CONTINUOUS PROCESSING: MEETING THE NEED FOR NEW MANUFACTURING STRATEGIES

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A number of trends in the pharmaceutical industry are placing pressure on drug manufacturers to reduce both development times and costs.

Clinical trials have been typically on the critical path, and the CMC section had less time pressure and moved forward according to clinical trial results; new regulatory avenues have changed this. New manufacturing strategies are needed to overcome these issues. Continuous processing of both drug substances and formulated drug products is championed by the U.S. Food and Drug Administration (FDA) as an effective approach to addressing the need for increased efficiency and quality, and some may be better suited to changing paradigms.

A confluence of factors is driving the need for a paradigm shift in pharmaceutical manufacturing strategies. Movement towards evidence-based medicine, rising generics competition, dramatically higher clinical trial costs and timelines, the shift away from blockbusters to niche products, and the growing number of candidates with accelerated development designations (Fast Track, Breakthrough Therapy, Orphan Drug) are all placing pressure on drug manufacturers to eliminate inefficiencies and increase productivity in order to reduce development costs and get new therapies to the market more rapidly.

Continuous processing, which has been utilized in numerous industries for many decades, is attracting significant attention as a plausible solution. Even the FDA reviewed the use of continuous processes as a way to improve efficiency and quality, and now a handful of technology and market leaders are taking the lead. Not surprisingly, given the conservative nature of the pharmaceutical industry, the transition to continuous manufacturing is occurring slowly.

We at Hovione are convinced, however, that as more branded drug companies and contract manufacturers begin to recognize the value provided by continuous processing, and any remaining questions about regulatory compliance and quality assurance are addressed, this manufacturing approach will be more widely adopted.

FLOWING IN THE RIGHT DIRECTION

There are a host of benefits associated with the use of flow chemistry for the production of active pharmaceutical ingredients (APIs); reduced operating costs, smaller manufacturing footprints, lower capital expenditures and operating costs, and improved process efficiencies, control, and product quality are at the top of the list. Additional advantages include increased development speeds, greater process safety when employing hazardous chemistries, and the opportunity to perform reactions that cannot be run under batch methods.

In general, reactions conducted in flow reactors are more selective, providing higher yields of the desired products and fewer impurities. As a result, purification processes are often much simpler and may

even be eliminated in some cases. Solvent use can often be significantly reduced compared to that needed for batch reactions, and energy consumption is reduced, given the smaller reaction volumes. As a result, flow chemistry often enables greener chemistry with reduced raw material and resource consumption combined with shorter production times.

Scale-up with flow chemistry is also typically much simpler, leading to much shorter commercialization times. In some cases, commercial-scale production is achieved in the same reactor used for development work by performing longer runs. In others, additional reactors are used in parallel – "numbering up" – which also requires no further development work. Even if flow reactors must be scaled up, there are often few difficulties given the design characteristics of these systems.

Many of these benefits can be attributed to the fact that continuous processes are operated at a steady state. Processes at steady state conditions are easier to maintain than processes in which an end point needs to be achieved through a transient state. Process conditions are also more consistent, and therefore product quality is more consistent. The batch-to-batch variability observed in traditional manufacturing processes is eliminated. In addition, continuous processes are much more homogeneous as the result of improved mixing, so the "hot spots" and variability observed during a single batch run are also largely avoided.

Equipment for flow chemistry has advanced significantly in recent years as well. For instance, where initially it was impossible to conduct flow chemistry with solid reactants or products, many of the reactors available today are designed to allow these more complex transformations without plugging. Solutions of continuous solids handling during downstream purification and separation processes – filtration and, particularly, crystallization – are also under development, with significant accomplishments being made by groups such as the Center for Continuous Manufacturing and Crystallization (CMAC) and the Novartis-MIT Center for Continuous Manufacturing, both partnerships between industry and academia.

TOWARDS CONTINUOUS DRUG PRODUCT MANUFACTURING

Continuous manufacturing has also been demonstrated to be advantageous for the manufacture of final drug products. Here again, the key advantages are reduced development times due to simpler scale-up (often using the same equipment for development and commercial-scale production) and more consistent and higher product quality. For small-molecule drugs, continuous tableting is in fact increasingly common for the production of oral solid dosage forms, and we believe at Hovione that in the future, continuous processing of tableted products will become a growing trend.

Equipment manufacturers have invested significantly in the development of effective systems for continuous tableting operations, from feeders to tableting machines to coaters. Advances in process analytical technology (PAT) have also increased confidence in the ability to adequately monitor and control continuous operations. Access to these reliable and high-performing equipment and analytical tools is contributing to the adoption of continuous processing for tablet production. Pharmaceutical companies are also realizing how such continuous processes can help them improve productivity and flexibility to meet changing market needs.

Monitoring and control are, indeed, at the heart of successful continuous manufacturing operations. Continuous processing is not possible without PAT; immediate and ongoing feedback of critical process parameters is vital if optimum processing conditions are to be maintained. Advances in PAT have been significant in recent years, and today there is a wide range of tools applicable for the real-time monitoring of manufacturing processes for both drug substances and drug products.

Ultimately continuous process is ready to succeed because of the maturing of a combination of advanced technologies: improved equipment, precise monitoring, automation, and software.

REGULATORY BACKING

Another impetus for increasing adoption of continuous manufacturing strategies has come from FDA. The agency has encouraged the adoption of continuous manufacturing since 2004, and has been increasingly more vocal about the issue, speaking at various conferences and workshops.[1,2] Congress also supports this innovation; the 21st Century Cures Act, proposed in 2015, would require FDA to support the development and implementation of continuous manufacturing for drugs and biologicals as one of several approaches to speeding up drug development and commercialization.[3]

Industry should take the lead and propose solutions for the new regulatory environment that will need to address this field.

