the batch granulation process, and that all CQAs were achieved using continuous direct compression. This would suggest that continuous direct compression can be used on a larger percentage of assets compared to batch direct compression, thus enabling a platform-based approach to solid oral drug product development. The efficiencies of platform-based approaches are further discussed later in this article.

Formulation development for a direct compression process is generally simpler than for granulation processes because direct compression formulations usually have fewer ingredients (see Table 2), which leads to fewer formulation ranging and robustness studies. Moreover, direct compression processes help enable laboratory-scale formulation development because direct compression processes do not alter a material's inherent compactibility properties as granulation processes can. As a result, prediction of how a formulation will compact on a continuous direct compression line based on batch laboratory data is much simpler than the analogous prediction for granulation processes.

The key information needed to successfully bridge laboratory-scale data with continuous data is an understanding of how lubrication in a laboratory-scale batch process translates to lubrication on the continuous line. Fortunately, models have been developed that are useful for predicting tensile strength changes as a function of lubrication for changes in scale of batch manufacturing processes [11]. Models such as these can be modified and adapted to understand the relationship between lubrication at laboratory scale (for example, at a 50-gram scale in a Turbula mixer) and lubrication in the continuous process. The ability to perform

Table 2: General formulations for the most commonly used solid oral dosage form manufacturing platforms.

Direct Compression	Dry Granulation	Wet Granulation
Drug substance	Drug substance	Drug substance
Diluent/filler	Intragranular diluent/filler	Intragranular diluent/filler
Disintegrant	Intragranular disintegrant	Intragranular disintegrant
Lubricant	Intragranular lubricant	Intragranular binder
Coating mixture	Extragranular diluent/filler	Intragranular solvent*
	Extragranular disintegrant	Extragranular diluent/filler
	Extragranular lubricant	Extragranular disintegrant
	Coating mixture	Extragranular lubricant
		Coating mixture

*The solvent in wet granulation processes is removed, but it still must be studied and optimized during formulation/process development studies.

formulation development at laboratory scale enables faster development timelines and reduced API consumption.

Finally, a continuous direct compression process in its simplest form only consists of three unit operations (loss-in-weight feeding, continuous mixing, and tablet compression), whereas granulation processes typically have at least three additional unit operations (e.g., roller compaction, milling, and blending of extragranular excipients). Not only does the simplicity of the direct compression process result in fewer process optimization studies due to fewer unit operations, it also leads to simplified control strategies, modeling, and material traceability/genealogy. Collectively, these advantages of continuous direct compression allow for more rapid formulation optimization, reduced process optimization studies, and accelerated development timelines.

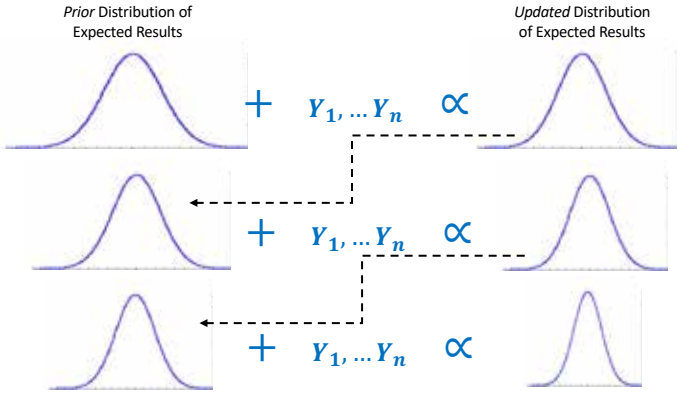
LEVERAGING PLATFORM KNOWLEDGE

The robustness of continuous processes described previously and the integrated nature of the unit operations allow practitioners of the technology to take a platform-based approach to the development of their solid oral portfolio. One of the greatest advantages to using a common platform across the portfolio is the ability to apply learning from one project to the next to increase development efficiency and accelerate timelines. Because continuous feeding and mixing are the two operations that are most different from batch processes, this section discusses approaches that have been used across continuous projects to streamline development.

Feeding

The first step in any drug product CM process is to feed the API and excipients into the process at the desired mass flow rates. The excipients used in continuous processes for solid oral products are generally the same as those used in batch processes, and a subset of excipients (e.g., microcrystalline cellulose, magnesium stearate, lactose, starch, and croscarmellose) tend to be commonly used across formulations [12]. Because the feeding operation is

Figure 1: Illustration of iterative updating of a Bayesian model as knowledge about the platform accumulates.



ubiquitous across continuous lines and many of the excipients are common across formulations, databases containing information on feeding performance have significant potential to minimize experimental work from one project to the next. For example, once feeding performance is established for a given material and equipment setup, that knowledge can be used on any subsequent projects that use the same material and equipment setup [13]. Moving beyond feeder performance databases, Yadav and colleagues [14] and Wang et al. [15] have combined feeding and raw material databases to build multivariate models that are used to predict feeding performance for drug product CM processes. These predictive models are particularly attractive during early process development not only because they minimize experimental work, but also because API availability is often limited at this stage of development.

Mixing

In addition to using knowledge from the feeding operation to streamline development, drug manufacturers have also successfully used mixing studies performed on one asset to inform risk assessments and simplify development for subsequent assets. Roth and colleagues evaluated the impact of mixer paddle orientation, total mass flow rate, and mixer speed on the CQAs of a difficult-to-mix formulation at relatively low drug load (6.25%) [16]. The only parameter that had a meaningful impact on CQAs was the total mass flow rate. The authors used this information to fix the mixer paddle orientation and mixing speed within the continuous line for all subsequent assets, thus simplifying and streamlining development.

On the same continuous line, work performed by Manley and Shi demonstrated that large step changes in concentrations of microcrystalline cellulose, lactose, and mannitol result in similar response curves [17]. Because the same equipment setup was used across these studies and only the formulations were changed, this finding suggests that the dispersion that occurs within a process across multiple formulations is comparable [17]. This knowledge can be used when developing work plans for a new asset to ensure that the amount of mixing and dispersion is commensurate with the level of quality risk for the asset. Moreover, this finding could provide development organizations with a flexible, drug-substance-sparing option to characterize process dynamics.

Statistical Model

A natural component of a platform approach would be the use of Bayesian statistical methods, which can explicitly combine prior knowledge with newly observed data to obtain more precise models of expected performance than could be obtained with the newly observed data alone (see Figure 1).

Each bell curve represents a distribution of plausible results (e.g., values of a release or in-process test): previous knowledge about the expected results is characterized by a "prior" distribution (left column), which is combined in the Bayesian model with new data (e.g., from characterization or design of experiments [DOE] runs of a new asset), resulting in an updated distribution of plausible results (right column), which then becomes the prior distribution for further experiments on the same or a subsequent asset. The width of the distribution reflects variability and statistical uncertainty, the latter being reduced in each update of the model as knowledge accumulates.

As represented in Figure 1, the model is iteratively updated as new knowledge about the platform is generated, resulting in an increasingly precise understanding of expected results with less new data needed than would be if this prior information were not leveraged in the modeling. This means that patients and manufacturers can benefit from reduced development costs and time without sacrificing understanding of process performance. For example, this prior information could be derived from DOEs performed in the development of previous assets or from validation or commercial runs of existing products. As with any use of information external to the asset currently being studied, the selection of prior information for a Bayesian model must be made carefully, ensuring that it is representative; once the representative prior knowledge is selected, the Bayesian approach provides a rigorous framework for using it, which mirrors the scientific process of continually updating knowledge [18].

For example, the knowledge gained about the impact of process parameters and/or concentrations of formulation components on mixing and dispersion in the examples described previously could be explicitly and rigorously incorporated into models for new assets, reducing the amount of additional experimentation required to estimate performance and provide assurance of quality. Although still a less well-known approach in pharmaceutical process development, the use of prior information in Bayesian models has been used in adaptive clinical trial designs for some time [19]. The approach is especially well suited to using a platform approach in the context of accelerated approval pathways, where the knowledge from previous assets on the same platform is "borrowed" to increase the precision of performance

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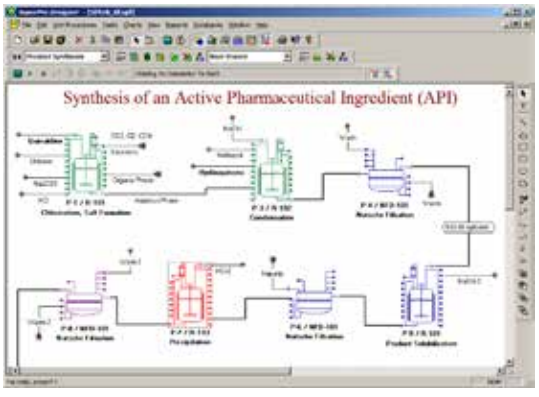

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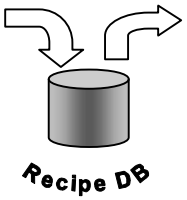

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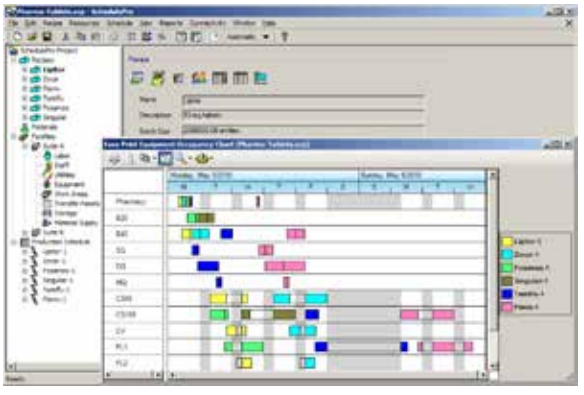

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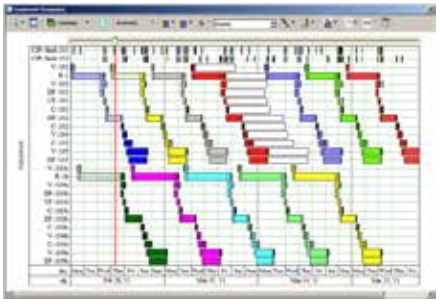

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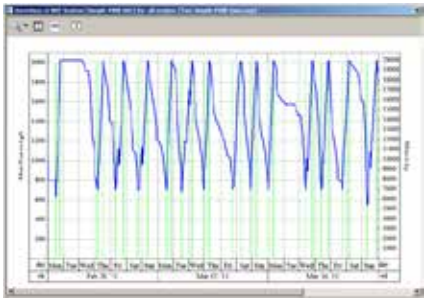

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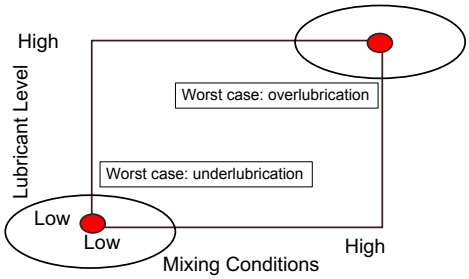
Figure 2: Comparison of batch and continuous lubrication studies showing the relative API savings achieved with CM while gaining additional process experience.



Variable	Batch	Continuous
API Concentration (%)	20	20
# of Batches	2	5
Batch Size	100	NA
Flow Rate (kg/h)	NA	40
Run Time (h)	NA	0.5
API Consumed (kg)	40	20

models with the new asset while using less new data than would be needed without leveraging this information.

Bayesian modeling has other important advantages for continuous processes, regardless of whether prior information is incorporated into the model; in fact, in some scenarios, a Bayesian model is the most suitable approach to evaluate process performance and risk due to the complex data structures that often arise from continuous processes. CM processes often generate a large amount of data, for example, from frequent process analytical technology (PAT) measurements incorporated into the control strategy (and sometimes as part of a real-time release testing strategy). In addition, validation of PAT measurement systems may involve confirmation of the comparability of PAT results to those from a traditional offline test method, such as high-performance liquid chromatography.

The resulting data structure is often complex, with multiple sources of variability represented within a single run (e.g., multiple measurements from each of multiple portions of a run [time intervals or in-process bins/hoppers]). Bayesian modeling is the optimal choice of statistical method in such cases to provide estimates of expected process variability (e.g., tolerance intervals), or the magnitude of expected bias between PAT and an offline measurement system for individual unit measurements, while accounting for these typical sources of process variability. Alternatively, Bayesian modeling can be used to directly predict the probability of meeting a specific release requirement related to the mean or variability within a batch (e.g., content uniformity), or to evaluate the probability of meeting requirements of a staged compendial test, such as dissolution, while still accounting for all sources of process variability. This approach was used by Roth and colleagues to evaluate the probability of meeting content uniformity requirements considering between- and within-location variability within a run [16], and these features of Bayesian modeling are discussed in detail by Scherder and Giacoletti [20].

Technical Transfer

Perhaps the most widely publicized benefits of CM are related to the ability to perform development studies at a commercial scale while minimizing the amount of API consumed in the study. With traditional batch manufacturing, the batch size is generally dictated by the equipment size available to process the material. Therefore, running commercial-scale experiments as part of development work plans would require significant amounts of API and is not feasible in most situations. However, with CM, commercial-scale equipment is used in development without consuming significant amounts of API because the process can be run long enough to collect the required data to ensure process robustness and then the experiment can be stopped.

As an illustrative example of this approach, consider lubrication blending of powder mixtures just prior to final dosage-form formation. Powder lubrication is essential to facilitate processing (e.g., preventing picking/sticking and minimizing ejection stresses during tableting), but over- or underlubrication can have a significant impact on CQAs such as dissolution or appearance. Powder lubrication in scale-up of batch processes has historically been poorly understood, and though scale-up models exist [11], they are empirical in nature. As a result, blending studies with batch processes are frequently performed at or near commercial scale prior to pivotal clinical studies to minimize risk of formulation changes after the pivotal studies have started. Parameters impacting these blending studies are often grouped together to represent worst-case scenarios for both under- and overlubrication (see Figure 2); in other words, the amount of API needed for full-scale studies is inefficient not only from a materials point of view but also from an experimental design perspective.

For illustration, consider a relatively modest batch process batch size of 100 kg with 20% drug load. A worst-case approach consists of two batches representing the extreme lubrication conditions, which provides information only at those conditions (i.e., one cannot mathematically interpolate to other combinations) and requires 40 kg of API. By contrast, a DOE can be implemented easily and efficiently using a continuous process, generating much more process knowledge using half the amount of API. For example, with a total mass flow rate of 40 kg/h and a run time of 30 minutes, a two-factor, two-level factorial DOE with a single center point (five runs) uses 20 kg of API but generates far more knowledge, which increases understanding and decreases risk. The additional process understanding (e.g., impact on mixing of conditions other than the worst case and at combinations not actually run but within the experimental space, detection of interactions is

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Figure 3: Replication of equipment, PAT, control strategy, and automation across development and manufacturing allows for streamlined and low-risk technology transfer, which can minimize the need for engineering or demonstration batches prior to clinical supply.

not only valuable for the present process but also can be leveraged for future assets as part of a platform approach. Collectively, this approach can be used to accelerate development because it reduces technical risk for the current asset and becomes prior knowledge for future assets while at the same time reducing API consumption.

As a result of being able to perform development studies in commercial-scale equipment, CM offers a unique opportunity to exactly replicate equipment sets across development and manufacturing. This approach has been implemented by companies [21, 22] and can result in significantly reduced technical risk, increased development efficiency, and accelerated time to reach the clinic. By performing development studies using the same equipment, PAT, control strategy, and automation, the benefits of running an engineering or demonstration batch at the manufacturing site prior to making clinical material are significantly diminished. By eliminating demonstration batches, technology transfer can be accomplished via a digital transfer of the automated control strategy and enable an organization to move directly into GMP clinical supply (Figure 3). This paradigm may be particularly advantageous for new molecular entities, which are targeted toward life-threatening conditions that may qualify for some type of expedited regulatory review. With approximately 25% of all new drug approvals in the US receiving the FDA's breakthrough designation [23], anything that chemistry, manufacturing, and controls organizations can do to accelerate medicine to the clinic is a win for patients.

