PHARMACEUTICAL ENGINEERING®

CONTINUOUS MANUFACTURING
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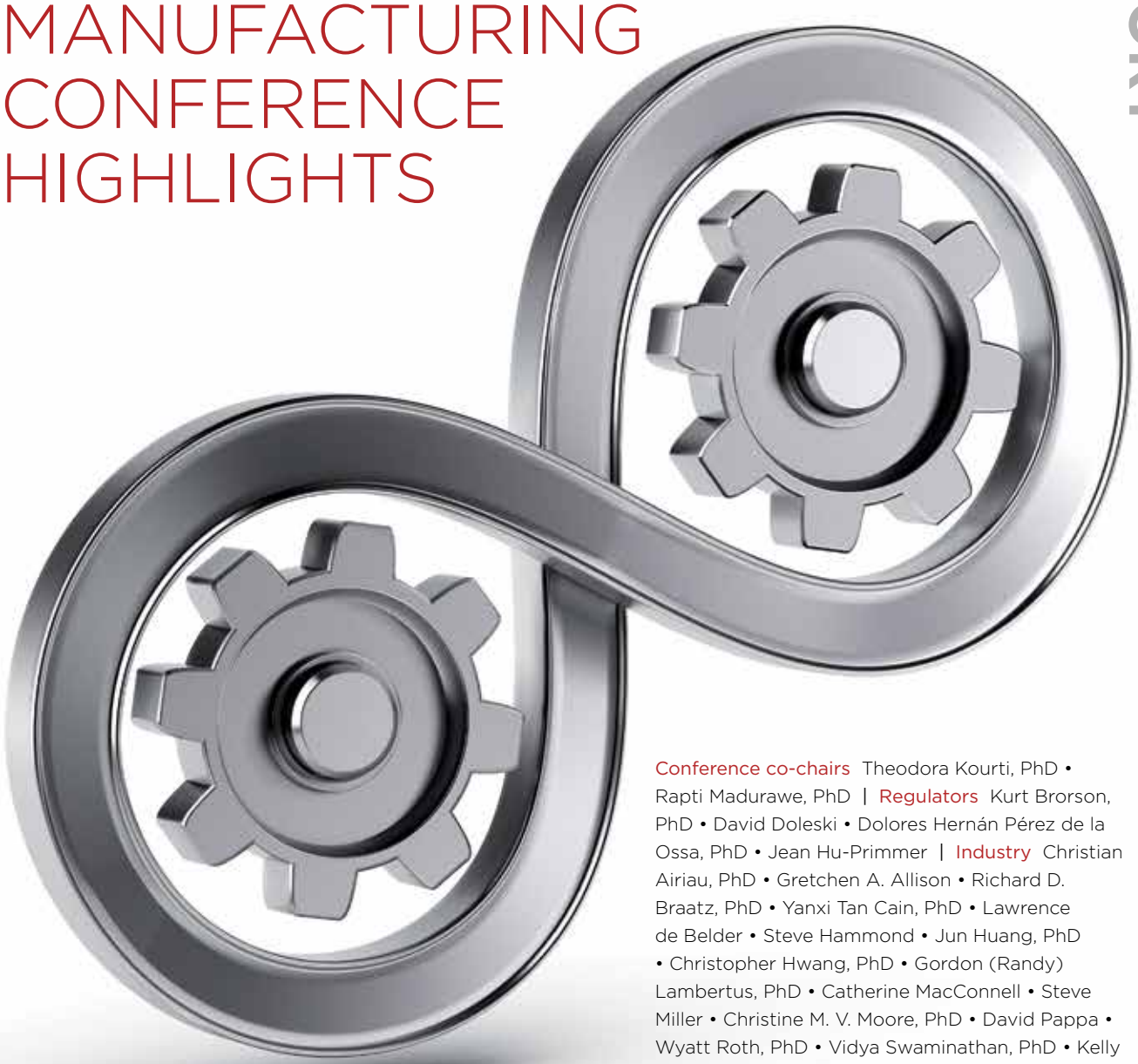
SPECIAL REPORT

ISPE 2016 CONTINUOUS MANUFACTURING CONFERENCE HIGHLIGHTS



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CONTINUOUS MANUFACTURING

A summary from the ISPE Continuous Manufacturing Conference

This paper discusses the findings and outcome of the ISPE Continuous Manufacturing Conference held 20–21 April 2016 in Baltimore, Maryland. While the ideas captured below reflect presentations and discussions both during the main conference and in breakout sessions, they are not necessarily the views of the authors or their organizations.

