ADVANCING SOLID DOSE PROCESSING EFFICIENCY AND EFFECTIVENESS

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Pharma is approaching continuous manufacturing with caution. However, equipped with fresh technical experience, plus decades of process design and control science across chemical synthesis and manufacture, pharma's confidence is growing in continuous manufacturing's cost, quality and risk-controlling benefits and its potential application to a broader range of oral solid dose processing environments.

Because oral solid dose (OSD) pharmaceuticals will remain the dominant dose form, the pharmaceutical industry will continue to be responsible for the high-quality manufacture of hundreds of millions of individual doses every day, every year for the foreseeable future. But as the world's uptake of solid-dosage pharmaceuticals continues to grow, so does the perception that drugs are too expensive and increasingly unaffordable, and even though there is evidence to the contrary, there has never been more pressure on pharma to produce its products at the lowest cost possible.

It's well established that the safety, effectiveness and value of a given OSD pharmaceutical is reliant on the quality and reliability of its manufacture. At a certain point the FDA – and, subsequently, the world's regulators – recognized that fact and ushered in a regulatory era focused on (among other things) how pharma manufactures its drugs. In its effort to promote, rather than hinder, the safe, reliable supply of drugs to patients and consumers, regulators began to collaborate more closely with the industry and its suppliers to forward an operational excellence agenda and work to implement technologies and systems like continuous manufacturing (CM).

The emphasis by regulators and the industry's technology suppliers on institutionalizing CM and similar technical innovation across drug manufacturing comes from a good place, one based on solid experience and empirical data gathered from real-world industrial manufacturing experience outside of pharma. Including chemical and petrochemical processors, electronics and steel manufacturers and food and beverage processors, most prominent industrial sectors have employed continuous and semicontinuous processing for decades. According to *BioProcess International*, there's one thing they all have in common: "Most of these industries are capital intensive and switched to flow manufacturing to increase productivity and flexibility; reduce cycle times, inventory, waste and costs; and achieve enhanced product quality."[1]

WARMING TREND

The FDA's drive to introduce continuous manufacturing innovation to pharma gained steam with Center for Drug Evaluation and Research (CDER) director Janet Woodcock's public advocacy of the processing technique. To assist industry in evaluating the technology and its implementation, FDA released its draft guidance in December 2015, "Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base." Intended to help manufacturers implement a variety of technological advancements, the guidance was developed by FDA's Emerging Technology Team and published to help further establish CM's viability and regulatory frame to support the transition from batch to CM and its ability to approve CM lines in step with drug development.[2] In hearings before Congress in January 2016, director Woodcock reminded lawmakers of the agency's desire to convince more manufacturers to consider switching to CM methods.

Within a year of FDA's guidance (April 2016), the agency approved a first-ever manufacturing change for Janssen's HIV-1 treatment Prezista from batch to continuous. According to CDER's FDA deputy director Lawrence Yu, Ph.D., from the Office of Pharmaceutical Quality, the event marked another significant step towards integrating CM into pharmaceutical production. FDA approved, for the first time, a manufacturer's change in their production method from "batch" to CM.[3] The change approved the manufacturing of tablets on its CM production platform installed at its manufacturing facility in Puerto Rico. According to Dr. Yu, continuous "enables much faster production and more reliable products through an uninterrupted process." How much faster is CM? In some cases, said Dr. Yu, "manufacturing that takes a month by batch technology might only take a day using continuous manufacturing techniques." He noted, though, that such speed alone would not matter if CM compromised quality. "But by eliminating breaks between steps and reducing opportunities for human errors during the stops and starts in the batch process, continuous manufacturing is more reliable – and safer. That's a powerful combination."