Flowsheet Models as Digital Risk Assessments

Continuous processes naturally lend themselves to flowsheet modeling due to the integrated nature of the unit operations that comprise them. Flowsheet models can serve many purposes, including facilitation of process design, process optimization, and material traceability and genealogy [24]. But when considering accelerated development scenarios, perhaps the greatest value that flowsheet models offer is the ability to leverage them as a way to perform digital risk assessments for the process and product being developed. When used in this manner, flowsheet models allow more targeted and focused experimentation on those elements of the process that may present higher risk to product quality.

An example of how flowsheet models can be applied to accelerate development is to consider one of the primary differences between batch manufacturing and CM: how the input materials are charged into the system and mixed. With batch processes, all materials to be mixed together are charged into the processing equipment at once. Mixing robustness studies and validation of the batch mixing process ensure acceptable uniformity of the material at the appropriate scale of scrutiny. In this regard, the homogeneity of the material in a batch process is assumed to be independent of time once blending is complete.

However, with continuous processes, materials are fed into the system at desired mass flow targets for a defined period of time. As such, the actual mass flow rates of the input material have the ability to vary over time based on material properties, natural process variability, and equipment performance. Flowsheet models can be used to understand the impact that this mass flow variability can have on the composition of the blended material prior to final dosage form formation (i.e., tablet compression or capsule filling). For example, García-Muñoz and colleagues built a flowsheet model that was used to predict the impact that a loss-in-weight feeder mass flow disturbance would have on the API concentration at the tablet press feed frame [25]. By using the model to simulate a range of feeder disturbances, contour plots were generated that depict the region where a disturbance is dampened within assumed limits [25]. Models such as these are invaluable tools for reducing experimental burden because they can be used as a digital risk assessment to focus the experimental plan and set limits as part of the control strategy.

CONCLUSION

In the increasingly competitive environment of the pharmaceutical industry, speed to the clinic and market has never been more important, not only for patients who are waiting for medicines but also to maintain business viability. As pharmaceutical scientists and engineers, we are well positioned to leverage technology to accelerate development of the manufacturing processes used to

supply medicine to the clinic. One such technology that can be used for accelerated development is CM, which is still in its early phase of implementation within the pharmaceutical industry.

CM offers multiple advantages related to reducing development timelines. As illustrated by the publicly known approvals of drug products made using CM, it appears that direct compression may play a larger role than other platforms commonly used for batch processes (e.g., dry or wet granulation). With fewer unit operations and generally simpler formulations than would be needed for a batch process for the same product, continuous direct compression allows for fewer formulation and process optimization studies, which in turn enables speed to market. In addition, continuous processes can save significant quantities of API during development for multiple reasons, including no scale-up, the ability to leverage continuous processes more consistently as platforms, and the integration of continuous processes with modeling that can be used to reduce and focus experimental plans. By saving API in drug product development, API manufacturing campaigns could potentially be reduced in size, resulting in faster deliveries and speed to the clinic.

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REGULATORY ASPECTS OF GLOBAL ACCEPTANCE

of Continuous Manufacturing

By Ahmad Almaya, PhD, and Kim Boué, MSc

Application of continuous manufacturing (CM) in the pharmaceutical industry is gaining momentum. Most of the current experience is based on oral solid dosage (OSD) projects but in the future CM should not be limited to these dosage forms. In this article, the regulatory acceptability of CM to produce pharmaceuticals is demonstrated in different regions, including the "rest of the world" (i.e., regulators in nations and regions other than the US, EU, Japan, and Canada) through case studies.

Compared with previous manufacturing approaches, CM offers greater process understanding and control combined with enhanced monitoring capabilities during manufacturing. The CM process may also incorporate process analytics and elements of real-time release testing (RTRT). As such, this emerging technology has potential for improving efficiency and flexibility of the manufacturing process. Therefore, some pharmaceutical companies are very eager to apply CM, as this enables acceleration of development timelines and improvement of supply chain flexibility.

Given the innovative nature of advanced manufacturing technologies, there may be a perceived regulatory risk with the application of such new technologies like CM on new chemical entities (NCEs) or already commercialized products. However, several interactions over the past decade with multiple regulatory agencies across the US, Europe, Japan, and many other regions have revealed that those agencies encourage the adoption of modern manufacturing approaches. This has been clear throughout regulators' site visits, as well as formal and informal interactions with multiple regulatory agencies across the globe.

Additionally, information presented at numerous conferences, workshops, and other scientific exchanges has highlighted robust manufacturing approaches and higher assurance of quality possible through adoption of CM. In the past 10 years, the value of CM has been supported across the industry, academia, and regulatory agencies through various forums sponsored by organizations such as ISPE, the Product Quality Research Institute, the American Institute of Chemical Engineers, the Massachusetts Institute of Technology and the Manufacturing and Crystallisation Consortium, the International Foundation–Process Analytical Chemistry, the American Association of Pharmaceutical Sciences, and others.

An examination of the currently available regulatory guidance documents, GMPs, quality systems, scientific publications, and various mechanisms for regulatory interactions as well as the increasing number of regulatory approvals with CM highlight that CM is compatible with the existing regulatory framework. Moreover, there are specific avenues for pharma manufacturers to interact with regulators to seek advice on specific CM questions, if needed, including the US FDA's Emerging Technology Team (ETT), EMA's Process Analytical Technology (PAT) team, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) Innovative Manufacturing Technology Working Group (IMT-WG). FDA's ETT was established in 2015 for discussions of all types of emerging technologies. FDA encouraged utilizing the ETT mechanism to discuss plans for development and commercialization of CM applications. EMA's PAT team was established in 2006, and CM topics were considered for discussions. PMDA's IMT-WG was established in 2016 for discussions of all types of innovative technologies, including CM topics.

Further, recently published regulatory guidance documents amplify the overall acceptance of CM. These include:

- FDA's 2019 draft guidance for industry "Quality Considerations for Continuous Manufacturing" [1]

- PDMA's 2018 provisional draft document "PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry" [2]
- "Points to Consider Regarding Continuous Manufacturing" from the National Institute of Health Sciences, Japan [3]
- "State of Control in Continuous Pharmaceutical Manufacturing," also from the National Institute of Health Sciences, Japan [4]
- EMA's 2017 "Guideline on Manufacture of the Finished Dosage Form" (EMA/CHMP/QWP/245074/2015), a non-CM-specific guidance document that includes expectations for situations in which the manufacturing processes are CM [5]
- The upcoming ICH Q13, "Continuous Manufacturing of Drug Substances and Drug Products" [6]

CASE STUDIES

Eli Lilly's Application of CM on NCEs

Application of CM at Eli Lilly and Company has focused on NCEs, mainly driven by the realization that CM could help accelerate the development and commercialization of new medicines. As such, the drug product chemistry, manufacturing, and controls (CMC) development has focused on use of CM for commercialization and launch of NCEs, without leveraging parallel or backup batch manufacturing process development options.

Lilly's first product on the market manufactured with CM was Verzenio (abemaciclib tablets), which was approved by the FDA in 2017, and approved soon after in Europe, Japan, and multiple other countries. Verzenio is currently approved in more than 50 countries around the world [7].

As Verzenio was Lilly's first commercial implementation of CM for drug products, and its development took place prior to the publication of the recent CM-specific draft guidelines, Lilly did leverage some of the avenues mentioned previously to share plans and seek advice from regulatory agencies on various CM topics. Such topics included items related to:

- The approach proposed for definition of "batch"
- Equipment design
- Control strategies
- Application of existing regulatory guidelines
- Process and PAT models and what these models are used for
- RTRT plans
- Plans for process validation

In Lilly's experience, CM has been globally accepted and there has been no pushback on use of CM for the production of pharmaceuticals. Most of regulators' questions during marketing authorization application processes have been driven by the need to obtain clarity. This is to be expected given some of the unique aspects of CM that needed additional considerations. Examples of such items include:

- Clarity around commercial batch size and whether a batch size range is proposed
- Clarity regarding controls of critical steps and whether process or PAT models were used for those controls

In Lilly's experience, CM has been globally accepted and there has been no pushback on use of CM for the production of pharmaceuticals.

- If process or PAT models are used, clarity of their intended purpose, as well as their planned life-cycle management approaches
- Clarity around RTRT approaches

In Lilly's experience, it is clear that regulatory agencies are supportive of CM, as evidenced by the large number of countries where products manufactured with CM have been registered. Although existing regulatory guidelines can serve as the foundation for implementing CM, CM presents some complexities that may require unique approaches. As such, Lilly' experience is that communication with regulators to receive feedback and guidance is essential, especially until new specific regulatory guidance on CM is available and the industry has more experience with CM filings.

Janssen's Batch to CM Conversions

The current experience of Janssen is based on postapproval batch to CM conversions, starting with Prezista (darunavir) 600-mg tablets.

Prezista 300-mg tablets were initially approved for standard batch manufacturing in 2006 in the United States. Subsequent regulatory supplements were approved to introduce 75-, 150-, 400-, and 600-mg tablets. These dosage strengths are all made from a common blend and then compressed to the appropriate strength. Janssen selected the approved Prezista 600-mg tablets manufactured by direct compression of a dry powder blend using standard batch manufacturing equipment as a proof-of-concept candidate for the application of CM technology. The selection of this strength was due to the robustness and stability of the formulation and manufacturing process. Janssen's intention was to leverage this experience and use CM in the development and commercialization of future projects as a preferred platform for oral solid dosage forms. In 2016, Janssen received the FDA's first approval for the use of CM as an alternate process to the batch manufacturing process for Prezista 600-mg tablets [8].

The switch from a batch to continuous process for a marketed product presented many regulatory challenges. The company's strategy was to file the CM process as an alternate manufacturing process to the batch process to allow for supply chain flexibility. Janssen did not introduce any significant differences to the nature of the unit operations (e.g., blending, compression, and coating) used in the proposed CM process compared to the batch process. For manufacturability reasons, a minor adaption was required in the quantitative composition of the tablet formulation.

Janssen selected the US as the initial country to file the Prezista 600-mg CM process because the FDA's ETT had the infrastructure in place to meet and discuss the CM strategy with Janssen.

Similar to the Lilly case, because the development of the CM for Prezista 600-mg tablets took place prior to the publication of CM-related guidance documents, Janssen interacted with the FDA early on several CM topics, such as:

- Demonstration of comparability of the tablets manufactured using the CM process to the tablets manufactured using the conventional batch process
- Definition of batch size
- Amount of required stability data
- Process validation strategy
- Elements of RTRT

Janssen used the review and approval process by the FDA to gain insights and experience, which were used for submission preparations in other regions. Janssen also conducted meetings with, or otherwise requested scientific advice from, other health authorities such as EMA (PAT), Health Canada, Swissmedic, the Therapeutic Goods Administration of Australia, PMDA, and the Brazil National Health Surveillance Agency (ANVISA). Similar topics to those listed previously were discussed.

Given the potential impact on the quality of the product and the magnitude of the manufacturing change, the postapproval variation file was considered a "wait for approval" change (e.g., Prior Approval Supplement, Type II) in all countries.

Another case study within Janssen was the postapproval conversion in Japan of Tramcet (tramadol hydrochloride + acetaminophen) combination tablets from batch manufacturing to CM, using the wet granulation platform. Approval for this Partial Change Application (PCA) was granted by PMDA in 2019. Early and frequent interactions with PMDA were key. During the review process, the questions from PMDA mainly focused on the process parameters justification and control strategy aspects.

Janssen received approval in all countries where CM postapproval variation files were submitted. However, the acceptance of two different manufacturing techniques in parallel for the same product may be more challenging. Potential formulation changes may be necessary to accommodate the conversion to CM, thereby adding complexities to the dossier. In general, Janssen's experience is that no differences were encountered in review timelines for the CM-related post-approval variations compared to conventional postapproval variations.

Lessons Learned

As can be seen from both the Lilly and Janssen experiences, it is advisable to communicate early and frequently with health authorities, at least until additional industry experience is available and CM-specific regulatory guidance documents are published. Inviting health authorities to visit CM manufacturing sites proves to be valuable to gain mutual understanding of the proposed strategies. The additional avenues installed for regulatory interactions to seek advice on specific CM questions, such as FDA's ETT, EMA's PAT, and PMDA's IMT-WG, encourage early engagement. The ICH Q13 Expert Working Group has made visits to early-adopter companies to learn about their implementation strategies to ensure the Q13 guidance is as practical as possible.

Overall, the companies' experience has been that regulators are supportive of innovation as the global acceptance and understanding of CM increases rapidly. Additional specific regulatory guidance on CM will be helpful as more experience is gained; thus, efforts like the new draft FDA guidance on CM, the provisional draft document from PMDA, as well as the ongoing drafting of ICH Q13 are key in the continued CM journey.

CONSIDERATIONS WHEN INTRODUCING CM PROJECTS

Given the complexity of pharmaceutical development, it may be necessary to initiate product development with conventional batch processes, with the intent to pivot to CM processes for commercial production. For example, companies may need to consider a conversion from batch manufacturing to CM processes during the later stages of the development program prior to initial marketing authorization applications. Additionally, some companies may consider batch to CM conversion for approved products that are already on the market.

Potential changes to the formulation composition to address manufacturability considerations upon conversion to CM may add regulatory complexities, especially if these changes are introduced late in development, or as a postapproval change. Similarly, changes to the main manufacturing platform as part of the batch to CM conversion may introduce complexities as well (e.g., changes from dry to wet manufacturing platforms). While initially not applicable to CM, the 1995 US FDA guideline on scale-up and postapproval changes (SUPAC) for immediate-release (IR) OSD forms [9] may be consulted to assess the level of changes and justification that needs to be provided.

Based on the case studies, it is advisable that companies carefully assess the potential formulation or main manufacturing platform changes as part of the process conversion, as well as the time of introduction of CM. In general, the earlier changes can be introduced, the easier it will be to build a suitable package to justify the conversion to CM, including considerations involving in vivo performance or stability data packages of the drug product. Science- and risk-based approaches should be leveraged in these cases. Additionally, early dialogue with regulators to seek advice in such cases may be warranted, at least until additional industry

experience is gained, and CM-specific regulatory guidance documents are made available.

GUIDANCE DOCUMENTS

The upcoming ICH Q13 guideline, "Continuous Manufacturing of Drug Substances and Drug Products," is intended to describe scientific and regulatory considerations for development, implementation, assessment, and life-cycle management of CM processes. It will build upon the existing ICH guidelines, many of which remain relevant to CM, by adding clarifications and additional scientific and regulatory considerations specific to CM. ICH Q13 will facilitate international harmonization of regulatory expectations and could reduce barriers to the adoption of CM technology across regions. It will encompass drug substances, and drug products in both the chemical entities (small molecules), and therapeutic proteins (biologics) domains for both NCEs and approved products. From the published final concept paper [6], it can be seen that the upcoming ICH Q13 guideline will cover aspects such as CM-specific definitions and regulatory concepts (e.g., start-up/shutdown, state of control), key scientific approaches (e.g., material traceability, detection and diversion of nonconforming material, process models), and regulatory expectations with regard to initial marketing applications and batch to CM conversions.

As noted earlier, the US FDA published a draft guidance, "Quality Considerations for Continuous Manufacturing: Guidance for Industry," in 2019 [1]. This guidance delineates in detail the quality system considerations for CM, such as control strategy and process validation. Although it is a document in draft stage, it provides valuable detail in all aspects of CM implementation, from input material control to regulatory filing considerations, with important technological concepts described in between.

In Japan, the published provisional draft of "PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry" [2] provides insights for OSD small molecules on the following CM-specific aspects: control strategy, batch definition, validation, and stability testing. The two publications from the National Institute of Health Sciences, Japan, mentioned earlier [3, 4] provide additional details on CM-specific aspects such as understanding of process dynamics, handling of products obtained during process disturbance, and understanding steady state versus state of control.

These guidelines were preceded by ASTM E2968-14: *Standard Guide for Application of Continuous Processing in Pharmaceutical Industry* [10]. This standard aimed to present key concepts and principles related to CM and its implementation, while focusing on definitions of terms and concepts such as feedback/forward

control, process dynamics and operational aspects, process design and quality assessment and quality control.