Continuous manufacturing (CM) can offer significant quality and cost advantages over batch manufacturing of active pharmaceutical ingredients (APIs) and drug products. Benefits are delivered through design for high-quality product and manufacturability—these include safety from reduced human intervention, smaller manufacturing footprint, higher process efficiencies through fewer process steps, and reduction in post-manufacture testing for release. CM also allows for end-to-end manufacturing where drug substance and drug product operations are connected without drug substance isolation and release.

While these benefits are recognized by industry and regulators, barriers and challenges to the adoption and implementation of CM remain. Notably, the existence of facilities with depreciated batch manufacturing equipment assets may be a barrier to new capital investment. There are also technical and regulatory risks in coupling an untried manufacturing technology with new product development and registration—possibly more acute in accelerated development scenarios. One approved product manufactured via CM, however, is designated as breakthrough therapy, which implies that the perceived risks are manageable.

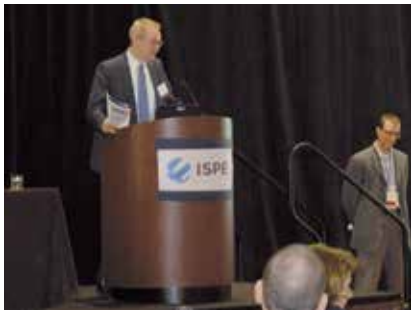
Successful implementation of CM requires an organizational commitment to the CM paradigm, a long-term strategy, and a well-defined implementation plan for either new product development or a batch-to-CM switch of already approved products. Advancement of CM requires an investment in infrastructure and capabilities, a comprehensive product quality management mindset, development of a CM framework and practice, new skillsets and expertise, and continued investment in CM platforms.

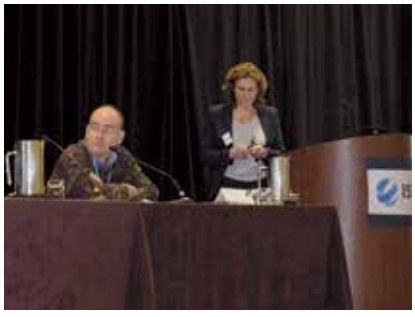
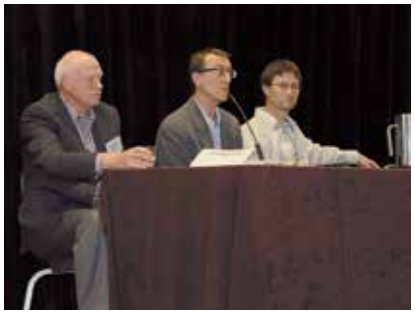
BUSINESS BENEFITS

Business cases for CM in the pharmaceutical industry can be grouped as development, technology transfer, and commercial benefits, each with its own set of assumptions. For senior leaders to support these assumptions, they must trust in the team charged with implementing CM—trust that is built with data and implementation success stories. Sharing data, discussing lessons learned, and seeking ways to collaborate can help the team grow the critical mass of knowledge needed to speed up the initial deployment phase of this technology. The initial investment in CM must be understood and supported throughout the organization from development to manufacturing; the business case may vary for each organization.

Initially, investments in effort and resources are needed to grow learning for parallel development of process analytical technology (PAT) and analytical methods. Because these costs are often difficult to estimate, it may be beneficial to keep learning cost separate from the business case. Reducing technology-transfer time only improves speed to market for some accelerated launch products, typically for Phase 3 data when it is on the critical path. Equipment should be designed with business case drivers in mind and transition towards modularity and standardization, and equipment design must also consider robustness and preventive maintenance to minimize failure/deviation risks during operation.

To ensure that development products are successfully transferred to commercial line, probability of success and comprehensive risk assessment/mitigation should be estimated; a backup transfer plan should also be in place, if required.



REGULATORY CONSIDERATIONS

Regulators are aligned with industry's goal of delivering high-quality medicines to patients. Most can see the potential that pharmaceutical CM offers for quality and cost advantages, thereby benefitting industry, patients, and regulators. By improving the consistency of drug manufacture and adjusting production to meet demand, faster response to shortages and emergencies can be enabled.

