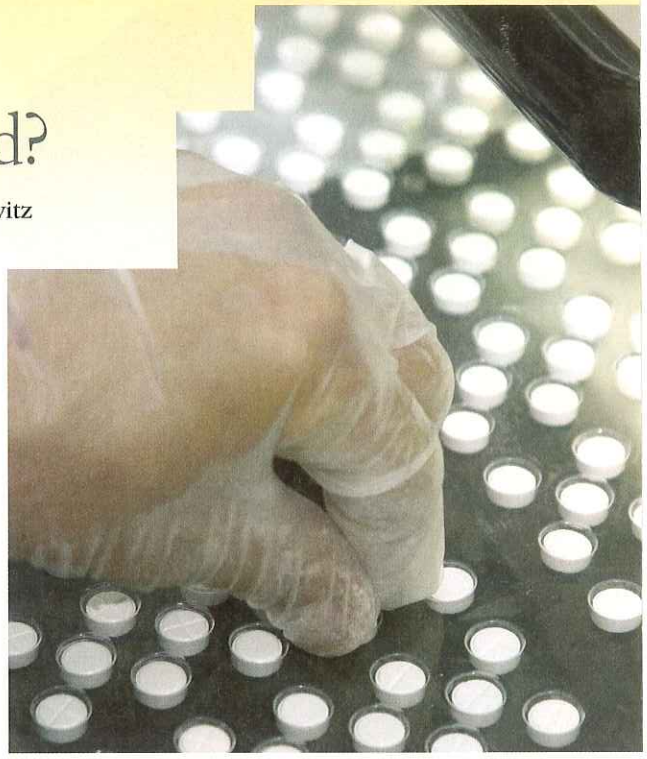
Is The Reign Of Batch Processing Coming To An End?

By Alan Horowitz



On a freeway, start-and-stop traffic indicates a problem. A steady state is the desired condition, where traffic flows continuously and consistently. Not so with the manufacture of pharmaceuticals. Depending on what is being produced and the processes the manufacturer wants to use, start-and-stop can be as desirable as continuous. But that will likely change in the future, as the pharmaceutical industry moves increasingly in the direction of continuous processing.

Pharmaceuticals are produced using one of two processes: batch and continuous. Batch, as defined by the FDA, refers to: "A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture." Batches have defined beginning and ends, which is why batch processing is inherently a start-and-stop operation.

Continuous processing is the opposite of batch, with input being continuously fed into the process and output being continuously removed. "With a continuous process, you are making a stream, one continuous large batch or a series of batches where you continually add starting material but never stop," notes John Salvagno, VP of operations at Norwich Pharmaceuticals.

Continuous processing is widely used by manufacturers outside the pharmaceutical industry. Car makers do not start building one car, only to finish it before starting the next. Henry Ford taught the world the power of continuous mass production, and more recently, companies like Toyota have refined and perfected it to a high degree, such as with just-in-time inventory, making for highly efficient manufacturing. In many industries, if not most, including food and chemicals, continuous processing is the norm, and the efficiencies it produces make batch processing almost unthinkable.

John Kossik, a process engineer at Beacon Engineers who has written about pharmaceutical manufacturing, notes that companies as diverse as pulp mills, chemical manufacturers, and oil refiners use continuous processing. And while for years he advocated continuous processing for the pharmaceutical industry in his writing, it did not happen. Pharmaceuticals remain a holdout for batch processing.

Hard-and-fast numbers about how much of the pharmaceutical industry's production is batch versus continuous are not available, but batch's market share is dominant, agree observers. Ralf Kretzschmar, managing director of Glatt Systemtechnik, estimates that today, not more than 5% of pharmaceuticals are made by continuous processes. This is in line with GlaxoSmithKline's senior technical manager Mayur Lodaya's estimates that continuous processing accounts for a "single digit" percentage of the industry's overall production.