While the application of RTRT is optional with CM, the integrated and data-rich intensity nature of CM processes can facilitate the adoption of RTRT. An important element of RTRT may be near-infrared spectroscopy (NIR), one of the major techniques applied in PAT. Several regulatory guidance documents relevant to PAT are available, including FDA's 2015 draft guidance document "Development and Submission of Near Infrared Analytical Procedures" [11], as well as FDA's 2004 guidance for industry on PAT [12]. In Europe, there are also relevant guidance documents [13, 14]. In Japan, the 2014 Sakura Bloom example for registering RTRT provides insight into the content of the pharmaceutical development section of a Common Technical Document when the drug product is developed using elements of the quality by design methodology, where RTRT and PAT are applied.

CONCLUSION

CM is a globally accepted manufacturing technology, which is being achieved without unexpected regulatory hurdles, for both NCEs and postapproval batch to CM conversions. Although initial cases for application of CM to produce pharmaceuticals required additional efforts by regulators and the industry to enhance understanding and gain alignment on approaches, more products are now being approved with CM in multiple markets, indicating continued global acceptability and support. Where the current CM experience is focused on OSD forms for small molecules, there are opportunities for CM in other classifications, such as for drug substances, generics, over-the-counter products, as well as CM by contract manufacturers. Ongoing activities in creating and updating CM-specific regulatory guidance documents are highlighting the support of regulators and their interest in seeing more adoption of CM going forward. Efforts like the finalization of FDA's guidance on CM, continued publications of Japanese CM-specific guidelines, as well as the adoption of ICH Q13 will be key milestones in the pharmaceutical industry's journey with CM.

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CONTINUOUS MANUFACTURING GOOD PRACTICE GUIDE Is Planned

By Gregory Connelly, PhD

The ISPE OSD Community of Practice Continuous Manufacturing Subcommittee is planning a Good Practice Guide to capture information developed over several years by the team to establish equipment requirements, identify opportunities for harmonization and flexible integration, and suggest where current equipment may be enhanced to work with continuous manufacturing platforms of the future.

The ISPE OSD Community of Practice Continuous Manufacturing Subcommittee was formed in 2017. Its mission is to be a forum that will advance the use of continuous manufacturing (CM) platforms and increase the long-term efficiency and affordability of CM oral solid dosage drug product equipment for vendors and users. The forum provides an opportunity for participants to share supplier-independent engineering-focused knowledge, strategies, and practices; deliver technical and operations solutions; and drive harmonization where it makes sense for CM.

Over the past few years, the international subcommittee has conducted a comprehensive assessment of pharmaceutical production systems for oral solid dosage (OSD) medicines manufactured using CM technology. Composed of industry practitioners, equipment vendors, academics, and leading service providers, the team has endeavored to produce a reference work with the following objectives: 1) establish a set of minimum equipment requirements for various pharmaceutical unit operations to be integrated as components of a CM line, including design considerations for the automated control systems; 2) identify opportunities for future harmonization and flexible integration of both physical equipment and control systems; and 3) identify areas where currently available equipment can be enhanced to meet the needs of the industry as the next generation of CM platforms are developed.

GPG PLANNED

The information is being organized as a Good Practice Guide, planned to be published by ISPE as part of its overall mission to be a leader for the pharmaceutical industry by producing various guidance documents to inform both practitioners and regulators. The planned guide, tentatively titled *Good Practice Guide for Continuous Manufacturing of OSD Medicines*, will provide a valuable reference for new and existing companies that design and integrate CM production equipment into their manufacturing operations. It will also serve to highlight best practices and opportunities for enhancement to both vendors and end users already engaged in implementing CM lines of the future.

Several unit operations currently used in the manufacture of OSD products are themselves inherently continuous. However, most pharmaceutical production has historically been carried out using a batch paradigm, where all material proceeds through each unit operation separately, with defined starting and ending points for each step. While industries such as chemical and petroleum products, semiconductors, and food production have successfully employed integrated CM platforms for years, the pharmaceutical sector has only recently begun to implement similar fully continuous platforms. Many companies have made significant investments in batch production equipment, process understanding, measurement systems and personnel, and the process of applying to regulatory agencies to change any existing (already approved)

The guide will provide a valuable reference for new and existing companies that design and integrate CM production equipment into their manufacturing operations.

process typically incurs significant costs in time and money. But the potential benefits of developing and producing pharmaceutical products using CM have been recognized by both industry practitioners and regulators, and since 2015 multiple products manufactured using integrated CM lines have been successfully developed and approved.

WORKING GROUP ACTIVITIES

The CM Working Group began by forming a subteam for automation and PAT, and multiple subteams focused on the various unit operations typically involved in the manufacture of OSD products: material handling, feeding and blending, wet granulation, roller compaction, and compression and coating. Membership consisted of subject matter experts from major pharmaceutical companies, individuals from academic institutions doing CM-related research (e.g., on granulation, tablet compression, residence time distribution, advanced process control), and vendors and suppliers.

Each unit operation subteam conducted a comprehensive survey to understand the key requirements for their respective systems to be successfully integrated into a continuous line. Recommendations were made independent of equipment type and vendor. Several groups also inquired about opportunities for enhancement of current offerings, including both specific pieces of production equipment and fully integrated CM platforms. The automation and PAT subteam conducted a survey of the requirements for achieving a sustainable and modular CM automation control system, focusing on challenges unique to CM such as achieving flexibility in line configurations, expediting equipment change-out on an integrated line, standardizing communication protocols, and structuring material tracking capabilities in support of these items.

Review of the data gathered from the unit operation subteams led to the development of a set of minimum equipment attributes for each type of equipment. These attributes acted as inputs for the automation and PAT group, enabling them to define a set of minimum system requirements and design considerations for controlled operation of integrated CM platforms. Current equipment and system offerings from vendors were analyzed against those requirements, and discussions were held to identify opportunities for further enhancements to both equipment design and operation. The desire for future systems to be more modular and flexible in their integration into CM production lines was also recognized.

As more companies integrate CM into their development and commercial operations, increased demand for more flexible, modular, and robust systems that can accommodate a wider range of products and production control strategies is likely. The planned *Good Practice Guide for Continuous Manufacturing of OSD Medicines* can serve as a comprehensive resource for pharmaceutical companies, regulators, and vendors in the industry as this nascent field continues to develop.

About the author

Gregory Connelly, PhD, is a Director of Continuous Manufacturing at Vertex Pharmaceuticals in Boston, where he has been a key driver of the Vertex CM program since its inception. He has guided the development of several Vertex products that are filed and approved as fully continuous processes. His team works to increase fundamental understanding of the various unit operations that comprise Vertex's CM platform, and they manage all design and qualification of system process equipment and control software. Greg holds a BS in physics and mathematics from Loyola University and a PhD in biophysics from the University of Pennsylvania. Greg is a member of the Working Groups for Continuous Manufacturing in both ISPE and the IQ Consortium, and he is the Vice Chair of the Drug Product Leadership Group within IQ. Greg's 20-year career in the pharmaceutical industry has spanned from early-stage research to commercial product development. He has been an ISPE member since 2020.

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NAVIGATING THE LIFE CYCLE for Cell and Gene Therapies

By Luciana Mansolelli, PharmD, and Diluks De Silva

Cell and gene therapies are complex. As more therapies come to market in the hope of bringing advanced treatments and cures to rare, orphan, and difficult-to-treat diseases, designing quality standards for these personalized medicines is equally as complex [1]. Throughout the journey of bringing these cell and gene therapies to market, companies need to collaborate with manufacturing partners, supply chain partners, regulators, and policymakers to manage the complexity of these therapies and establish appropriate quality standards.

Designing these standards requires agile approaches—similar to the agility essential for the strategic development, manufacturing, supply chain, and distribution that bring these disruptive innovations to patients worldwide. Successful quality standards creation also requires collaboration between regulators and pharmaceutical companies, which must all work together through uncharted waters and move swiftly to bring these therapies to market.

REGULATORS' ROLE

In a 2019 interview [2], Peter Marks, MD, PhD, Director of the US FDA Center for Biologics Evaluation and Research (CBER), stressed the part that regulators play in this collaboration:

> *We have an important role in providing regulatory clarity to innovators. Our job as regulators is to set the bar in accordance with statutory authorities for the degree of uncertainty that we are comfortable accepting for our society in reaching product-approval decisions.*

In support of innovation, agencies have created pathways to help product developers increase the speed of development. For example, the CBER Advanced Technologies Team (CATT) has created the Initial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) program to encourage early engagement between gene and cell therapy developers and the FDA. This collaboration provides enhanced flexibility and guidance for products requiring accelerated review paths, such as products that might receive the breakthrough or regenerative medicine advanced therapy (RMAT) designation as per section 3033 of the 21st Century Cures Act [3].

In the EU, the development pathway for cell and gene therapies involves the EMA Committee for Advanced Therapies (CAT), which is responsible for assessing the data and preparing a draft opinion on the quality, safety, and efficacy of the advanced therapy medicinal products (ATMPs). Additionally, the EMA Committee for Medicinal Products for Human Use (CHMP) issues an opinion recommending (or not) the authorization of ATMPs by the European Commission, which has the final decision [4, 5].

However, industry and regulators still have a ways to go on the journey to designing quality standards for the agile development and commercialization of these therapies. By collaborating with regulators and building strong partnerships, leveraged from professional and industry associations invested in the development of guidances, pharmaceutical companies can have a great impact on these standards.

PREPARING FOR SUBMISSION

Companies developing cell and gene therapies must involve health authorities early on to drive collaboration. Company representatives should plan presubmission meetings throughout the development process with all health authorities that will receive the submission. During these meetings, representatives should use available data to provide an up-to-date overview of the product—including information about the disease state, product attributes, the clinical and nonclinical data set, labeling, and safety—and preemptively discuss concerns, such as any potential issues that need to be resolved prior to submission.

Because of the unique nature of personalized medicine therapies, where one size does not fit all, companies need to ensure:

- All studies are tailored based on risk assessments related to the route of administration, viral vectors, target tissues, indications, and other factors.
- Product development complies with all good laboratory practices (GLP).
- Safety endpoints in disease models, including cytotoxicity and potency tests, are considered.

Companies also must ensure they will be able to respond quickly to regulators' questions. Onsite GMP inspections are not solely for evaluating quality systems and auditing the process; they also enable health authority representatives to deepen their knowledge about cell and gene therapies and chemistry, manufacturing, and controls (CMC) processes [6]. As the reviewers on the inspection team more frequently augment the preapproval inspection team, these inspections also provide the opportunity for company representatives to answer deficiency questions. A question database can help a company expedite and facilitate responses to questions from health authorities. Ensuring a quick response to regulators is also necessary during any periodic meetings with agencies and for requests point filing. During the COVID-19 pandemic, industry has experienced an increase volume of questions coming from regulators, as a means to fill in the gap of not being able to directly inspect sites. Some health authorities also performed remote inspections; in the virtual setup, the pace of questions and in depth reviews were heightened.

PROCESS DESIGN

In commercial manufacturing of cell and gene therapies, meeting patient and physician needs must be balanced with end-to-end product and process robustness. For example, because hospitals and collection centers are key contributors to incoming material variability (e.g., patient sample or donor), it is essential to provide clear requirements around cell collection protocols or to establish human cell collection programs at the collection centers, whichever best fits the design space based on the development experience of the product.

The organization must develop and implement decision-making processes that are aligned with the organization's quality systems while providing mechanisms to manage the complexity and variability of personalized medicines. Where possible and applicable, consideration should also be given to process and analytics automation to reduce process and throughput times and increase overall process robustness by controlling variability (e.g., using flow cytometry for incoming and final product characterization with automated cell classification and enumeration).

Because traditional GMP approaches do not always work in processes for cell and gene therapies, organizations should challenge the "whys" of every decision, while ensuring compliance and flexibility are maintained during the product release testing that confirms the safety, identity, strength, purity, and quality of each personalized patient batch. The extent of the patient material characterization should be commensurate to the process design and requirements to minimize unnecessary steps.

PRODUCT SPECIFICATIONS

For cell therapies, important usual attributes include viability, purity, and other functionality-related parameters that are product specific. Although defined on a case-by-case basis, these attributes are part of a release specification that is created in a phase of the development process when there is a still limited understanding of critical quality attributes (CQAs). Defining these specifications is further complicated by limited manufacturing experience and difficulties in characterizing the drug product, drug substance, and in-process materials. Furthermore, incoming cell characteristics are difficult to identify due to the complexity of the disease state and human genetics. In other words, there is no genetic match between two human beings.

Final product release, in this context, is an interesting example of the balance required between rigor in documentation and the urgency of the medication. Achieving this balance may require exceptional release pathways, which is another reason to maintain an ongoing dialog with health authorities. In many cases, these therapies are treating unmet serious conditions, and therefore, releasing product that does not meet the approved specification may be acceptable for compassionate use—the benefits of use may outweigh the risks.

From development to commercialization, cell and gene therapy companies should also consider:

- How, given the limited manufacturing experience, the organization will adequately define meaningful specifications that capture the true attribute ranges of acceptable quality, safety, and efficacy
- Which analytical methods are appropriate and fit for intended use
- How to appropriately set the acceptance criteria (e.g., upper and lower numerical limits)
- The inherent variability of the assay versus the variability of the product due to the variability of incoming starting material (i.e., incoming cells)

For example, if number of patients at the time of filing for an advanced therapy is small, the organization may have very limited manufacturing experience as it approaches the clinical pivotal phase. Therefore, the approach to setting process parameters and specifications should be conservative.

Although it would be ideal to design and conduct studies that identify and confirm the associations and relationships of attributes and process parameters to drug substance CQAs, this strategy is not always possible. Comparability runs will inherently be full scale and highly complex in terms of established acceptance criteria around process parameters and specifications (target values versus ranges).

The high variability of the cellular starting material—which is unique for each patient and affected by different treatment

protocols—may have additional impact on the consistency of the manufacturing process. It may generate out-of-specification or trend results that cannot be fully characterized for the final product.

This high variability in cellular starting material is why organizations must focus on the continuous control of variability in process and analytical methods during development and post-approval. It also reinforces the importance of close collaboration between industry and regulators so time-sensitive decisions in the interest of saving patient lives can be made.

In sum, when developing and manufacturing cell therapies, it is paramount to communicate with regulators as early as possible, build systematic approaches for constantly evaluating process performance, and improve understanding of the relationship between established CQAs and process robustness and consistency.

US FDA regulations, for example, bring clear expectations around safety testing. Sterility, endotoxin, and identity testing must be performed on samples from the final drug product stored in the final container. The sample strategy should accommodate this requirement, although it will not meet the "final container" requirement. Companies must be sure to validate the rapid methodology and demonstrate comparability to traditional methods, such as rapid sterility.

SUPPLY CHAIN CONSIDERATIONS

To ensure continued supply of cell and gene therapy products and a reliable supply chain during product development, alternative approaches and analytical pathways must constantly evolve. Supply-related issues may range from the need for waivers for local import testing to standardizing primary container labels to reduce handling of drug product and specific shipping validation that need to be executed.

Additionally, major CMC changes prompted by new sourcing for raw materials, such as viral vectors [7, 8], certain expansion media components, and others, must be carefully evaluated, as the newly sourced materials may require a comparability study and report. Companies can consider using impact-based comparability assessments—a risk-based approach that applies the concepts of ICH Q11 [9]—even if the variations are not directly in scope. Company representatives should be sure to discuss the planned changes or studies with the health authorities prior to implementation—and to establish appropriate controls along with second sources for all critical materials.

These considerations—along with other elements and the complexity of cell and gene therapies—have resulted in regulatory agencies shifting from prescriptive industry guidance to pharmaceutical companies being responsible for properly justifying the approach they adopt for sampling plans, batch disposition, retention samples, and provision to patients.