At the conference, some points to consider were further discussed by US Food and Drug Administration (FDA) regulators:

- Connected unit operations and continuous material addition, processing, and product formation introduce unique challenges compared to batch manufacture.
- Defining batch size in a flexible way is warranted in a continuous process.
- A sound control strategy is built upon the knowledge of residence time distributions at the desired mass throughput rate or range and the system dynamics of connected unit operations. In continuous bioprocessing, this may trigger the need for short-term hold vessels when volumetric throughputs of sequential steps differ, for example.
- Further, the output of some continuous processing steps like periodic countercurrent chromatography can be viewed as a continuing series of small batch operations, rather than a constant stream.

This knowledge can be used to develop plans for material traceability, rejection of potentially nonconforming material, and sampling. Identification of the potential sources of variability and their control ensure that products are made under a state of control and the process is robust. Characterization and control of input material attributes for CM, a process monitoring and control system to maintain the process within acceptable operating ranges, and an appropriate in-process sampling scheme are some key elements of a successful control strategy. Process models may also be used to enable real time release approaches.

Representatives from the European Medicines Agency (EMA) further elaborated that dossiers must be self-comprehensive for the regulators to understand how the product and process have been developed and to discern the sponsor's intentions for future manufacturing process control. The level of detail in the regulatory submissions should be commensurate with the significance of the outcome to the commercial manufacturing process and the control strategy.

Considerations around development (e.g., evaluation of raw material specifications and lot-to-lot variability, process dynamics, potential interactions between design spaces for different steps); manufacture and control strategy (e.g., batch definition, PAT tools, use of models and their roles, feedback and feedforward loops, sampling plan, justifications for IPCs, handling of nonconforming material, real time release testing [RTRT], and process validation strategy); and equipment (e.g., potential for fouling) were also discussed.

Since both industry and regulators have limited experience, EMA and FDA encourage early dialogue when innovative technologies/approaches are being used. Advice from EMA can proceed through the Committee for Medicinal Products for Human Use scientific advice/protocol assistance,[1] or early discussion meetings with the PAT team, established in 2003.[2] Although currently EMA provides no specific guideline on CM, it was indicated that this approach fits well within existing guidance—e.g., the EMA guideline on process validation for finished products, which introduces the concept of continuous process verification.[3]

Early dialogue with FDA should greatly facilitate acceptance of such processes. FDA can be expected to support the implementation of CM in cases where it is justified by a science- and risk-based approach. Industry should recognize that it is important to address how regulatory aspects can affect the decision of when to implement new technology—early in the development process, midstream, approval, or licensure. Each may trigger different levels of risk considerations by regulatory authorizes.

To help address issues such as these, the FDA's Emerging Technology Team (ETT) was formed in 2014. ETT draws membership from all Center for Drug Evaluation and Research quality review, research, and inspection functions, including the Office of Biotechnology Products. The ETT provides a primary point of contact for external inquiries regarding emerging technology in pharmaceutical and biotechnology manufacturing and quality control. The ETT will partner with review offices in a cross-functional manner to identify regulatory strategy and resolve roadblocks to implementation of new technologies relating to existing guidance, policy, or practice related to review or inspection. The team's initial focus will be innovative products, manufacturing processes, or testing technologies or processes to be submitted in an Investigational New Drug Application, Biologics License Application, New Drug Application, or Abbreviated New Drug Application.

CGMP CONSIDERATIONS

Current good manufacturing practice (CGMP) considerations for CM include:

- An effective pharmaceutical quality system (PQS)
- Appropriately validated facilities and software
- Determining a state of control
- Dealing with deviations in real time
- Managing segregation of "potentially nonconforming" materials (Note that for consistency with ICH Q7, "nonconforming" should only be used to describe material that does not meet appropriate specifications

or standards; segregated material can be referred to as "potentially nonconforming" until its disposition is determined)

GMP regulatory considerations for CM should consider if any modifications are needed to the existing PQS. In general, the structure of an effective quality assurance unit should be flexible enough to cover CM, although processes and definitions may need revisions. For example, the definition of a "lot" or "batch" should be consistent for its use in the continuous operation. Batch record review should consider the timelines for RTRT operations, the quantity of information reviewed, and the sequence of batch record review vs. the production run. Further quality considerations include how the PQS deals with process upsets. Material traceability should be understood and process events should be evaluated for their potential impact to other segments or batches.