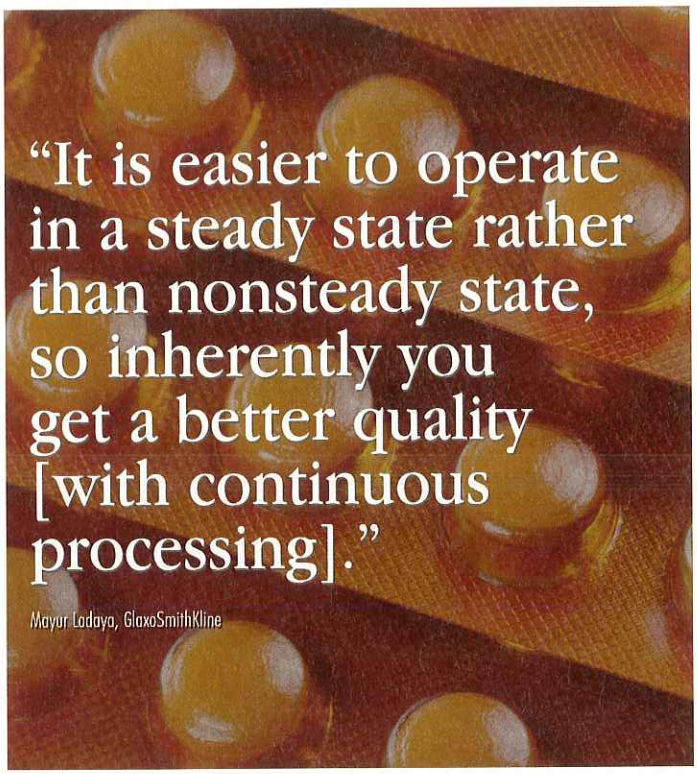
However, the trend is decidedly away from batch toward continuous production, though the pace of change is hard to predict. Kretzschmar believes that within five years, continuous processing could account for as much as 20% of the industry's production, while Lodaya is more conservative, estimating it will take 10 years to reach 20%. What seems certain is that the trend is underway and not likely to weaken.

Seven of the 10 largest pharmaceutical companies are doing some continuous processing, says Robert Barnett, VP of global marketing for K-Tron Process Group. Lodaya says continuous has spread to even smaller firms: "I can tell you there is no tier-one or tier-two company that does not have an active program for continuous processing." Not every such company makes public its efforts in regard to continuous manufacturing, he notes, but that does not

mean they are not actively pursuing it.

ADVANTAGES OF CONTINUOUS PRODUCTION

The move toward continuous production is being propelled by several advantages it offers compared to batch processing. "The efficiencies of continuous are immense, because you do not have a lot of handling of materials," comments Salvagno. "Batch is start-and-stop. Once you start a continuous process, you can run it 24/7. There's very little downtime. You don't need as many people because you just need monitors. You don't need people at every step. Instead of 10 or 12 people, you can have just 2 or 3."



Salvagno adds that with batch you have to make sure you stop to clean before you start up again. That means if you have 15 batches, you have to stop and clean 15 times. With continuous, you don't shut down the process.

Efficiency is also improved by the space requirements of continuous versus batch. Batch material must be stored, then conveyed to the process area, received, fed sequentially into a hopper, and weighed and checked for tolerance levels, comments Barnett. "This all takes time and space. There is a lot more volume of plant capacity required with batch. And because an inventory and test must be done at each step, there is a tremendous amount of inventory control and storage required," he says. The continuous feeding of material into a continuous production line reduces the storage and testing needed, thus producing efficiencies.

Efficiency also comes in another way. Lodaya gives an example: Suppose a yield on a step in a process is 99%. With batch processing, there may be five steps — granulation, drying, milling, blending, and tableting. If you lose about 1% at each step, at the end of the process you have lost about 5% of the overall process yield. If the same conditions were true with a continuous process, since there is only one step, you would lose only 1%. "Having to take material out and putting it back in inherently causes more losses," he says.

Quality and reliability are also advantages of continuous processing. With batch process, material is constantly in a new state. "At any given time your material is not the same as it was a minute before," Lodaya explains. "Essentially, you are in a dynamic state from beginning to end." Not so with continuous. Once the process is up and running, it operates in a steady state. "It is easier to operate in a steady state rather than nonsteady state, so inherently you get a better quality [with continuous processing]," says Lodaya.