In the 2019 interview mentioned earlier [2], Marks said:

> *In some ways, this can be likened to a razor-and-razorblade model. In instances where there is something that we have seen before—the razor—we might have an established set of expectations. We could then focus our attention on the razorblade: the unique and different aspects of a particular product compared to all the others that we have seen.*

For cell and gene therapies, there are products that use a common set of technologies—such as some of the vectors, closed systems, and bioreactors. Collaborating across the industry and with regulators in these areas may bring more comfort as more products use the same underlying technologies, equipment, and processes. When the underlying technologies are nearly identical, there is no need to reinvent the wheel with each new product. Standard practices already exist in cell counting, measuring flow cytometry, and assuring cell viability. Collaborating on approaches that can be validated and highly characterized may streamline how therapies are brought to market and lead to increased assurance on behalf of the industry, regulators, physicians, and patients.

CONCLUSION

Like other pioneers, gene and cell therapy companies must continually learn, and be prepared to course correct when necessary. As the regulatory guidance on risk identification and mitigation for advanced therapies evolves, long-term safety and efficacy data on such therapies must be collected via long-term follow-up of clinical trial participants. Additionally, data from patient registries can play an important role in monitoring the safety and efficacy of cell and gene therapies, so ongoing discussions and guidelines are needed in this space [10]. The EMA initiative for patient registries launched in 2015 is one step in this direction [11]. This initiative and other efforts to promote regular discussions with registry holders, patient groups, marketing authorization holders, and agency representatives should be encouraged.

The possibility of enrolling postmarketing patients in existing disease registries with secondary use of data must be explored. Risk management should focus on risks related to quality characteristics, storage, and supply chain distribution of finished product—along with risks involving the donor, administration procedures, third-party transmission, and issues related to the use of viral vectors (immunogenicity, insertional mutagenesis, viral latency, and reactivation, etc.).

Great strides will be made if industry and regulators work together to continuously pursue advanced manufacturing and analytical technologies, develop strategies to provide robust and efficient pathways for manufacturing innovative therapies, and create sufficient flexibility in standards to support the innovation.

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ISPE Iberia Affiliate: Coming Together for Training and Support

By Marcy Sanford

The pharmaceutical industry in Spain and Portugal is growing, and the ISPE Iberia Affiliate—which has merged the Spain and Portugal Affiliates to take advantage of synergies between the two Affiliates—is working to train and support this expanding market.

With a population of 46 million, Spain is one of the largest European Union (EU) economies and the Spanish pharmaceutical industry is among the top four in the EU in total drug sales volume. It also ranks fifth in the EU in pharmaceutical production and fourth in the EU in laboratories [1]. Portugal, with a population of more than 10 million, also has an expanding and growing pharmaceutical industry, especially in biotech [2]. In 2008 several Portuguese research institutes, along with health authorities, universities, hospitals, and pharmaceutical companies, formed the Health Cluster Portugal, which has worked to strengthen Portugal in the research, design, development, manufacture, and marketing of health-related products and services [4]. This is a testament to the importance of the pharmaceutical industry in Portugal.

A GROWING INDUSTRY

Collectively, the pharmaceutical industry in Spain and Portugal generates 230,000 jobs, with more than 5,000 professionals working in research and development. Some of the top pharmaceutical companies in the region include Bayer Hispania SL, Grifols, S.A., Bioibérica S.A.U., Laboratorios Liconsa SAU, Kern Pharma SL, MSD, Teva Pharmaceuticals Industries Ltd., Sanofi S.A., AstraZeneca, Novartis Farma SpA, and GlaxoSmithKline plc [4, 5].

"National pharmaceutical companies are growing in both countries," said the ISPE Iberia Affiliate President Alfred Terés, Advisory Director, Aseptic Mind. "International companies are also investing in the region with more facilities specializing and focusing on specific products, especially injectables. Companies focused on high value products and animal health pharmaceutical companies are seeing more growth than companies dedicated to generics or low-cost pharmaceutical products."

Because of the industry growth, and thanks to interest from Portuguese ISPE members, in 2019 the Spain Affiliate (founded in 2007) started discussing the possibility of establishing an ISPE Affiliate that would include members from both countries. "We realize that Portugal and Spain have many synergies," said Terés. "We decided that the best solution was to merge into one Affiliate with two country-specific committees. Each committee promotes activities in their country in their own language but we allow the members in Portugal or Spain to participate globally in the activities of both. Since COVID-19, most of our activities have been virtual. This has made it easier to share activities across multiple regions. Depending on the topic and experts involved, sessions may be in Portuguese, Spanish, or English."

AFFILIATE GOALS

The main goals of the Iberia Affiliate are to create a training program for new pharmaceutical professionals and provide a place for members to ask questions and exchange knowledge and experience as well as offer information about developing industry standards. Terés said training initiatives are being led by the Affiliate in both countries. "In Portugal we started a pilot program where senior members of the Affiliate train new professionals in the pharmaceutical industry in different knowledge areas. In Spain we are working with other training programs. We will evaluate the pros and cons of each and come up with one program that combines the best practices of both."

Despite the challenge of creating a new Affiliate while people in both countries have been on lock down, members of the Iberia Affiliate were able to organize a robust offering of webinars and training in 2020 and 2021 including ones on Pharma 4.0™, GAMP®, Annex 1, water for injection (WFI), and single-use technology versus standard systems. Like most people around the world, Iberia Affiliate members began using teleconferencing platforms for meetings and conferences. Terés said that has actually expanded the exchange of information options between people in the two countries. "Using conference tools has made it easier to share activities in multiple regions. We have been able to offer a lot of different programs and webinars including programs to allow members to share their experiences and changes inside the pharmaceutical industry due to COVID and the measures they have implemented to continue working."

Terés said the Iberia Affiliate has expanded the network, knowledge, and opportunities for all members. "ISPE is a meeting point. Being a member allows you to learn, to share experiences, to meet professionals carrying on similar job positions. The Affiliate helps you to grow professionally, gives you a better understanding of different points of view on a topic, gives you the knowledge to improve your skills, and helps you to stay updated on what is happening in the industry."

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About the author

Marcy Sanford is the Editorial Assistant for ISPE's Publications Group.

Quick Facts about the ISPE Iberia Affiliate

- **Founded:** 2007 (Spain Affiliate)
- **Name:** Changed to Iberia Affiliate in 2020
- **Region:** Spain and Portugal
- **Membership:** 184

Officers

- Chair: Alfred Teres, Aseptic Mind (Spain)
- Vice Chair: Amjad Wahbeh, Hikma Farmaceutica S.A. (Portugal)
- Secretary: Diego Rodríguez, Lonza AG (Spain)
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ISPE BRIEFS

ISPE Foundation Update: Diversity Internship Program

The ISPE Foundation Diversity Internship Program has received strong response from applicants and has launched a new partnership.

The ISPE Foundation and Nephron Pharmaceuticals Corporation have announced a partnership on the ISPE Foundation Diversity Internship Program's newest cycle to provide world-class opportunities to groups that are typically underrepresented in the pharmaceutical industry.

Established in December 2020, the pilot ISPE Foundation Diversity Internship Program received a strong response from applicants. The series with Nephron will be a 12-week experience that offers graduate and undergraduate students in their junior or senior year the opportunity to spend the summer working on priority projects for one of the fastest-growing pharmaceutical companies in the country.

NEPHRON INTERNSHIPS

Nephron, based in West Columbia, South Carolina, develops and produces safe, affordable generic inhalation solutions and suspension products. The company also operates an industry-leading 503B Outsourcing Facility division, which produces prefilled sterile syringes and IV bags for hospitals across America in an effort to alleviate their drug shortage needs.

"We pride ourselves on two things: first, we do everything we can to make sure that everyone has a chance to achieve their dreams, and second, we utilize interns and apprentices in everything we do—they are playing key roles in our expansion and growth," said Lou Kennedy, CEO, Nephron. "This is why I am so excited to partner with the ISPE Foundation to rollout these new internship opportunities. They represent a win-win—for participants and for our company. We are proud to invest in talented young people, and we are excited they want to invest in us. We cannot wait to get started."

Multiple internship opportunities through the ISPE Foundation-Nephron partnership will include the following departments: Analytical Services and Formulation, Molecular Biology, and Engineering. The individuals participating in these internships will play key roles in Nephron's ongoing projects. They will work directly with the entire Nephron team and they will make a difference for patients across America.

GILEAD INTERNSHIPS UPDATE

Two interns have been selected from a pool of highly qualified applicants for the ISPE Foundation Diversity Internship Program with Gilead Sciences. The program with Gilead was the first to be established in the Diversity Internship Program. Abbey Kim, a senior at San Jose State University, graduated in May with a bachelors degree in chemical engineering. Wendy Wong is a senior at the University of Southern California, and graduated with a masters degree in mechanical engineering in May.

The inaugural cycle is a 12-week summer program focused on high-priority, impactful engineering and facilities projects and workstreams in Gilead's Corporate Operations organization. The two interns will engage in a wide range of activities, such as creating standard equipment or discipline specifications with input from subject matter experts, developing standard installation details in AutoCAD as part of GEP, supporting various PI projects, e.g., checking on data integrity (non-GMP related work).

FOR MORE INFORMATION

Visit ISPEFoundation.org/Diversity-Internship-Program to learn more about the program.

For information about the ISPE Foundation, visit ISPE Foundation.org

Share Your SIG, CoP, Chapter, or Affiliate News!

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

New Good Practice Guide on Knowledge Management Debuts

The new *ISPE Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* discusses the benefits of knowledge management (KM) in the pharmaceutical industry and how KM can enable a more effective pharmaceutical quality system (PQS).

"Knowledge management focuses on how organizations create, manage, and use knowledge throughout the lifecycle of a product. Along with quality risk management (QRM), KM is one of the two enablers of an effective pharmaceutical quality system as defined by ICH Q10," said Paige Kane, Guide Team Co-Lead, Director Knowledge Management, Merck & Co., Inc., in Rahway, New Jersey. "Employing KM methods and tools enables organizations to better manage their knowledge as a key asset, which then improves the effectiveness of the pharmaceutical quality system, providing operational benefits and more."

While the pharmaceutical industry has made significant progress in adopting QRM into systems and processes, it has been slow in implementing KM, thus missing the quality, operational, and employee engagement advantages KM practices have to offer.

"There are currently few resources, and no industry guidance available, to address the role of KM specifically for the pharmaceutical industry. This guide works to demystify KM and provides practical guidance, templates, case studies, and references to related ISPE industry guidance to help organizations better understand what KM is, the benefits of effective KM, and how to deploy KM," said Melanie Byrne, Guide Team Co-Lead, Knowledge Management Lead, Pfizer.

For more information about the guide, visit ISPE.org/publications/guidance-documents

—Marcy Sanford, ISPE Editorial Assistant

MEET THE ISPE STAFF

BRANDON PASTORE

In each issue of *Pharmaceutical Engineering*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Brandon Pastore, Senior Director, Professional Development.

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

At ISPE, my focus is on our members by continuously searching for new content and opportunities to share the knowledge and experience necessary to be successful in the world of pharma. I work closely with Tina Li, Training Coordinator, in my role, which includes the operations of our professional development programs as well as future endeavors in partnerships and content expansion.

What do you love about your job?

I love working with the people at ISPE. My colleagues are a true team. There is a spirit of partnership at ISPE that is refreshing, and I enjoy being a part of that every day. That partnership is also alive and well in our volunteers. Both hold to one common goal: improving the knowledge and expertise of our pharmaceutical community around the globe. The value that being a part of this team brings me is unlike any other that I have experienced.

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

I am a family man and I love to spend time with my wife, Marlo, and two kids, Natalie and Lorenzo. We love to look for adventurous opportunities together as we explore our new state of Florida.

SOFTWARE AS A MEDICAL DEVICE FUNDAMENTALS

By Whitney Hartung, Dr sc, John Schalago, Claudio Rossi, and Richard Pavkov

Software as a medical device (SaMD) is software intended to be used for one or more medical purposes without being part of a medical device [1, 2]. Although SaMD applications have the potential to improve patient care and expand the pharmaceutical industry's product lines, companies must understand the distinctive characteristics of this software and address the risks and challenges related to SaMD design, development, regulation, and life-cycle management.

SaMD is one of many medical and nonmedical uses of software in healthcare (Figure 1). For regulatory purposes, SaMD products should not be mixed up with (a) wellness apps or (b) software with a medical purpose that is embedded in a medical device. There are many connected devices and apps that can be used exclusively for wellness or general well-being purposes, such as weight management, physical fitness, sleep tracking, and stress management. Given that these types of devices and apps pose little risk to consumers, the US FDA exempts them from premarket review [3]. However, if an app includes medical-related functionalities, such as analysis of data from a sensor for physiological monitoring for a medical purpose that poses moderate to high risk, the app is regulated as a medical device subject to a higher risk classification and premarket review. (SaMD regulation is discussed in greater detail later in this article.)

Regulators exclude software with a medical purpose that is embedded in a medical device from the definition of SaMD because the embedded software (e.g., insulin pump software controlling pump functionality and managing data) is an integral part of the hardware/medical device [4]. In contrast, an SaMD typically runs on a nonmedical computing platform, either directly on a smartphone or on remote servers running in the cloud.

SaMD products fall into two main categories [1]:

- Software connected to/interfaced with a medical device
- Standalone SaMD

Examples of connected/interfaced SaMD products are companion apps with scheduling, monitoring, and sharing functionalities, which are connected via Bluetooth Low Energy to drug delivery devices [4]. Standalone SaMD products are used to assist in the treatment of substance use, schizophrenia, amblyopia [5] and stereopsis vision disorders [6], as well as for diagnosis (e.g., for ophthalmic disease progression) [7].

For pharmaceutical companies, SaMD products are attractive opportunities to offer additional services to patients and caregivers, such as tools for educating patients and managing diseases and tracking symptoms and treatments. Companies can take advantage of many new technologies, such as innovations in imaging processing, data mining, artificial intelligence, and machine learning, to develop digital products that complement their existing portfolios and development pipelines.

For example, SaMD products may help patients adhere to their drug regimens, build good habits, and manage symptoms actively and remotely. The software or app may even offer features that help physicians diagnose a disease or monitor disease progression.

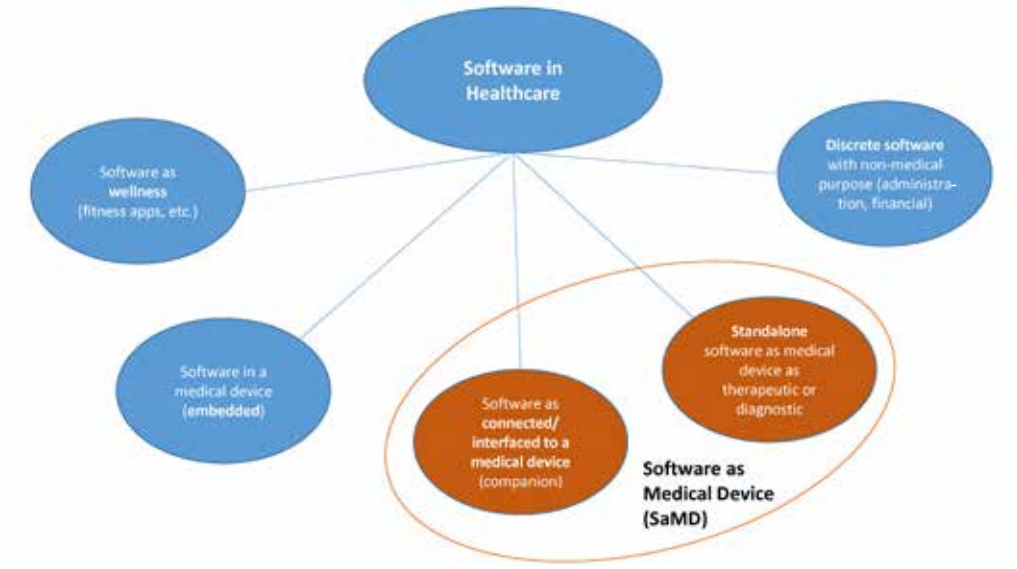
Additionally, digital therapeutics can strengthen or reinforce other forms of therapy. For example, a digital therapeutic currently in development for amblyopia utilizes gaming to train the eyes [5].

DATA COLLECTION BENEFITS AND RISKS

With the consent of the patient, SaMD can be used to collect data, either inside or outside of a clinical setting. SaMD tools may be developed to track patients' medication use or adherence, or to monitor disease progression or therapeutic effect. Pharmaceutical companies, healthcare providers, researchers, and regulators can analyze such data to learn more about how patients use particular drug products, how often they are prescribed, or what habits patients have in relation to the use of the drug product.