Considerations for equipment are similar to traditional manufacturing and include decisions related to the choice of dedicated vs. multi-product and single-use vs. reusable equipment. The ability to verify cleaning of the equipment is important, including observability of accumulated material within the system. Additionally, the materials of construction should be durable and not have leachable impurities. Finally, it is essential that the equipment operates reliably over the desired length of a manufacturing run or campaign.

For automation, the level of software validation depends on the associated risks. Requirements for functionality should be documented. There should be clarity on automated actions vs. operator actions and adequate training of the operators to use software. A clear procedure for resolution of alarms is expected, and resolution of the issues should incorporate an understanding of the impact on product quality.

Determining a state of control should be based on defined operating ranges and historical experience to deliver product with adequate assurances of quality, strength, identity, and purity. Understanding the process and the system dynamics is essential to support CGMP-related decisions. CM control strategies typically allow for adjustment of drifts. Deviations can include both process (true) deviations and sensor deviations; alarms are not necessarily deviations. Action limits should indicate when to segregate potentially nonconforming material. It is essential that procedures be in place that predefine how and where material segregation will occur. Considerations for segregation of potentially nonconforming material include the location of product diversion, preestablished diversion criteria, expected response to expected and unexpected events, and persons accountable for making the diversion decisions. Additionally, the data required to support decisions on product collection or diversion should be defined for start-up, pause, and shutdown operations.

CM IN DRUG SUBSTANCE, DRUG PRODUCT, AND END-TO-END MANUFACTURING

As of April 2016, CM was approved by the US FDA for a new chemical entity for Vertex Pharmaceuticals—which was developed as a CM process—and for a Janssen legacy product converted from batch to continuous. Although a case of approval for end-to-end CM of drug substance is not known, several companies have had single continuous drug substance reaction or purification steps approved.[14]

Manufacturing equipment for drug substance is highly flexible and variable in the number and complexity of unit operations. As such, the online analytical equipment required to support a process control strategy should be highly adaptable, provide representative sampling with minimum fouling, and be robust over extended periods of use without sacrificing accuracy or precision relative to traditional quality control lab counterparts.

Development organizations can leverage the data-rich analytics provided by online spectroscopies and chromatography to build process understanding. As experience is gained in manufacturing, then opportunity exists to reevaluate and, when possible, simplify the analytical instrumentation for long-term installations. As the industry gains familiarity and experience with these processes and measurements, online analytics may soon be commonly used for in-process controls of drug substance manufacturing.

CM for drug product has been adopted by a number of companies. Pfizer, G-Con, and GEA have formed an "open innovation" consortium as cofounders, with GSK as a member. This consortium is focused on development and deployment of a "portable, continuous, modular, miniaturized" (PCMM) and flexible continuous solid dose manufacturing train contained in a "POD." The POD concept can provide local manufacturing through rapid deployment of manufacturing capability. POD is capable of being disassembled, shipped to another location (country), reassembled, and commissioned in a few months. Version one of the manufacturing train includes both direct compression and wet granulation. Version two will include coating operations. The system has a "smart manufacturing" architecture that includes PAT, advanced process control, and data integration. This system won the ISPE 2016 Facility of the Year Award for Equipment Innovation.[8]

A continuous-flow process that produces active pharmaceutical ingredient and the drug product in one integrated system is referred to as end-to-end CM. A four-step approach for the design of end-to-end continuous pharmaceutical manufacturing process control uses first-principles models:

1. Select the strategy for assurance of each critical quality attribute (CQA) specification
2. Build first-principles dynamic models and control systems for each unit operation
3. Place unit operation models and controls into a plant-wide simulation
4. Design plant-wide control strategy based on plant-wide simulation

Four strategies were described for the first step:

1. Direct measurement of the CQA
2. Prediction of the CQA based on a first-principles model that is fed measurements of related variables
3. Prediction of the CQA based on an empirical or semiempirical model
4. Operation of the critical process parameters (CPPs) to lie within a design space—that is, some specified set shown in offline studies to provide assurance.[11]

The control systems in the second step are designed to suppress the effects of local uncertainties and disturbances.[12] For the third step, design procedures were described for optimization of start-up and real time diversion of off-spec material procedures, and for the justification of RTRT. The plant-wide control strategy in the fourth step is designed to suppress effects of remaining uncertainties and disturbances on the final product CQAs.[2]

PAT AND MSPC

Several approaches have been taken for the design and implementation of PAT in CM.

