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Pharma's move toward small-batch processing

For experts in lean manufacturing, batch processing is sub-optimal. One-piece flow represents the ideal—a widget created as the customer demands it, satisfying the customer, optimizing the company's resources, and delivering higher quality in real time.

In the pharmaceutical industry, batch manufacturing has long been standard practice. Making batches bigger drove down unit cost because of high fixed costs on a per-batch basis. Historically, market demand has supported this strategy, but bigger batch sizes are no longer better. As blockbuster drugs lose patent protections—and sponsors, distributors, and patients seek ever-greater flexibility in terms of access, cycle times, and cost—the pharmaceutical industry is moving toward smaller batch processing.

Other factors driving this trend include:

• *Highly potent medications.* Research shows the global high-potency API market should reach almost $27 billion by 2023, up from $16.5 billion in 2017—a 63 percent increase [1]. Highly potent drugs often require fewer dosage units.

• *Specialty drugs.* Specialty drugs represent the fastest growing segment of the industry, with their share of industry revenues expected to double between 2013 and 2023 [2]. Given the highly targeted patient audiences of these drugs, required dosage units by strength are often small. In 2019, my own company's CDMO, Metrics Contract Services, commercialized a 27-kilogram batch of a novel oncology medicine. This was the batch size for a global supply chain. Currently, we have another product being transferred in with a commercial batch size of 10 kilograms. Such batch sizes are now common.

• *Personalized medicine.* Personalized medicine is a fast-evolving field that employs diagnostic testing to determine which medications and dosages work best for a patient. According to the Personalized Medicine Coalition, hospitalization rates among patients taking warfarin dropped 30 percent when prescribers took into consideration the patients' genetic information [3]. More targeted dosing—titrating to specific dosage levels—means healthcare providers and their patients will require access to more dosage strengths in smaller quantities of each.

• *Orphan drug specialization.* The orphan drug market is expected to nearly double by 2024, accounting then for 20 percent of all prescription drug sales [4]. By definition, an orphan disease affects 200,000 or fewer patients. Although that population is small, when you multiply 7,000 known orphan diseases by patients affected, up to 30 million Americans live with an orphan disease.

• *Availability and growing complexity of drug substances.* Our industry is seeing a growing number of compounds with poor stability, which causes the finished drug product to have a shorter shelf life. This drives a need for smaller lots—enabling high turnover of fresh material with lower risk of obsolescence. A lack of drug substance availability can also trigger a decision to produce smaller batches.

For contract drug product developers and manufacturers, these trends have implications for facilities and operations:

• Traditionally, oral solid dose facilities have been designed such that rooms accommodate a single unit operation such as blending, granulation, compression, encapsulation, and coating. The demand for smaller batch sizes makes such a design difficult in terms of planning, scheduling, and cleaning. A single suite with flexible configuration, portable equipment, and localized containment solutions is more convenient and productive as well as easier to schedule.

• The fixed costs associated with large batch manufacturing are a significant proportion of overall drug product cost—typically greater than 50 percent. To keep fixed costs from becoming commercially prohibitive for small batches, manufacturers must be efficient in room and equipment setup, cleaning, and changeover.

• Precision in mitigating material losses becomes more critical in small batch production, as the impacts of "normal" losses in dispensing, material transfers, or charging equipment become amplified.

• Quality control is generally a material component of the cost in producing drug products. A reduction in batch size does not change how much it costs a manufacturer to sample and test to confirm compliance with validated parameters and filed specifications. As a result, techniques to build quality into the product during manufacturing are critical to ensure quality without excessive testing.

The ideal of lean manufacturing—that is, a batch size of one—is a tall order for any industry. This is especially true for the pharmaceutical industry, which has traditionally experienced comfortable profit margins and viewed large amounts of inventory as insurance against unreliable supply chains. Latent inefficiency has been considered "affordable" when compared to the profit margins of a drug product.

But the move toward small batch sizes is here to stay and will drive more efficient pharmaceutical opera-

tions as the industry seeks to reduce non-value-added costs. *T&C*

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