About that same time, Hovione announced its plans in a press release to "host and operate a commercial-scale continuous manufacturing facility as part of an agreement with Vertex Pharmaceuticals," another continuous innovator deploying CM.[4] In June 2016, Hovione announced the groundbreaking for a significant expansion of their New Jersey facility to more than double drug substance manufacturing capacity at the site.[5] Hovione explained that the "site will be unique in offering a single location for drug substance, spray drying, hot-melt extrusion and drug product manufacturing services using innovative continuous manufacturing technology." The company said the investment was part of the company's strategy to increase its global development and commercial capacity to meet the increasing demands of Hovione's customers.

Industry and academia have formed alliances to help bring the benefits of advanced CM process to pharma – for example, the Center for Structured Organic Particulate Systems (C-SOPS), a National Science Foundation engineering research center led by Rutgers University. Prominent engineering schools, including Purdue and the University of Puerto Rico, also participate, along with Glatt, which has contributed equipment, engineering and material support to the R&D collaboration. The Novartis-MIT Center for Continuous Manufacturing is another similar collaboration. According to the group, the 10-year research alliance is aimed at transforming pharmaceutical production by combining the industrial expertise of Novartis with MIT's scientific and technological leadership.[6]

CONTINUOUS BENEFITS

According to C-SOPS, "Continuous manufacturing represents an innovative shift from the traditional multistep, multilocation batch production process, which can take up to four weeks or more to make commercial-ready medicines." C-SOPS finds that "Continuous manufacturing is well suited for the production of precision

medicines and those with breakthrough therapy designations where development time lines may be short and there are patients in urgent need of transformative new treatments."

CM can also be deployed in a smaller footprint than conventional batch process and is proving to be an efficient solution, regardless of proposed product volume. Producing product at commercial volumes becomes a time exercise rather than a capacity/scale issue because making more product means running the process longer as opposed to making it bigger. Suddenly the capital outlay to support a high-demand product becomes a more affordable and sustainable exercise.

QBD-FORWARD

Among the many things regulators and process engineers point out about continuous processing is that a transition from batch to continuous processing enables the development of processes within the cGMP principle Quality by Design framework. To achieve equipment coordination and predictive capabilities that CM promises, process analytical technologies (PAT) are required if the relationships between critical quality attributes, critical material properties and critical process parameters are to be correlated sequentially between the multiple unit operations in product manufacturing.

GAIN CONFIDENCE HERE

In spite of its successes, the industry is understandably recalcitrant to more fully accept and integrate CM, largely because of fears regarding additional capital investment required beyond existing batch processes, as well as the prospect of new equipment and staff training that would be required.

To help drug innovators gain the confidence it's going to take to make the necessary capital and operational investments behind a transition to CM, not to mention instituting CM more comprehensively, Glatt opened a multimillion-dollar innovation center in Binzen, Germany, in 2016. Within the center, Glatt has configured two stand-alone CM process lines to support drug innovators and manufacturers and provide a chance to evaluate the performance of specific compounds and formulations in a CM scheme. Anyone considering a move to CM can bring their molecule and formulation to Glatt for a comprehensive real-time trial within the CM processing environment.

These lines feature Glatt's CM solution called MODCOS (Modular Continuous System). MODCOS offers flexible configuration and consists of dosing feeders and a dry mixer for powder or microgranulates, followed by granulate production using a twin-screw extruder or single shaft granulator, drying in a fluidized bed processor (including a new rotary chamber), followed by a tablet press, which can be supplemented with an extra dry mixer or sizing mill, if required. Both lines are similar in scope, with one sized for R&D and the other for manufacturing. A supervisory control system is employed for each system integrating PAT for monitor and control of (critical) quality attributes and process parameters, such as particle size and moisture. Regardless, drug manufacturers now have a great opportunity to evaluate and pilot the CM process without an intensive financial or operational commitment.

Evidence is mounting that the pharma industry has reached the technical limits of batch processing when it comes to quality control and production efficiency. Any new gains in reliability, cost control or flow optimization from this point are increasingly incremental and expensive to implement. In the coming decades, and as pharma moves well past the blockbuster era, the incentives supporting CM's efficiencies, quality optimization and cost control will continue to mount and prompt the industry to more universally embrace CM as the common standard. P

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