PAT has been employed as part of an automated commercial control strategy for in-process control and RTRT. Equipment capability, process complexity, segregation, and the need for real time decision making were considered in the implementation of the control strategy. Sampling plans and associated statistical sampling plan justifications were developed and implemented in a manner to ensure real time compliance.

For the Pfizer PCMM, PAT applications and their interfaces were designed to match the low retained mass and low mean residence time of the primary mixer. PAT measurements of multiple properties take place after each unit operation in the continuous system. Measurements can be taken post-mixing, post-granulation, post-drying and milling, and in the feedframe before compression. The speed of the measurement systems in the PCMM continuous processing equipment has been shown to be timely in relation to the speed of the process and movement of material through the equipment train.

Multivariate statistical process control (MSPC) can be used in CM for process monitoring. Examples exist from other industries where MSPC is being used to monitor not only steady-state operations but also to guarantee reproducible and optimum start-ups and shutdowns.[7] Use of lagged variables, residence time distributions, and frequency of sampling should be considered in such models. Model maintenance is an integral part of MSPC.

CONTROL STRATEGY, PAT, AND SOFT SENSORS

The choice between using PAT instrumentation to infer a property or soft sensors (where the property is calculated from process parameters) depends on the applications, taking into account many factors such as method accuracy, robustness, maintenance, cost, etc. Business cases, management support, and knowledge transfer for lifecycle management are all topics of great interest and ongoing debate. Many questions still exist related to process validation, measurement redundancy, and gaps due likely to lack of experience in the manufacturing implementation of PAT and soft sensor–based control strategies industry wide.

Only a few pharmaceutical companies have developed and implemented control strategies integrating PAT or soft sensor–based advanced process control for CM, proposing, for example, a soft sensor model to predict dissolution of core tablets. Specific concerns exist regarding the lack of skillset currently in place in the pharmaceutical industry to support advanced process control methodologies and to some extended PAT-based applications when used as a core component of the control strategy. However, the need for and interest in these technologies are growing rapidly, with a desire for a continued push forward in the use of soft sensors, PAT in control strategy for CM of pharmaceutical products.

PAT equipment and model maintenance

During the product lifecycle, there will be changes in the analyzers due to reasons like age-related equipment drift, nonroutine maintenance repair, replacement, and upgrades for improved functionality or additional functionality. There will also be process changes related to aging equipment, changes in equipment, continual improvement, process adjustments, and movement within the design space.

There will also, of course, be raw material variability related to new suppliers, changes in raw material manufacturing process, or changes in raw material bulk properties or grade. All these changes may require updating the PAT models.

Continuous manufacturing drivers	
Commercial	□ Improved cost of goods: significant reduction of capital expenditure (CAPEX), less direct and indirect effort (labor, materials, consumables), less energy and water consumption, better yields □ Higher supply chain flexibility: flexible campaign size □ Better process understanding with PAT □ Potentially more consistent product quality and fewer rejected batches: only partial rejected, depending on circumstances □ Lower inventory for finished goods and work in progress □ If driven by capacity increase, cost avoidance of additional equipment or additional facilities can play an important role to create a good net present value □ If the equipment can be fully loaded, high throughput equipment often decreases equipment down time and maximizes capacity utilization
Development and technology transfer	□ Faster and cheaper development: fast design of experiments, less development material □ Faster development can help speed to market □ More robust formulations if API availability is a constraint □ More products developed as direct compression vs. wet granulation □ Less material and effort needed to scale up from development to clinical and to commercial processes

From a regulatory perspective, models can be categorized based on intended use as high, medium, and low impact.[9–10] The expectations for model maintenance and subsequent variations related to post approval updates are category dependent.

It is suggested that users discuss criticality in advance with the regulatory agencies to help determine requirements for post-approval changes. It may be possible that a post-approval change management plan can be filed and used for model maintenance. In that case, models can be maintained with some greater flexibility within a company's quality system (e.g., flexibility with preprocessing condition, number of principal components). It may be possible that redundancy of control can help keep the process running while models are being updated.