This type of data collection can be a source of information that is different or less expensive to capture than data from a clinical study or focus group. Additionally, SaMD data may be collected from a significantly larger population or sample size than those studied in traditional clinical studies. For instance, an app associated with a diabetes medication can give the patient an opportunity to track weight, blood sugar, or dietary changes [8]. The

Figure 1: **Software in healthcare.**



collected data can be used to improve therapies by identifying preferences of patients or healthcare professionals. When a diagnostic tool is based on machine learning, continuous data collection can be used to validate assumptions and collect further data to improve later versions of the products.

Although data collection can be an opportunity for pharmaceutical companies, it is also a risk. Companies must comply with various rules and regulations regarding storage, privacy, and use of data, which can differ significantly from country to country. User agreements and consent forms must include all ways the company wishes to use the data, and the user must be informed of and give consent for how the data will be collected and used. In many cases, user anonymity must be guaranteed, as this is required by regulation and expected by consumers and patients. Finally, data must be stored and accessed in a secure way, and protective measures against cybersecurity attacks must be taken. Pharmaceutical companies are experienced in the collection and protection of clinical study data, but the rules and regulations for data collection and storage activities related to data collection via software may be unfamiliar territory.

DEVELOPMENT PREREQUISITES

Before embarking on SaMD development, companies should carefully consider the resources needed, the timelines, how the organization will need to adapt its processes and culture, and the potential return on investment.

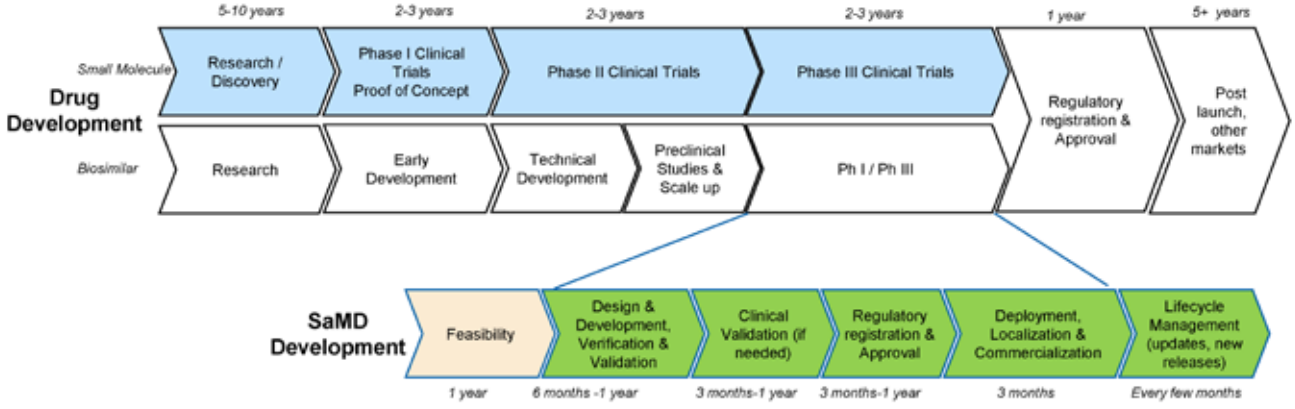
SaMD involves many activities outside of the core competencies of pharmaceutical companies, and this contributes to the risks and challenges of offering digital products. For example, although a pharmaceutical company will likely have a large IT organization and experts in GxP and computerized system validation, managing SaMD products requires different types of IT expertise, which will need to be built within the company and may also depend on help from external vendors.

Similarly, medical device knowledge is typically limited to the relatively small part of the company that develops, tests, and registers medical devices, and the expertise of those working with medical devices may itself be limited to conventional devices for delivery of pharmaceuticals (e.g., single integral combination products, such as prefilled syringes), which may not be considered medical devices from a regulatory perspective. As a result, some companies may not have any employees with sufficient knowledge of the regulatory pathways of medical devices, especially SaMD products.

The phases in the product development and design control process for SaMD products are the same as those for other medical devices, but the phases are often compressed and combined in unaccustomed ways that require specialized expertise and organizational flexibility. For instance, the design and development phase of an SaMD application may make use of agile project management methodologies that combine the development and verification phases, and these kinds of software tests can be performed in a matter of hours (and repeated in case of changes during the development). Also, in contrast to the relatively linear development processes of drug products and other medical devices, SaMD development is a process that continues over the life cycle of the product, with repeated development loops aiming to continuously improve the product.

As a result, the timelines for developing digital products can be in the range of months or a couple of years, which means the time to market for an SaMD product is likely to be much shorter than the decades-long effort that may be needed to develop a new drug product in combination with a "standard" mechanical device such as an inhaler (Figure 2). All parts of the organization, including the marketing and commercial divisions, may need to learn to adapt

Figure 2: Drug development versus SaMD development.



to the shorter timelines of SaMD development and ongoing update/release cycles.

On the other hand, the organization may have unrealistic expectations of extremely short timelines, similar to those for nonmedical apps. The time to market for an SaMD app is longer than for a wellness app because SaMD products are subject to regulatory requirements and must undergo regulatory submissions that can take months, especially if the SaMD product involves novel technologies. (A de novo submission to the FDA may be expected to take a year to complete.) Additionally, compared to wellness apps, SaMD products usually take longer to develop because they involve greater risks, including security risks.

Large pharmaceutical companies have very complex business processes and governance procedures. These are well suited for the risks and payoffs of developing drugs, but they may not be a good fit for an agile and efficient software life-cycle management process, which requires frequent software releases and updates. Organizations will therefore need a business case and value proposition comparatively early in the development of SaMD products to ensure that the products can be designed to meet the needs and requirements of the patients, healthcare providers, and payers.

As the business case is built, the company must recognize that although SaMD products show great promise in general, their value proposition is still not proven. While SaMD products cost much less to produce than new drug products, they will likely generate only a fraction of the revenue of a typical drug product. This discrepancy can make it difficult to fit digital projects into a company's overall strategy. It can also be easy to underestimate the real costs (including life-cycle management) of these types of projects, especially when there is a learning curve for the company. The payoff will not be instantaneous.

To guarantee a quicker path to digital product realization, good planning, clearly defined requirements/needs, and stakeholder management are essential. First, it is necessary to identify stakeholders early in the project. Whereas branding, labeling, and packaging typically come into later phases of a project, the visual nature and importance of language in most SaMD products requires that these stakeholders become involved earlier in the process.

The various user needs and requirements of patients and healthcare providers should be identified as early in the project as possible, to ensure clarity and avoid delays in the project. Language, country-related treatment differences, and even cultural requirements must also be identified before work on user interfaces is begun.

Relevant regulations should also be identified before work begins. These can include specific requirements for medical devices, SaMD apps, and data collection, use, storage, and security (e.g., the EU's General Data Protection Regulation [9]).

Questions about the design of the SaMD product, such as which operating system or platform (smartphone, tablet, or web service) will be used, should also be clarified in the early stages of development.

The company must also be aware that vendors used for SaMD fall under the scope of the vendor management system, and the vendor qualification must be carried out as for any medical device. It is not unusual for a single project to use multiple vendors—for instance, one for the user interface, one for the back end, and another for cybersecurity testing—as well as various consultants. Vendor management, including the management of inter-vendor communication, can add significant complexity to a project; however, choosing the right vendors for the components of the software will also help ensure the success of the project.

Design validation of the SaMD product is another area that may pose challenges for pharmaceutical companies. As with other medical devices, the design validation must show that product fulfills the user needs. Many of these user needs can be assessed by performing human factors evaluations to ensure that ergonomic and usability requirements are met in the final product.

Clinical evidence is also necessary in validation to show that desired clinical outcomes can be achieved. Clinical studies for SaMD products may be a challenge for a pharmaceutical company used to performing Phase I, Phase II, and Phase III studies.

Although the methods for SaMD clinical studies are the same as those for other medical devices, SaMD studies may be somewhat smaller, depending on the product's level of risk. However, companies need to be aware that EU and US regulations for SaMD clinical data are becoming more complex, and the types of clinical data to be collected for a given SaMD product depend highly on the product's purpose and risk classification.

DEPLOYMENT AND LIFE CYCLE MANAGEMENT

The life cycle of an SaMD product differs to some extent from the life cycle of a classic medical device, and significantly from the life cycle of a drug product. Once a drug product is approved, it typically undergoes as few changes as possible, since a change often necessitates filing an amendment with the regulatory authorities and possibly requires new clinical data. In contrast, software must be updated continuously to keep up with operating system updates, security concerns, and ever-changing hardware. Also, software updates provide opportunities for the developers to make changes based on customer feedback and add new features to stay competitive.

Although software updates are necessary, making frequent updates to SaMD products can be difficult because medical devices have stringent change control requirements—any change in a design or process must be verified and validated unless it can be shown to have no impact on the function and safety of the device. Depending on the organization, the change control process can last weeks to months.

Pharmaceutical companies may need to adapt their processes for handling complaints from patients and healthcare providers to address SaMD-related complaints. Depending on the software design, it may be easier for a user to register a complaint, which may lead to an increase in the frequency or volume of complaints. The distributor and/or developer of software is required to investigate complaints and report any adverse events to the health authorities within a defined time frame [10, 11]. Since updates are released frequently, the company must be prepared to investigate (and report, if required) potentially large numbers of complaints within the time frame required by internal company processes and health authorities. The complaints may also be received directly by a vendor or partner, if they are hosting the software; therefore, a robust quality agreement detailing the various responsibilities of all parties in the complaint investigation and reporting is essential for an effective product vigilance process.

To effectively manage the demands of SaMD life-cycle management, the company may need to establish a so-called DevOps organization to react quickly to customer complaints or bugs and promptly implement changes and product improvements. This most likely will involve a flexible, cooperative arrangement with vendors, and reactive product vigilance and complaint-handling processes.

To expedite certain activities, the DevOps organization may operate outside of the normal business processes used for nonconnected medical devices or drug products. For instance, the change control process may allow software vendors to make certain types of security-critical updates without the approval of all departments of the pharmaceutical company, as long as the updates do not affect any function-critical or regulatory aspects. To maximize its efficiency, the change control process must have clear criteria for which departments should be involved in particular types of change. For instance, many types of change may not require regulatory reporting, so the criteria for involving the regulatory team must be clear. In some companies, the DevOps organization may have a streamlined structure, including a specialized regulatory department to assist in reporting any regulatory-critical changes to ensure that the essential functions are available for life-cycle management.

During contractual negotiations with third parties providing software, companies must make sure to address service management. This includes not only the provisioning of services in a normal situation but also setting up protocols to manage potential service disruption scenarios. These protocols should be designed to mitigate any inconvenience to the pharma company or the users of the software, including the transfer of services to a third party where possible. This ensures that contingencies are in place for managing to the extent possible the potential risks that data used for a specific application will be lost or inaccessible.

There are currently a number of standards for SaMD deployment; the most important is IEC 62304: *Medical Device Software–Software Life Cycle Processes* [12]. Additionally, the ISPE *GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications* [13] provides information specific to mobile phone apps, including guidance on when to retire a mobile app, data privacy, and issues related to connectivity.

REGULATORY CONSIDERATIONS

There are two types of regulated software for medical devices:

- Software integral to a medical device (software in a medical device)
- Software as a medical device

Table 1 summarizes how the US FDA and the EU currently classify regulated medical device software according to their level of risk. Note that as many new types of software, such as clinical support software, as well as new technologies, such as artificial intelligence and machine learning, are being developed, regulations are developing concurrently. For instance, the FDA has issued a draft guidance on clinical support software [14].

FDA

Over the past decade, the FDA has developed a risk-based approach to regulating SaMD while aligning its regulatory approach with the evolving nature of digital devices. FDA regulations vary by risk classification and aim to set the level of control required to ensure a safe and effective medical device:

- Class I SaMD products are subject to general controls, including manufacturer establishment registration and device listing, but most are not subject to a review process prior to being placed into US commerce.

Table 1: US FDA and EU medical device classifications

US FDA	EU
Class I: low risk • Example: otoscope mobile application	Class I: low risk Example: fertility tracker
Class II: moderate risk • Example: mobile app to monitor physiological processes	Class IIa: low–medium risk • Example: mobile app to monitor physiological processes that are not considered to be vital Class IIb: medium–high risk • Example: mobile app intended to analyze a user's heartbeat, detect abnormalities
Class III: high risk • Example: Closed-loop application (e.g., artificial pancreas)	Class III: high risk • Example: Closed-loop application

- Class II SaMD products are subject to general and special controls and 510(k) premarket notification marketing clearance.
- Class III SaMD products are subject to the premarket approval application process and must be supported by clinical evidence of safety and effectiveness.

For more information on the FDA approach to regulating medical device software, refer to the agency's "Policy for Device Software Functions and Mobile Medical Applications" [15] and its webpage dedicated to SaMD [16].

EU

In the European Union, medical devices are regulated under the Medical Devices Directive (93/42/EEC) [17] and the In vitro Diagnostics Directive (98/79/EEC) [18]. Pursuant to the directives, standalone software has a "medical purpose" if it is intended by the manufacturer to be used for humans for the purposes of (a) diagnosis, prevention, monitoring, treatment, or alleviation of disease; (b) diagnosis, monitoring, treatment, or alleviation of, or compensation for, an injury or handicap; (c) investigation, replacement, or modification of the anatomy or of a physiological process; or (d) control of conception.

Under the 93/42/EEC directive [17], the conformity assessment for a Class I device is performed by the medical device manufacturer. A certified Notified Body (NB) assessment of conformity is required for devices in Classes IIa, IIb, and III.

Under the 98/79/EC directive [18], in vitro diagnostic devices are classified into four categories: general in vitro diagnostics, self-testing in vitro diagnostics, List A, and List B. A general in vitro diagnostic device is self-certified by the manufacturer. NB assessment of technical documentation is required for self-testing, List A, and List B in vitro diagnostic devices.

Guidance about the classification of standalone healthcare software is offered in the European Commission's "Guidelines on the Qualification and Classification of Stand Alone Software Used in Healthcare Within the Regulatory Framework of Medical devices" [19]. In these guidelines, the criterion for medical device classification is whether the software is intended to interpret or facilitate the interpretation of data by modifying or representing health-related individual information.

In 2019, the European Working Group on Borderline and Classification issued an updated version of the "Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices" [20], which provides guidance for cases in which the classification of a device as medical is not straightforward.

In 2017, the European Commission promulgated the Medical Device Regulation (MDR) 2017/745 [11], which goes into effect in 2021, and the In Vitro Diagnostics Regulation (IVDR) [21], which goes into effect in 2024. Under the MDR, SaMD is classified under Rule 11 based on the level of risk associated with its use. The MDR also defines SaMD as software that drives a device or influences the use of a device. Further, the MDR specifically exempts software intended for general purposes, even when used in a healthcare setting, and states that software intended for lifestyle and well-being purposes is not a medical device.

In response to the COVID-19 pandemic, the European Commission postponed the application date for the MDR to 26 May 2021.

In October 2019, the Medical Device Consulting Group released "Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745–MDR and Regulation (EU) 2017/746–IVDR" [22]. The document defines the criteria for the qualification of software that falls within the scope of the new medical device regulations and provides guidance on the application of classification criteria for software.

CASE STUDY

The following case study of an inhaler and drug product packaged with a sensor highlights challenges that pharmaceutical companies face when introducing SaMD products to the market.

The Business Case

A major reason why asthma patients and patients with chronic obstructive pulmonary disease fail to respond to treatment is poor

Figure 3: Attachment of the sensor to the inhaler. (Image courtesy of Propeller.)

compliance to prescribed treatment programs. In particular, suboptimal adherence to asthma treatment can affect more than 50% of patients prescribed such treatment [23].