Companies may also consider the scalability of continuous processing a significant benefit. Lodaya notes that to double the throughput of a batch process typically requires doubling the amount of production equipment. But this is not true for continuous, where production capacity within a given production line has a range, with the high end often being three or four times the low end. In this case, production can start relatively small and ramp up as needed, without incurring additional investment in production capacity.

Lodaya gives as an example of continuous processing equipment qualified to produce between 10 kg and 40 kg an hour. In an 8-hour shift you could produce between 80 kg and 320 kg. "In a batch process, you can't do that. You would need another piece of equipment, and you would be processing all 320 kg at the same time," he says.

Dominique Roberge, head of microreactor technology business development at Lonza, expects that some of the benefits of moving to continuous processing will involve new ways of doing things. "With microreactors, it is possible to perform high-energy reactions and use unstable intermediates [with continuous processing], which will enable new out-of-the-box chemistries that you can't perform with batch processes," he says. "You can work in a new design space under conditions that are uncommon in batch manufacturing, which lead to new intensified, yet more sustainable flow processes." He expects

continuous processes to lead to new ways of manufacturing because they will allow work to proceed under higher pressure and with new reagents and catalysts, among other variables, that are unavailable with batch processing.

WHY BATCH PRODUCTION REMAINS POPULAR

A number of factors seem to be holding back the transition to continuous processing, not the least of which is the regulator's and industry's familiarity with batch. Batch is how it has always been done, and the challenges to change from what is proven and accepted to something new can overcome continuous processing's advantages.

In addition, over the years the industry has invested heavily in batch processing, and making investments into new processes is expensive. Continuing to use batch processing in order to recover one's investment in batch equipment can make financial sense. Plus, an existing product made in batches would be expensive to switch to continuous. Lodaya, however, notes that production is moving to new facilities in the Far East, such as India and China, and that these facilities do not have existing investments in batch and are therefore more likely to install continuous processing equipment. Assuming more pharmaceutical production will move to countries like India and China, it seems likely that more product will be produced using continuous processes.

Quality control has long been a challenge for continuous processing. With batch, a problem product is a discrete amount that can be identified. With continuous, identifying where the problem product starts and stops is more difficult. "With batch processing, you have the opportunity to take the time to resolve any problems. You can stop and consider where the problems are and resolve them," says Tim Freeman, director of operations at Freeman Technology.

However, improved technology is making quality control easier with continuous processing. Sharon Nowak, global business development manager at K-Tron Process Group, says that laser technology, for example, now allows for the constant measurement of product flows, which was not true a couple of years ago. K-Tron's Barnett comments that process analytical technology (PAT) can provide real-time measurements of output, and that newer feeding systems are able to deliver ingredients with a very high degree of accuracy and performance.

Some products are just better produced in batches, such as powders, says Freeman. "Powders are difficult to characterize. Liquids behave in a mathematically describable way, and even though the pharmaceutical industry uses a lot of powders, there is a lack of mathematical understanding behind their behavior," he says. Batch processing, he adds, can better handle the variables that come with powders, such as when active ingredients become concentrated in one area. Salvagno of Norwich agrees that fluid products, such as ointments, lotions, and creams are more suitable for continuous processing.

And some products just cannot be made continuously. Alex Kanarek, senior consultant at BioProcess Technology Consultants, says that traditional vaccines, for example, where an infectious agent is killed or changed in the production process so it is safe to use, must be made in batches, because the original material is destroyed. And, he says, "If you have a batch process to start with, everything you do upstream will be batch." K-Tron's Nowak adds that products produced in low volumes and those with extremely minute active ingredients are well-suited to batch processing.

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At least for some observers, underlying the pharmaceutical industry's slow transition to continuous processing is a lack of incentives. Says Kossik, "If you depend on the enormously high margins that drugs on patent have, the savings from continuous processing are miniscule. If it wasn't for their high margins, they would all use continuous processing." Freeman comments: "The pharmaceutical industry is uniquely affluent. There's lots of money available to accommodate inefficiencies in the manufacturing environment."

But this could be changing. The industry's struggles to find new blockbuster drugs has been widely discussed, as are the coming challenges of having a number of blockbuster drugs come off patent in the coming few years. Becoming more efficient manufacturers may increasingly appeal to the industry's major players. The need to boost margins could be a major driver in bringing respectability to continuous processing.