SAMPLING

CM offers a wealth of process information that should be able to be used in lieu of traditional release testing. Concerns related to sampling for release testing for continuous drug product manufacturing include potential for traditional release testing expectations by some health authorities. The intended purpose of the sampling plan (e.g., confirmatory testing of in-process data vs. ability to detect process disturbances) should be clearly defined and the sampling strategy should be based on product specific CQAs and risk assessments. Using an RTRT approach, rather than measuring end product attributes, it is possible to infer them based on process data, such as a relevant combination of measured CQAs of process intermediates and process controls. Several gaps currently exist in equipment offerings for sampling and testing. Automated, high frequency sampling/labeling equipment and technologies that enable monitoring of low detectability CQAs are critical unmet needs for CM.

VALIDATION

Process and cleaning validation have some unique considerations for CM. Stage 1 development data may require:

- □ How to evaluate raw material/excipient variability impact, process conditions defining end of start-up and start of normal process conditions (e.g., product flow, process residence time, residence time distribution)
- □ Time constraints, including coping with interruptions
- □ Maximum/minimum run time considerations
- □ Comparability between development CM equipment/scale and commercial equipment/scale may be needed if different or relocated, which may require requalification due to variability in operators, sizes, and utilities

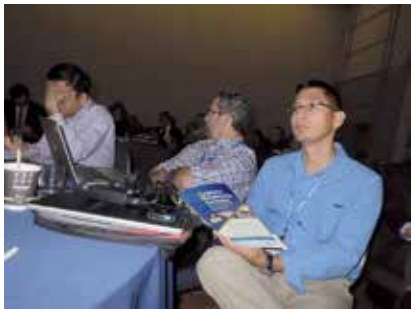
Stage 2 production of initial process validation batches should ensure that control and monitoring systems can take measurements at a frequency correlated to dynamic response time of the critical parameter/attributes. A commonly held opinion is that real time monitoring of each CPP/CQA (i.e., continuous process verification as described by ICH Q8) is more relevant than traditional batch testing. If online real time monitoring is not possible or available, a risk-based approach could potentially be used.

Important considerations include start-up/shutdown activities along with demonstrating the ability of the system to maintain intended process conditions over time. The number of Stage 2 "batches" may depend on the knowledge accumulated in Stage 1, as well as the control/monitoring strategy utilized (e.g., online real time monitoring, or offline testing). Stage 3 ongoing verification strategy would also depend upon the control and monitoring strategy used. Cleaning validation would be required for nondedicated CM equipment. The cleaning limits would depend upon how "batch size" was determined. Cleaning frequency, campaign length, and hold time considerations are considered the same or similar to traditional batch manufacturing.

POST-LAUNCH EXPERIENCE WITH CM

Commercial/shared filing and launch experience with CM includes the following:

- □ The small-scale nature of CM equipment facilitates streamlined quality by design process development on commercial-scale equipment early in development, making CM ideally suited for accelerated development programs (i.e., breakthrough therapies)
- □ Redundant in-process control methods were implemented as a business-driven strategy to increase operational efficiency, the availability of batch data, and manufacturing resiliency
- □ Real time release testing was also implemented to improve operational efficiency while providing increased assurance of product quality
- □ The anticipated hurdles related to developing and filing a CM process were manageable through early and frequent engagement with regulatory agencies



CM IN BIOTECH

Regulatory considerations

CM and PAT concepts have been adopted in many cases initially by the small-molecule industry; the progress in biotech is likely to be incremental and gradual, but the future is promising. To some extent, a hybrid form of CM has already been embraced. For example, individual unit operations like cell culture have been run in continuous mode for certain products since the 1990s. The output from these culture feed into more traditional batch processing. The next logical step is to adapt and link these continuous cultures to downstream CM unit operations. Addressing issues such as viral clearance and microbial control will be a challenge, but not an insurmountable one. One distinct advantage for CM over batch is that it minimizes the time labile intermediates are held between processing steps, an important advantage for the production of enzyme and clotting factor products.