To address this problem of poor treatment compliance, Novartis initiated a partnership with Propeller Health, a digital health company that develops and manufactures a variety of sensors that track when the patient takes a dose and communicate medication use to the app on the patient's smartphone. These sensors can attach to various types of inhalers, including dry powder inhalers commonly used for maintenance treatment as well as pressurized metered dose inhalers commonly used for acute rescue treatment of exacerbations with short-acting beta antagonists. Using Novartis-developed acoustic technology, Propeller developed a sensor that can be attached to a Novartis inhaler, enabling patients to use the Propeller digital health app to manage their condition in partnership with their healthcare providers.

Novartis and Propeller initially partnered to use the sensor in clinical trials to record when patients were taking their doses, as the recording of medication use by a sensor was expected to be more reliable than self-reporting. However, Novartis saw the drug-device combination as a way to distinguish its inhalation products from other inhaled therapies expected to reach the market at nearly the same time. Thus, the business case quickly evolved into an opportunity to co-package the sensor with a drug-device combination product, creating an SaMD-enabled product that can motivate patients to take their maintenance medication regularly by providing reminders to patients while tracking and trending their inhaler use.

Product Features

The sensor is provided to patients as a system pack, which contains an inhaler device, the sensor (shown in Figure 3), and app access, along with the first 30-day supply of the drug product, in the form of capsules for inhalation. For the subsequent months, the patient can be prescribed a typical inhaler/drug patient kit, which includes a 30-day supply of medication along with the inhaler. The patient will remove the sensor from the used inhaler and attach it to the fresh inhaler. The sensor can be used for up to one year, and then the patient can be prescribed a new system pack.

The sensor itself has several functions:

- It senses when the patient takes a dose.
- It reminds the patient when it is time to take a dose.
- It communicates with the smartphone app to show various dosing trends, dose reminders, and other useful information for people with asthma.

The associated smartphone app is an example of SaMD interfaced to a medical device. Its features, in addition to the sensor, are:

- It allows patients to review their asthma medication regimen for the day and receive useful information about their disease, weather, and other triggers.
- It provides information about the patient's weekly or monthly medication use.
- It allows patients to view details for each use of their medication, add rescue inhaler use events, and record symptoms.
- It contains reports that can be shared with a healthcare provider, information on prescribed inhalation therapies with specifics on when dose reminders are set, and other information related to the sensor itself (e.g., sensor attachment and removal instructions).
- It enables patients to add other medications (such as rescue treatment) for manual tracking.

Data from the sensor also creates a web-based report about the patient's use habits of their therapy, which healthcare providers

can access via email (with patient consent) or discuss with the patient during appointments. This report can help the HCP work more closely with the patient, make better-informed therapeutic decisions, and give appropriate advice to improve patient adherence to the treatment regimen.

Regulatory Approval

The sensor variants currently have FDA 510k approvals and are distributed within the US. In anticipation of entering the European market, the sensor underwent a conformity assessment to obtain the required Conformité Européenne (CE) mark, which demonstrates that the sensor meets the legal requirements to ensure it is safe and performs as intended, as required previously under the EU's MDD, and under the MDR when required.

The companies believed that healthcare providers would appreciate the convenience of prescribing a kit containing the inhaler and medicinal product as well as a sensor in the same package. Therefore, they decided to include the system pack (containing the inhaler, drug product, and sensor) in the submission for the drug product.

Among the many challenges in bringing the system pack to market was determining the precise role that Novartis would play in the distribution of the sensor. By supplying the sensor as a part of the system pack, Novartis took on the role of a "system assembler" under the EU regulations (MDD and MDR). Under the MDR, a system assembler is considered to play the economic roles of manufacturer and distributor. Because of this, Novartis needed to show that the sensor was appropriate to use with the inhaler and drug product. A full medical device development project was initiated for this system pack, with user needs, design inputs and outputs, risk management, verification testing, and validation testing, which included a human factors summative study.

This development process was risk based and consisted of assessing the interface/interoperability of the sensor and app with the user, inhaler, and drug product as a supplement to the existing technical documentation of the system. For instance, the use-related risks included setting up the system incorrectly and the effects of getting dose reminders from the sensor and/or app. Additionally, system risks were assessed for any potential effect that the sensor could have on the pharmaceutical performance of the inhaler (e.g., due to the sensor's electronics or by limiting inhaler functionality).This all had to be completed under ambitious timelines, before the scheduled drug product submission to EMA.

As a system assembler, Novartis had to ensure that the app content was aligned for EMA regulations. Although the sensor is CE marked, it did not undergo EMA approval, and the app content is considered by EMA as drug product labeling because it instructs users on how to administer the drug. To ensure that the initial version of the app as well as any updates conformed to EU regulations, a review process was developed, which included the country pharmaceuticals organizations because the app is available in many languages. This review process assessed, among other topics, the app content related to dosing. For instance, the app was required to instruct patients to take exactly one dose daily, as is instructed by the patient leaflet. Also, the app had to avoid any implication of direct-to-consumer marketing, which is forbidden in the EU.

Finally, the quality agreement between Novartis and Propeller had to define the various roles of both companies in the event of a customer complaint, as either partner could potentially receive complaints for the other's product. This agreement had to include the specific responsibilities of each party to pass on any information to the respective manufacturer of the components. For instance, Propeller, as the developer of the app, is likely to be the first point of contact for any customer questions or complaints; however, Novartis is responsible for the drug product safety. Therefore, if Propeller receives a complaint about the drug product, they are required by the quality agreement (as well as European regulation) to pass on this information within a specific time frame so that Novartis can investigate if an adverse event has occurred.

Despite all of these challenges, the project was a success. The joint EMA approval of the drug product, along with the system pack, was the first digital approval in Europe of a sensor with an inhalation product.

CONCLUSION

SaMD products are becoming increasingly important user-centric products for the pharma industry. A clear understanding of the SaMD risk categorizations and regulations is essential when determining the development and life-cycle management effort. As described in this article, SaMD products, especially when connected to sensors and drug delivery devices, have the potential to substantially improve therapy outcomes (compliance, training, behavior change, etc.) compared to what has been possible with conventional medical devices.

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MEDICAL DEVICE UDI COMPONENTS MANAGEMENT in the European Union

By Laurence Azoulay, Marie Coulon, PharmD, Christophe Devins, Bernard Durand, Etienne Granier, Amel Guerrida-Marchand, Ye-Lynne Lee, Valérie Marchand, Patrick Mazaud, Brigitte Naftalin, Michel Raschas, Nadim Wardé

Since 2019, the ISPE France Affiliate's Unique Device Identification (UDI) Medical Device Work Group has been producing tools to help project stakeholders within the EU or overseas understand and comply with EU regulations of UDIs in medical devices. Some of those tools are highlighted in the article.

The EU has regulated medical devices for decades. In the early 1990s, the Directive on Active Implantable Medical Devices (90/385/EEC) [1] and the Medical Device Directive (93/42/EEC) [2] were introduced, followed by the In Vitro Diagnostic Medical Devices Directive (98/79/EC) [3] in 1998. Building on those directives, the EU instituted in 2017 the Medical Device Regulation (MDR 2017/745) [4] and the In Vitro Diagnostic Medical Device Regulation (IVDR 2017/746) [5].

A regulation is a binding legislative act applicable in all EU member states without the need of transposition into national law, whereas a directive sets out goals that all EU countries must achieve. Therefore, it is often faster to put a regulation in place, as countries do not have to come up with their own laws on how to achieve a common goal. It can also avoid discrepancies in application [6]. The general application dates of the two regulations are 26 May 2021 for medical devices and 26 May 2022 for in vitro diagnostic medical devices; however, different timelines apply for certain specific provisions.

This article focuses on the UDI part of the new regulations. It does not cover all MDR and IVDR requirements for entering medical device data in the European database on medical devices (EUDAMED).

WHAT'S NEW IN MDR AND IVDR?

To advance the safety of medical devices, MDR and IVDR introduce a variety of new or reinforced requirements, ranging from stricter ex ante (forecast-based) control for devices via a new premarket scrutiny mechanism to more postmarket surveillance requirements for manufacturers. Compared to the directives, the new regulations have an extended scope (i.e., they include certain aesthetic devices and certain products specifically intended for the cleaning, disinfection, or sterilization of devices). They also provide more transparency and better coordination mechanisms between EU countries as well as a new risk classification system.

Among the major changes that impact medical device production, assembling, and packaging, as well as data management related to medical devices, are new traceability requirements based on UDI and rules for reporting medical device information to EUDAMED. UDI is intended to help track and trace medical devices throughout the entire product life cycle, increase transparency at all levels, and combat counterfeiting.

WHAT IS EUDAMED?

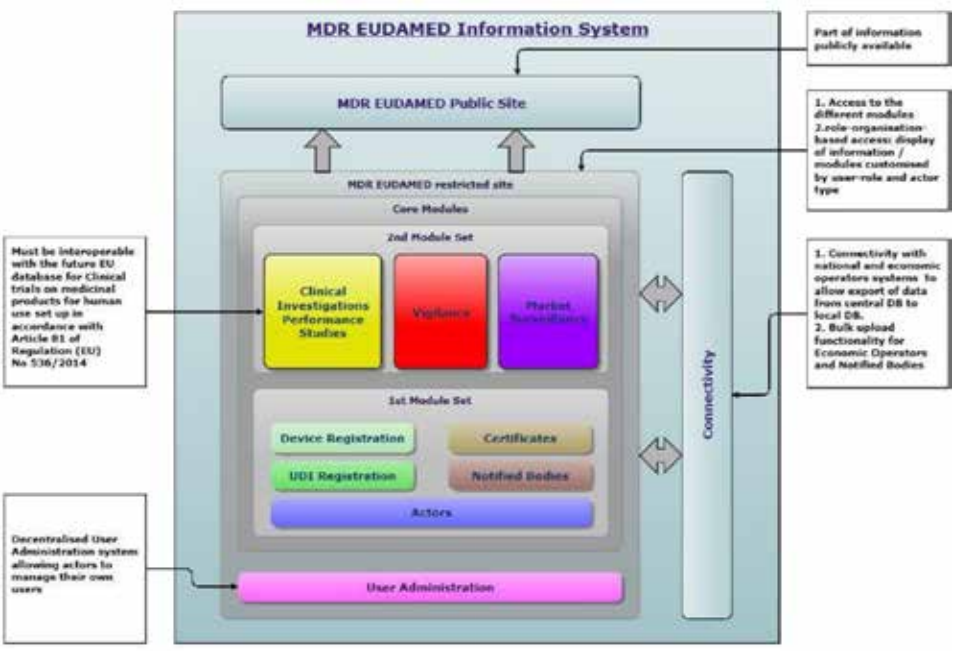
EUDAMED is the EU database developed to implement MDR and IVDR. This database will be much larger than the one that currently exists under the medical devices directives, and it is expected to improve transparency and coordination of information regarding medical devices available on the EU market.

The system will be multipurpose. It will function as a registration system, a collaborative tool, and a notification and dissemination system that is open to the public.

EUDAMED is structured around six interconnected modules and a public website (Figure 1) [7]. The modules are:

- Actors registration
- UDI/devices registration
- Notified bodies and certificates
- Clinical investigations and performance studies
- Vigilance and postmarket surveillance (related to the device quality when on the market and after)
- Market surveillance (related to the device market)

Figure 1: Overview of MDR EUDAMED (reprinted from [7]).



UDI SYSTEM COMPONENTS

According to MDR and IVDR, device identification applies to multiple levels of devices and packaging, but does not include logistics units. Part C of Annex VI of MDR [4] and IVDR [5] defines the different components of the UDI system, which relies on three identification elements:

- Basic UDI-DI, which identifies a group of products
- UDI-DI, which identifies a specific device
- UDI-PI, which identifies the production set of the device

The vocabulary seems a bit confusing, but it is intended to cover the complexity of the medical devices sector.

Basic UDI-DI

The primary EU identifier of a device model is the Basic UDI-DI; this is the device identifier at the level of the device unit of use [4, 5]. (Note that Basic UDI-DI does not exist in the US regulation.)

It is important to note that "unit of use" is not the unit of sale (the unit used by the healthcare professional or customer/patient). Rather, Basic UDI-DI is an identifier at the model level, covering a family of devices. According to European Commission guidance [8], "Any Basic UDI-DI shall identify the devices (group) covered by that Basic UDI-DI in a unique manner," meaning it covers all devices in a family/group whether they are single or multi-packaged, differently colored, and so on. Therefore, the Basic UDI-DI is independent/separate from the packaging and labeling of devices and does not appear on any trade item.

The Basic UDI-DI will be used as the main key in the EUDAMED medical devices database and on relevant documentation related to the device group, such as certificates, the declaration of conformity, technical documentation, and summary of safety and clinical performance. It connects devices with same intended purpose, risk class, and essential design and manufacturing characteristics.

The Basic UDI-DI is assigned by an issuing entity chosen by the manufacturer. UDI-issuing entities selected by the European Commission under Article 27.2 of the MDR [4] and Article 24.2 of the IVDR [5] are:

- GS1 (GS1 AISBL Association International Sans But Lucratif)
- HIBCC (Health Industry Business Communications Council)
- ICCBBA (International Council for Commonality in Blood Banking Automation)
- IFA GmbH (Informationsstelle für Arzneispezialitäten)

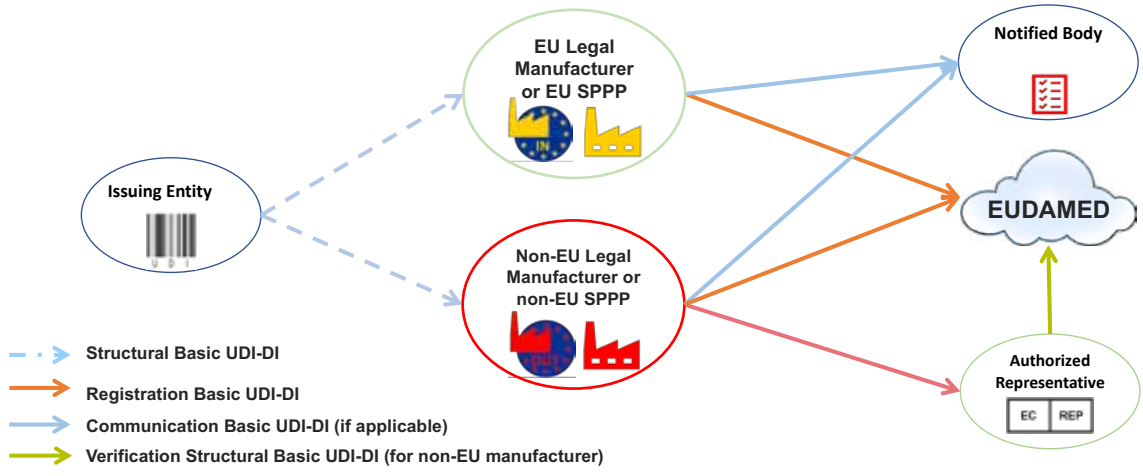
UDI-DI

Each UDI-DI is unique for the type of packaging of a device. It is a numeric or alphanumeric code (depending on the issuing agency's specifications) and is not case sensitive. This is the static part of the UDI code.

Under Annex VI [4, 5], a new UDI-DI is required each time there is a change to a name/trade name, version/model, use, sterilization requirements, quantity in packaging, or indications/warnings. The new UDI-DI is still linked to the same Basic UDI-DI. For example, a single-device package and a bulk pack have different UDI-DIs but the same Basic UDI-DI. Similarly, if the same device is

Figure 2: Basic UDI-DI RACI chart and data flow.

Responsible / Accountable / Consulted / Informed						
Item	Flow	Legal manufacturer or SPPP	Notified Body	EC Rep	Eudamed	Comments
Basic UDI DI EU manufacturer	Code attribution	A R	I	C	I	EC-Rep must check legal non-EU manufacturer
Basic UDI DI Non EU manufacturer	Code attribution	A R	I		I	
Basic UDI DI	Code registration	A R			I	



packaged with different languages on the packaging or is manufactured with various cosmetic differences, each variation has its own UDI-DI but all variations share a Basic UDI-DI.

Like the Basic UDI-DI, the UDI-DI is generated by the manufacturer in accordance with the allocation rules defined by the EU issuing entity chosen by the manufacturer.