WE ARE NOW RESPONDING TO THEIR NEEDS FOR **MORE INTEGRATED MANUFACTURING SUPPORT,** INCLUDING THE PRODUCTION OF **FINAL PRODUCTS USING STATE-OF-THE-ART TECHNOLOGIES.**

Industry is the common denominator to all the regulators; therefore, if we want clear, harmonized guidelines, it is up to us to take a greater role in the standard-setting process and to present constructive solutions to real problems.

ADDING VALUE

As with any new technology, deployment of continuous processing must bring value. For API synthesis, continuous manufacturing is most likely to add value when it enables the use of process chemistry that cannot be performed under batch manufacturing conditions, or performs better continuously. Criteria to argue for a continuous process typically include: safety, yield, purity, and waste, as well as investment for the installed capacity for large volumes.

Continuous manufacturing of tablets has been the object of more innovation across many dimensions. Advances in processing equipment are overcoming many of the challenges posed by ingredients with physical properties that can cause difficulties with handling and processing. As a result, the percentage of APIs that can be reliably and consistently processed into high-quality tablets using continuous manufacturing equipment is expanding.

Continuous tableting can be a game changer when development time is highly compressed. When FDA grants Breakthrough Therapy designation, the CMC section becomes immediately critical to project success, and compliance. In these situations FDA may approve the NDA based on Phase II data alone; however, FDA has

been crystal clear that they will not compromise on the sponsor being able to demonstrate complete understanding and control over the manufacturing process.

Continuous tableting may be a preferred route in this case, as minimal amounts of API will suffice to define and validate a single-scale production; that can work continuously for a few hours to prepare clinical trial materials and generate validation data. The same production solution is then operated for 1,000 hours to deliver commercial quantities. In breakthrough therapies there may not be time to scale up drug product multiple times as the API may simply not be available in the given time frame. When an API costs ten thousand to tens of thousands of dollars per kilogram, there may well be considerable savings in API costs by opting for continuous dosage form manufacture.

A NATURAL EVOLUTION

Hovione has been producing small-molecule APIs for decades. In response to customer needs for assistance with overcoming formulation challenges posed by increasingly complex drug substances, we developed expertise in particle engineering. We are now responding to their needs for more integrated manufacturing support, including the production of final products using state-of-the-art technologies.

IMPLEMENTING PAT AT A CDMO

Hovione is committed to supporting an increased number of NDA programs, providing integrated solutions to CMC challenges and delivering a robust process for "right-first-time" commercial launch of much-needed medicines. Understanding the needs of fast-moving clinical candidates, we have as an organization decided to develop know-how and installed capabilities for continuous manufacturing for the production of both APIs and solid dosage drug products, particularly tableting. Throughout its history, Hovione has been a pioneer in technologies, and an early adopter. As early as 1982, patents were issued for Hovione claiming higher chiral purity when reactions were performed below -45°C; for example, a commercial process was inspected by FDA where liquid nitrogen was introduced into the jacket of a 2,000-liter vessel that same year.

Indeed, Hovione has, since 1997, made all new reactor capacity fully automated with distributed control systems (DCS) approaches, and all control strategies have been designed in-house and applied in a standardized way at all sites. PAT was implemented in 2005 with extensive expertise in its use for productivity and quality improvement. In other examples, Hovione has multiple installations in industrial processes (described in FDA filings) in drying operations, in controlling completion of reactions, and in the control of particle formation – in some cases in large-scale commercial continuous processes.

We also have been deploying advanced PAT solutions in our development and analytical labs. This experience makes Hovione ideally positioned to face the challenges of continuous manufacturing and be a CDMO that enables our clients to realize the maximum benefits of this revolution. To do so, we focus on utilizing continuous processes where they add value for the company, for our customers, and for our patients.

A CONTINUOUS FUTURE

The pharmaceutical industry is in a period of rapid change and innovation. Those companies – both brand manufacturers and contract service providers – that are able to adopt new technologies into their operations that result in better understanding, better control, and lower cost will come out winners during the turbulent times ahead. New manufacturing strategies will be essential, and we at Hovione believe that continuous manufacturing capabilities are part of the kit of the best partner CDMO for tomorrow's innovators. Many large pharmaceutical companies have, or are already investing in, continuous manufacturing systems for both small-molecule and biologic APIs as well as drug products.[4] Most have at least created internal groups focused on evaluating its potential. A few leading contract development and manufacturing organizations, such as Hovione, have also focused on the development and implementation of capabilities for continuous processing.

Adopting continuous manufacturing is a challenge in an industry that is risk averse and where for over 100 years everything has been done in batch production. This requires a change in mind-set, a whole reeducation of our scientists, and a re-kitting of our facilities at every scale – a big ask in a world of tightened budgets.

Hovione is convinced that our industry requires CDMOs that believe in this new paradigm and are prepared to invest, hire, and develop the right talent, and take on projects that have this extra dimension of risk. When a CDMO offers services in the area of continuous process, a wider range of pharmaceutical manufacturers will be able to discover the benefits of continuous processing without having to make significant up-front investments.

It is an exciting time for our industry; never has there been an environment where regulatory and manufacturing innovation combined to find ways for new drugs to go forward to approval in shorter time frames. We expect continuous processing to serve as fertile ground for further innovation. P

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