Implementation of CM will likely require advanced PAT tools. Various existing or novel analytical tools for measurements during, rather than at the end of, a process (PAT) can provide more information about the process and allow control in real time. With biopharmaceuticals, process intermediates and APIs are highly complex; and even when using the most current technology, not everything can be tested. Further, the API may be a minor species in the process intermediate in the upstream part of the process. However, targeted research and development may eventually evolve PAT approaches even for complex protein properties such as secondary structure and glycosylation patterns. PAT has been evolving from real time measurement of operational parameters to measurement and control of the actual product or raw material critical quality attributes. Achievement of full control by PAT will require surmounting significant technology barriers through intense and purposeful R&D, multivariate analyses, and data analytics.

CM and PAT have the capacity to revolutionize the biopharmaceutical industry, but only if the opportunity is seized. The development and implementation of such technological advances have, and will continue to receive, strong support from the FDA. To speed up CM and PAT implementation, it is vital that success stories be shared.

Industrial perspective

Over the past 5 years, there has been significant progress made by the biopharmaceutical/biotechnology industries, academia, and suppliers in applying CM to production of biologics. The drivers for the biopharmaceutical industry to adopt continuous technologies are the same as for other industries: increased productivity and flexibility, reduced cost and cycle time, enhanced process control, and product quality.

Many companies have been successful in intensifying their operations through perfusion cell culture processes, developing and implementing continuous chromatography systems suitable for manufacturing, integrating various unit operations to eliminate non-value-added steps, and streamlining production process while achieving state of process and product attribute control. Some have demonstrated proof-of-concept of fully continuous process (bioreactor to formulated drug substance), while others have successfully scaled integrated processes to commercial scale. As the industry drives toward continuous commercial operation, there are increasing efforts to develop and implement robust PAT, process monitoring, and automation while addressing remaining key technology gap, such as continuous virus inactivation, virus filtration, and buffer exchange. With continued strong support and active engagement with health authorities, it is envisioned that a continuous architecture will emerge and become established as a very competitive, universal platform for the production of biologics.

The willingness of regulators to support innovations provides a positive backdrop for CM, although challenges for end-to-end biologics manufacturing process are substantial. A created inventory of existing or desired technologies with considerations for equipment, measurements, process knowledge, and regulatory challenges for each unit operation could be helpful in progressing adoption. Continuous cell culture and harvesting is already quite common in the industry, and although long-term sterility can be a significant challenge, proven operation is possible with good design and operating principles. Continuous chromatography technologies have been demonstrated by cleverly configuring multiple “batch” column processes so that the process stream flows without interruption.

Although bioreactor integration with continuous product capture has been demonstrated at bench and production scale, key technology gaps remain before the entire production process can be made fully continuous; these challenges includes continuous unit operations for viral inactivation, viral filtration, ultrafiltration/diafiltration, and fill/finish. Smartly designed automation as well as online/inline PAT to monitor product attributes are additional key enablers that will need to be developed and fully tested in the pilot/production environment, along with optimized operational practices and comprehensive risk assessment/mitigation, before end-to-end CM and real time release can be implemented and fully realized in biomanufacturing.

Lastly, although there are many important strategic advantages of CM over conventional batch processing, it will be very helpful to fully assess the impact of CM on cost reduction (operating expense and CAPEX), which will help to support business case.

CONCLUDING REMARKS

Although the benefits of CM seem obvious and significant, large-scale deployment in the commercial environment is still in its infancy. Many companies are either in the exploratory or wait-and-see stages for adoption of these new technologies. At the time of this publication, there exist two known approvals by the US FDA using CM for tablet manufacturing; one of these is also approved in Europe. Scattered examples of approved CM for single-unit operations exist for small-molecule and biotechnology drug substances.

The regulatory interest in adoption of CM is substantial. Health authorities from several regions have formed special teams to aid in the adoption of this and other emerging technology. FDA has posted that "continuous manufacturing has a strong impact on drug quality,"[6] making a clear statement of encouragement. FDA and the US Biomedical Advanced Research and Development Authority also have ongoing opportunities for innovations in medical countermeasure CM.[5] Additionally, in April 2016, the Executive Office of the President, White House National Science and Technology Council, declared CM in pharmaceuticals as a manufacturing area of "emerging priority,"[4] and specific funding for CM was provided in the 21st Century Cures Act, which was adopted at the end of 2016.[13]

With a framework being laid by regulators in many regions, the onus is now on industry to deliver the new technology. With its enhanced assurance of quality and availability of supply, CM is expected to have positive impact for industry, regulators and patients. ‹›

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