UDI-PI

Under MDR and IVDR Annex VI part C [4, 5], the UDI-PI is a numeric or alphanumeric code, not case sensitive, that identifies the unit of device production. The UDI-PI must be applied to all grouping (or packaging) levels for production traceability purposes. This is the dynamic part of the UDI code.

There are different types of UDI-PIs, and a medical devices manufacturer is, depending on the risk class their devices fall under, free to choose which type of UDI-PI to use:

- Serial number
- Lot number
- Software identification (for software classified as medical device)
- Manufacturing or expiry date or both types of date

Note that under US regulations of medical devices, if the expiry date and manufacturing date are available, both dates can be included in the UDI-PI [9]. According to EU regulations, if the expiry date and manufacturing date are available on the label, only the expiry date must be included in the UDI-PI; if only one date is available, this date must be included.

In EUDAMED, the manufacturer must indicate the UDI-PI type they have chosen together with other reportable UDI data. Specific UDI-PIs are not part of EUDAMED reportable data, except when adverse events or counterfeiting are reported in the Vigilance EUDAMED module.

VISUALIZING UDI DATA FLOWS AND RESPONSIBILITIES

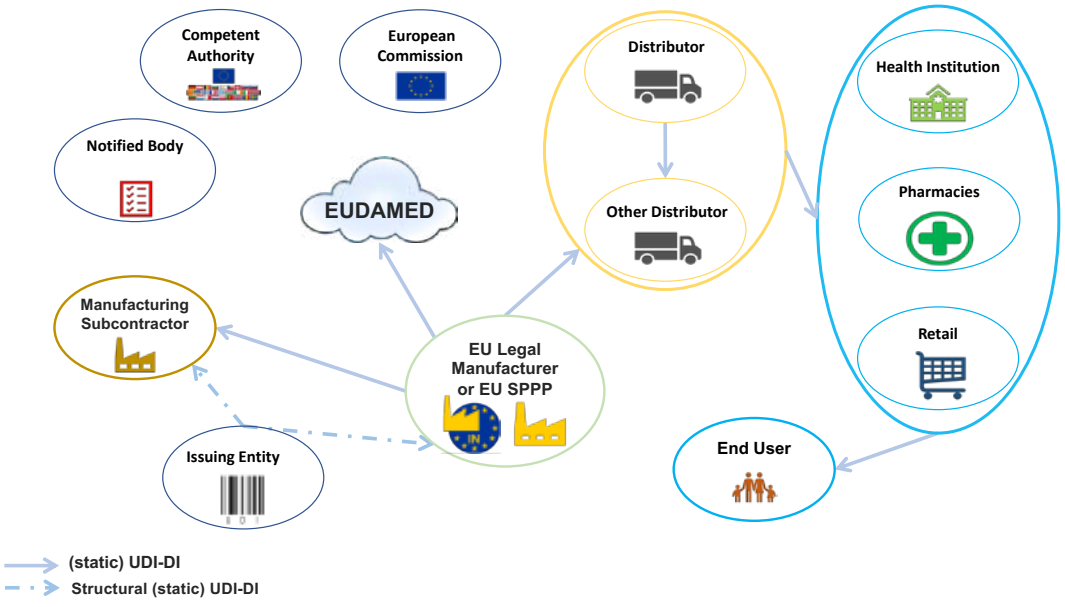
Among the tools produced by the ISPE France Affiliate's UDI Medical Device Work Group for UDI stakeholders are a graphical presentation of the flow of UDI components and a RACI responsibility assignment matrix, where *R* stands for responsible (in charge of the flow), *A* stands for accountable (controlling the flow), *C* stands for consulted (part of the flow), and *I* stands for informed (aware of the result, but not part of the action).

In these tools, we take into account both legal manufacturers and system and procedure pack producers (SPPPs). The legal manufacturer is the legal entity with final approval authority on design changes and assumes quality systems responsibility for the development, design, and manufacture of the product.

When referring to SPPPs, procedure pack means a combination of products packaged together and placed on the market with the purpose of being used for a specific medical purpose, and system means a combination of products, either packaged together or not, which are intended to be interconnected or combined to achieve a specific medical purpose.

Figure 3: UDI-DI RACI chart and data flow for a legal manufacturer located in the EU.

Responsible / Accountable / Consulted / Informed									
Item	Flow	Legal manufacturer or SPPP	European Commission	Eudamed	National Authority	Issuing Entity	Distributor & other distributors	Health institutions	Pharmacies Retail End Users
(Static) UDI DI EU manufacturer	Code attribution	A R				C			
(Static) UDI DI EU manufacturer	Code registration	A R		I					
(Static) UDI DI EU manufacturer	Code checking		R	A	R		R	R	R
(Static) UDI DI EU manufacturer	Shipment	A R					R I	R I	I



The following sections use the work group's tools to help answer important questions about UDIs.

WHO IS IN CHARGE OF BASIC UDI-DI?

The Basic UDI-DI will be used for communications between stakeholders, such as technical documentation provided to the notified body in a conformity assessment application, the EU declaration of conformity, the product certificate, the certificate of free sale, the summary of safety and clinical performance (SSCP) for medical devices, the summary of safety and performance (SSP) for IVDs, vigilance and postmarket surveillance reports, and clinical investigation forms for postmarket studies. As noted previously, the Basic UDI-DI shall never appear on the packaging labeling or on the product itself.

The Basic UDI-DI is mainly the responsibility of the legal manufacturer (Figure 2). They are accountable and responsible for the code attribution and must communicate the code to the notified body and EUDAMED. This responsibility applies whether or not the legal manufacturer is in the EU.

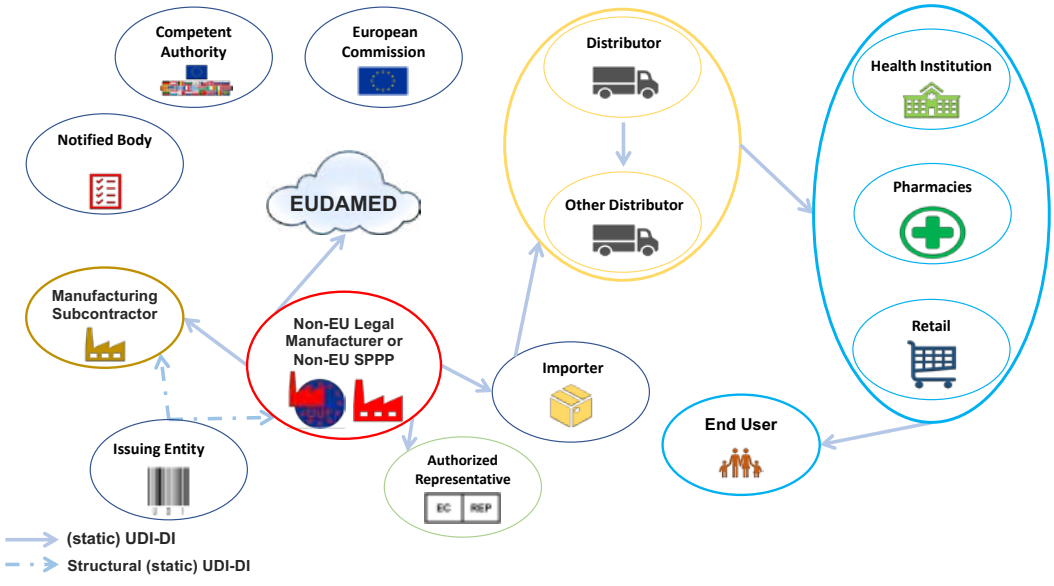
The legal manufacturer is free to assign the Basic UDI-DI to a group of items, using the Basic-UDI-DI code structure it obtains from an issuing entity of their choice.

SPPPs are natural or legal persons that combine medical devices with other medical devices or with other products that are not medical devices. To place a combination on the market as either a system or a procedure pack, the SPPP must act as legal manufacturers. They are responsible for ensuring that the medical devices in the combination bear a Conformité Européenne (CE) mark, the combination is intended to achieve a specific medical purpose, and the devices and combination are compliant with all applicable legislation.

When the legal manufacturer is based outside of the EU, they must provide the Basic UDI-DI code to their authorized representative in the EU, which will verify the code in EUDAMED.

Figure 4: UDI-DI RACI chart and data flow for legal manufacturers not located in the EU.

Responsible / Accountable / Consulted / Informed											
Item	Flow	Legal manufacturer or SPPP	European Commission	EC Rep	Importer	Eudamed	National Authority	Issuing Entity	Distributor & other distributors	Health institutions	Pharmacies Retail End Users
(Static) UDI DI Non-EU manufacturer	Code attribution	A R						C			
(Static) UDI DI Non-EU manufacturer	Code registration	A R				I					
(Static) UDI DI Non-EU manufacturer	Code checking		R	R	R	A	R		R	R	R
(Static) UDI DI Non-EU manufacturer	Shipment	A R			R I				R I	R I	I



WHO IS IN CHARGE OF UDI-DI?

The static part of the UDI, the UDI-DI, will be used for communication among the stakeholders and appears on the packaging labeling and/or on the product itself.

The legal manufacturer is responsible for the UDI-DI code attribution and the code registration in EUDAMED (module: UDI/Devices registration).

The legal manufacturer will assign one unique UDI-DI to a model of device (identifying form, fit, and function). UDI-DI is specific to a legal manufacturer (or brand owner in the GS1 standard) and a device. UDI-DI will be used throughout the supply chain.

The legal manufacturer obtains the code structure for the UDI-DI from an issuing entity of their choice. See Figure 3 for the UDI-DI RACI chart and data flow for legal manufacturers in the EU.

The responsibilities for legal manufacturers outside the EU are the same as those for EU-based manufacturers. In addition, manufacturers outside of the EU need to communicate the UDI-DI code to their authorized representative (see Figure 4). The importer must verify that UDI-DI has been assigned by the legal manufacturer and that the device is registered in EUDAMED.

UDI-DI will be used by actors all along the supply chain, including the importer.

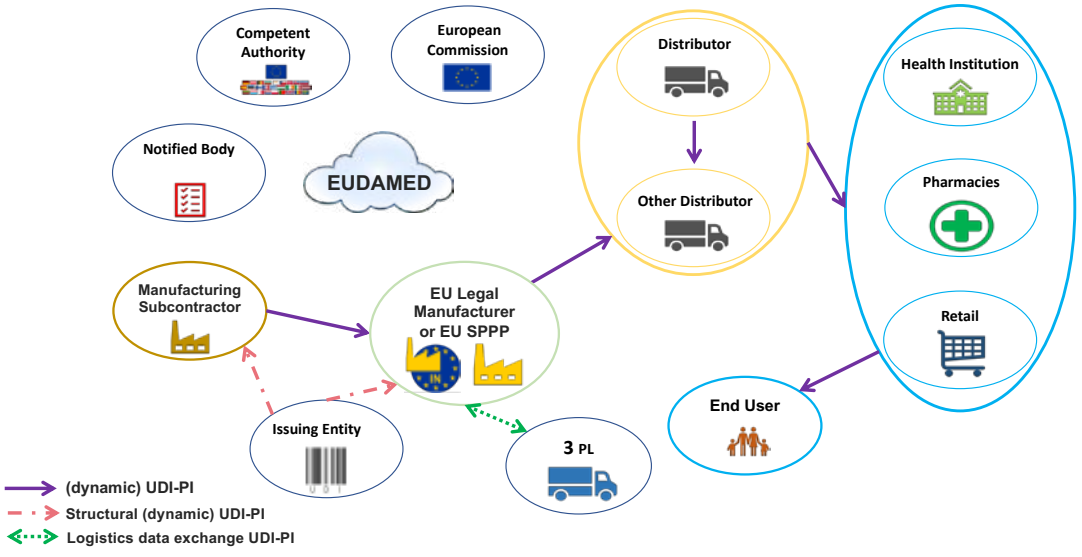
WHO CAN SEE UDI-DI INFORMATION?

To increase transparency for end users and patients, large amounts of information registered in EUDAMED, including the Basic UDI-DI and UDI-DI of devices, will be publicly accessible.

Transparency is such an important element of the new regulations that the European Commission intends to develop two interfaces for each module of EUDAMED, one for the actors (member states, operators, and notified bodies) and one accessible to the public. It is anticipated that the public module of EUDAMED will be available at ec.europa.eu/eudamed.

Figure 5: UDI-PI RACI chart and data flow for legal manufacturers located in the EU.

Responsible / Accountable / Consulted / Informed						
Item	Flow	Legal manufacturer or SPPP	Issuing Entity	Distributor & other distributors	Health institutions	Pharmacies Retail End Users
(Dynamic) UDI PI EU manufacturer	Code attribution	A R	C			
(Dynamic) UDI PI EU manufacturer	Code checking	A		R	R	R
(Dynamic) UDI PI EU manufacturer	Shipment	A R		I	I	I



WHO IS IN CHARGE OF UDI-PI?

The dynamic part of the UDI, the UDI-PI, will be used for communication among the stakeholders and appear on the packaging labeling and/or on the product itself.

The UDI-PI is key data for EUDAMED vigilance and market surveillance modules. Individual UDI-PIs are not registered in EUDAMED except when adverse events or counterfeiting are reported.

The UDI-PI is mainly the responsibility of the legal manufacturer, beginning with the manufacturing subcontractor for the code attribution.

The manufacturer will assign one unique UDI-PI to each unit of device production.

The UDI-PI is specific to a legal manufacturer (or brand owner in GS1 standard) and a unit of device production. The manufacturer can choose whether to use lot number, serial number, software version identification, manufacturing date, and/or expiry date as the UDI-PI. The UDI-PI will be used for tracking and tracing throughout the supply chain.

The legal manufacturer will obtain the structure to generate the UDI-PI from an issuing entity of their choice. Third-party logistics will use the data included in the UDI-PI for the logistics management of the device. See Figure 5 for the UDI-PI RACI chart and data flow for EU-based manufacturers.

If the legal manufacturer is not located within the EU, they have the same responsibilities as an EU manufacturer. In addition, manufacturers outside of the EU must communicate the UDI-PI to the importer (Figure 6). The UDI-PI code will be used throughout the supply chain, including by the importer.

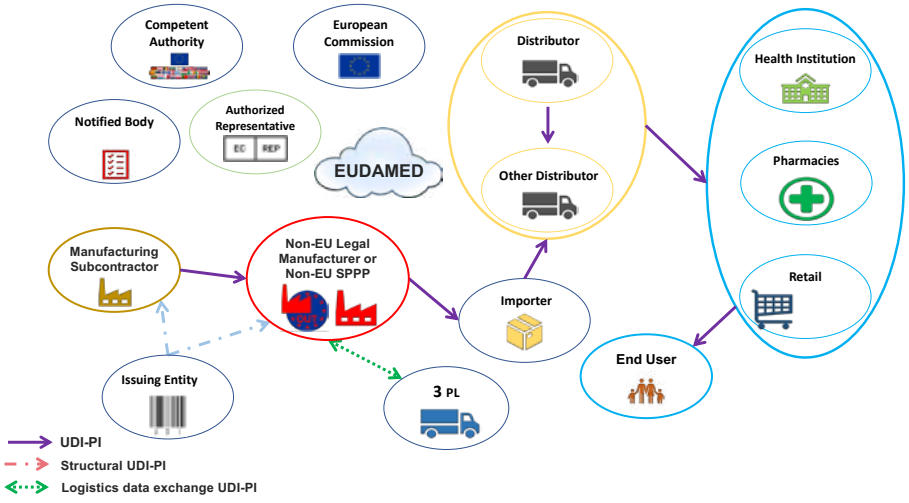
DO MANUFACTURERS HAVE TO SERIALIZE ALL DEVICES?

Some confusion has arisen about EU regulations regarding the serial numbers of medical devices.

As stated previously, the manufacturer chooses how they

Figure 6: UDI-PI RACI chart and data flow for legal manufacturers not located in the EU.

Responsible / Accountable / Consulted / Informed								
Item	Flow	Legal manufacturer or SPPP	Importer	Eudamed	Issuing Entity	Distributor & other distributors	Health institutions	Pharmacies Retail End Users
(Dynamic) UDI PI Non-EU manufacturer	Code attribution	A R			C			
(Dynamic) UDI PI Non-EU manufacturer	Code checking	A	R			R	R	R
(Dynamic) UDI PI Non-EU manufacturer	Shipment	A R	R I			I	I	I



control production of their devices. According to MDR Annex VI [4], part C, point 6, serialization only applies to "specific devices":

> *6.1.1. Implantable devices shall, at their lowest level of packaging ("unit packs"), be identified, or marked using AIDC [automatic identification and data capture (a technology to read barcodes)], with a UDI (UDI-DI + UDI-PI).*
>
> *6.1.2. The UDI-PI shall have at least the following characteristics: (a) the serial number for active implantable devices, (b) the serial number or lot number for other implantable devices.*

This means that the MDR requires serialization only for active implantable devices. The serial numbers for active implantable devices need to appear on the label or device itself.

Implantable devices fall into the highest risk class for medical devices, and faulty implantable devices can have severe consequences for the health and safety (or even the life) of the patient. Therefore, active implantable devices require the highest level of traceability, which can only be achieved with the help of unit-level identification, and at least batch-level identification is required for not-active implantable devices. As previously noted, the batch- or unit-level identification information does not need to be reported to EUDAMED, but the manufacturer must keep track of it and state the unit- or batch-level identifier on the device label.

Like in the EU serialization requirements for pharmaceutical products (Falsified Medicines Directive [10]), the unique identification of an active implantable medical device is based on the link between the device's identifier and its serial number (e.g., in the GS1 framework, the link between the global trade item number [GTIN] and the serial number). However, unlike the management of prescription drugs in Europe, there is no need to decommission the implantable medical device's serial number when the device is used, although hospitals must register the serial number in an internal repository.

Note that for reusable implantable medical devices, MDR requires direct marking on the device itself (direct part marking). Local authorities can require identification at the unit of use level for reusable devices.

Also note that the IVDR Annex VI rules for UDIs of reusable devices that are part of kits and require cleaning, disinfection, sterilization, or refurbishing between uses [5] differ from the UDI rules for reusable implantable devices in Annex VI of the MDR [4].

IVDR states:

> *6.1.1. The UDI of such devices shall be placed on the device and shall be readable after each procedure to make the device ready for the next use;*
>
> *6.1.2. The UDI-PI characteristics such as the lot or serial number shall be defined by the manufacturer.*

CONCLUSION

MDR and IVDR are complex regulations with complex implementation challenges. Stakeholders need to create multidisciplinary teams including commercial, manufacturing, quality assurance, data management, regulatory affairs, logistics, information technology, and other stakeholders to thoroughly implement the requirements of the new regulations. Device identification is a global development, and stakeholders cannot ignore the regulatory changes.

UDI will bring a common language for the whole supply chain, improving the efficiency of the transactions as well as improving customer/supplier relationships. The new EU regulations will increase transparency for consumers and healthcare professionals alike and, most important, will improve the security of medical devices for end users/patients.

This article presents only a part of the work being done by the ISPE France Affiliate's UDI MD Work Group. We have also created, for example, a UDI glossary and an analysis of the management of incident reporting. The work group is available to share further details and exchange ideas about this article.

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EFFECT OF GUM on In Vitro Dissolution of Powder for Oral Suspension

By Ajay Babu Pazhayattil, Amol Dattatreya Galande, and Sudhakara Rao Badabhagni

Powder for oral suspension (PfOS) bioavailability is mostly on the basis of drug absorption from the gastrointestinal tract. PfOS formulation pH, viscosity, vehicle buffer capacity, drug particle size distribution, density, and viscosity are often critical for absorption. Therefore, careful design and selection of excipients—including suspending agents—are necessary during PfOS formulation development. This article describes experiments that were conducted to determine whether gum concentration should be considered a key attribute in PfOS formulation development.

Dry powder for reconstitution to suspension is a preferred formulation for certain populations, such as pediatric [1] and geriatric [2] patients. Oral suspensions are commonly prescribed for patients in these age groups if they cannot swallow tablets or capsules. Because the formulation attributes affect absorption, excipients must be carefully selected and designed. In PfOS formulations specifically, many key formulation attributes—suspendability, potential for reconstitution inaccuracies, solubility, etc.—must be addressed during development to provide optimal biopharmaceutical performance. The experiments described here explored the benefit of using gum as an effective release modifier as well as examined gum's functional property as a suspending agent. The studies were done on various PfOS prototype formulas, with an active content of 200 mg/mL, to expand on the body of knowledge for robust PfOS formulation development.

MATERIALS AND METHODS

In the experiments, the suspending agent used in the formulations was the polysaccharide xanthan gum, a type of sugar made by the bacterium *Xanthomonas campestris* through a process of fermentation [3]. The other excipients used in the formulation were selected based on those used in the Reference Listed Drug (RLD) and excipient compatibility studies on the active pharmaceutical ingredient (API).

An increase in the concentration of the suspending agent in the formula composition may lead to the formation of lumps in the reconstituted suspension, whereas a decrease in the concentration of xanthan gum may lead to a faster dissolution profile. Three batches were manufactured, each with a varying concentration of xanthan gum, for two different drug substance sources (six batches total). The assay, related substances, pH, and water content by Karl Fischer titration results were found to be acceptable. The xanthan gum functionality was verified with the observed rate of sedimentation in all six experimental batches.

The drug substance is a Biopharmaceutics Classification System (BCS) class II compound displaying low aqueous solubility across the physiological pH range, where dissolution in the stomach and absorption in the upper small intestine are expected. Because the drug substance is a BCS class II compound, particle size distribution of the drug substance may effect dissolution [4]. The experiment considered two sources (and batches) where the solid-state form of the drug substance batches did not have any impact on the dissolution of the drug product. The same processing parameters were applied for manufacturing all experimental batches.

The API exhibits pH-dependent solubility across a pH range of 1.2–7.2, and pH 4.5 dissolution media was selected for the analysis. The pH in a fasted state of the stomach is 4.5 [5], and pH 4.5 acetate buffer media therefore has the benefit of serving as an effective biorelevant media with larger discriminative power. Another advantage of this preparation is that it is does not require the complex processes necessary to prepare samples using simulated gastric fluid.

To compare the dissolution profiles, we used a model-independent mathematical approach using a similarity factor (f_2) to measure the closeness between two profiles [6, 7]. The equation is as follows:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{n-1}^{n} (R_t - T_t)^2 \right]^{-0.5} * 100 \right\}$$

where n is the number of observations, R_t is the average percentage of drug dissolved from the reference formulation, and T_t is the average percentage of drug dissolved from the test formulation.

When two profiles are identical, f_2 equals 100. An average difference of 10% at all measured time points results in an f_2 value of 50 [8].

RESULTS

The f_2 results of pH 4.5 acetate buffer and xanthan gum concentration fit a reciprocal model where the slope is a function of 1/X (Figure 1). The R-squared value is 0.867, where 86% of the variation in the y axis (f_2 value) is explained by the x axis (xanthan gum concentration) and the root mean square error is 5.9, implying a good reciprocal model fit to the two variables. The f_2 value was considered the primary criteria here because the higher the f_2 value is, the closer the drug product formulation is to the desired RLD in vitro dissolution behavior. The t ratio and p value (prob>|t|) indicate that the slope is significant at the 0.05 level. The dark-shade region indicates a 95% confidence level and the light-shade region indicates a 95% prediction interval at any given point.

The assessment with f_2 is expected to be linear; however, it must be noted that f_2 is bound (i.e., it cannot be less than 0 and cannot be greater than 100). Although the sample sizes are low, the nonparametric correlation coefficients deduced (Figure 2) indicate a positive correlation of sedimentation volume and xanthan gum concentration percentage to pH 4.5 acetate buffer dissolution.

It is noteworthy that a previous study compared generic drug products and RLD tablet dissolution profiles and concluded that important differences exist among the different generics in the market with regard to their in vitro performance in pH 4.5 acetate buffer; therefore, the authors recommended clinical safety evaluations prior to switching patients from one generic to another [9]. Analysis of the results of our formulation development

Figure 1: Summary of fit: pH 4.5 f_2, xanthan gum concentration (%XG). * is a denotation in the software to indicate high probability/correlation.

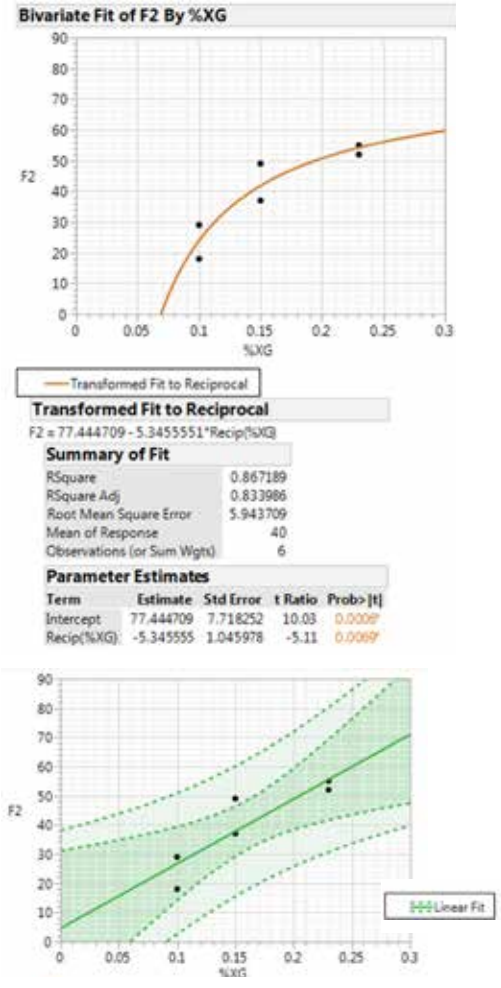

Figure 2: Nonparametric correlation coefficients.

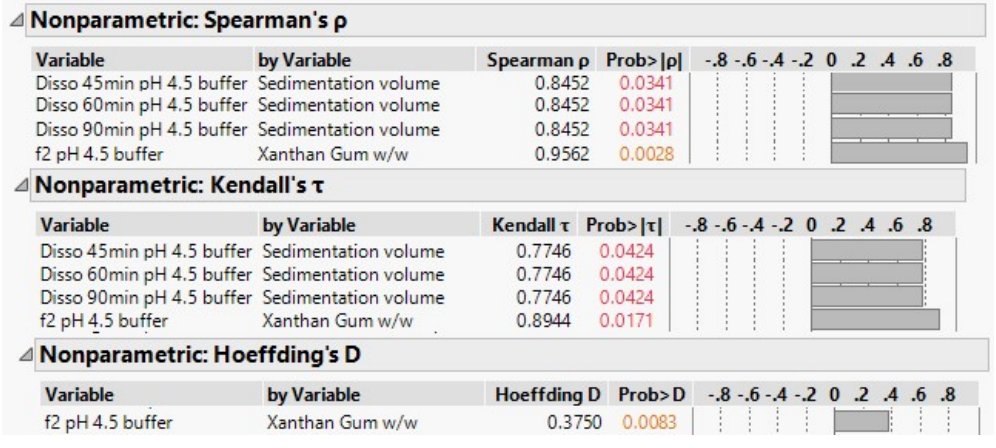

Table 1: Experimental batch results manufactured with two different APIs.

Test	RLD	Batch 1 (API 1)	Batch 2 (API 1)	Batch 3 (API 1)	Batch 4 (API 2)	Batch 5 (API 2)	Batch 6 (API 2)
Xanthan gum (% w/w)	N/A	0.1	0.15	0.23	0.15	0.1	0.23
Water content by Karl Fischer KF titration (% w/w)	N/A	0.89	1.4	0.88	0.8	0.8	0.84
pH of suspension	N/A	6.52	6.6	6.57	6.76	6.71	6.55
Assay by high-performance liquid chromatography (% w/w)							
	RLD	**Batch 1 (API 1)**	**Batch 2 (API 1)**	**Batch 3 (API 1)**	**Batch 4 (API 2)**	**Batch 5 (API 2)**	**Batch 6 (API 2)**
API	N/A	98.1	98.8	97.4	100.2	97.5	102.2
Methyl paraben	N/A	96.1	101.7	101.7	97.4	92.3	101.4
Total impurities	N/A	0.411	0.374	0.364	0.353	0.299	0.244
Sedimentation study for batches manufactured with different xanthan gum concentrations (volume observed [mL])							
Time	**RLD**	**Batch 1 (API 1)**	**Batch 2 (API 1)**	**Batch 3 (API 1)**	**Batch 4 (API 2)**	**Batch 5 (API 2)**	**Batch 6 (API 2)**
10 minutes	30	60	40	60	60	30	60
30 minutes	30	59	40	60	60	30	60
60 minutes	>29	59	40	60	60	29	60
8 hours	29	59	39	60	59	>28	60
2 days	28	59	39	> 59	58	>28	> 59
4 days	>27	59	39	59	58	>28	59
2 weeks	26	59	39	59	58	>28	59
4 weeks	26	59	39	59	58	>28	59
45 days	26	59	39	59	58	28	59
60 days	>25	59	39	59	58	28	59
Sedimentation volume	0.86	0.98	0.98	0.98	0.97	0.93	0.98
Dissolution profile of batches manufactured with different xanthan gum concentrations in pH 4.5 acetate buffer (% release)							
Time (min)	**RLD**	**Batch 1 (API 1)**	**Batch 2 (API 1)**	**Batch 3 (API 1)**	**Batch 4 (API 2)**	**Batch 5 (API 2)**	**Batch 6 (API 2)**
0	0	0	0	0	0	0	0
5	24	67	33	19	41	14	22
10	37	82	52	34	51	21	37
15	48	90	66	47	58	26	49
20	54	93	75	58	63	31	57
30	63	96	86	72	69	35	69
45	69	99	91	83	75	39	79
60	72	100	92	87	79	42	84
90	77	102	95	90	85	45	91
120	82	NP	NP	93	89	48	95
Infinity	89	106	97	94	90	63	96
f_2 value	N/A	18	37	52	49	29	55

Note: N/A = not available.

Empirical studies on biorelevant media are warranted when selecting gum as a suspending agent for PfOS formulations.

experiments (Table 1) suggests that formulators should be cautious about gum concentration. The pH 4.5 acetate buffer media dissolution profiles are useful predictors of clinical differences among formulations [10].

CONCLUSION

The experiments validate the hypothesis that the concentration of the suspending agent affects dissolution performance. The statistical data analysis of the experimental batches projects that the concentration of xanthan gum has an effect on the dissolution profile of the drug product released in biorelevant pH 4.5 acetate buffer dissolution media.

Empirical studies on biorelevant media are warranted when selecting gum as a suspending agent for PfOS formulations. The findings of the study may encourage use of gum as an effective release modifier and improve understanding of its functional properties more than being a suspending agent.

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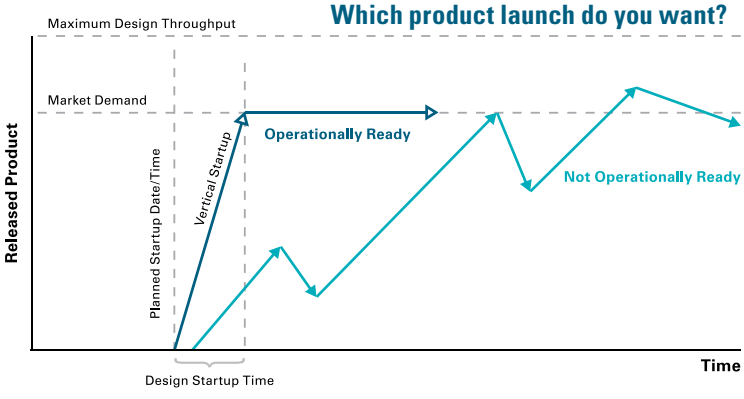

Operational readiness brings all workstreams together to get your product to market on time. We have the experience and expertise to integrate these workstreams and support your successful product launch.

Mfg Science & Tech | Facilities, Equipment, Utilities | Engineering | IT & Data Integrity | Quality Control | QA & Regulatory | Operations & EHS | Supply Chain | Org Health & Talent

OPERATIONAL READINESS WORKSTREAMS

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