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Product Development For An Oral Solid Dosage Using Continuous Manufacturing

When bringing a new drug to market, product development is typically aligned with the clinical trial schedule; therefore, as the patient pool grows, so does the supply of drugs needed for the study. Phase I calls for a small trial formulation using the easiest and least expensive manufacturing methods for just getting the drug to the patient.

Once you move into Phase II, a prototype batch process is often most cost effective, especially since most drug candidates do not make it past this stage.[1] However, as clinical trial data begins to come in from Phase II, confidence in the product grows and important decisions about next steps need to be made. This is the best time to consider whether continuous manufacturing is a good fit for your product, as the formulation and process developed for Phase III are the final ones that will be used during commercial manufacturing.

Several small-scale studies should be completed to help determine whether continuous or batch manufacturing is the best fit for your product. These can include characterization work to understand the materials and how they interact with the process as well as proof of concept or range-finding studies on the manufacturing equipment. When continuous is a fit, the workflow can be reduced by as much as six months. This is due to the ability to compress the scale and timeline of the studies, making the process not only continuous but also more flexible.

By considering continuous manufacturing in development, manufacturers ensure they are creating the most optimal path over the life cycle of their program that includes quality, flexibility, and economic benefits.

Critical studies to develop a continuous process

The first steps to developing a continuous process for an oral solid dose is to examine the material properties of various formulation components, as the ability to control the material rate of an application or input into a system is at the heart of continuous manufacturing. Therefore, the first thing you want to understand during the development process is how well the materials are going to behave in your equipment. The more and earlier you understand, the easier it is to tailor the development program to meet the needs of your product. This also helps identify how long a program is going to last and the costs involved, which determines whether continuous manufacturing is the right path forward.

Thermo Fisher Scientific uses about 100 grams of material and several techniques to complete these initial studies. These material characterization tests are used for batch processing but from the perspective of the continuous system. The goal is to examine the materials and compare the properties to any materials used previously in a continuous set. If the material properties are similar to what has been previously observed, then it is safe to use continuous. If any issues are observed, mitigation strategies used in a batch process can be examined to see if they will work again in a continuous situation. These studies can also be used to produce conditions for the process and model them in way that improves efficiency once the process moves to a larger scale.

The next study is to characterize the performance of the feeders with materials that are either in the formulation or are “like” materials (in terms of characteristics but may be less expensive to leverage for these studies). This is done in a lab space with actual manufacturing equipment in order to gain experience with materials in the feeders. This includes verifying that the configuration is correct, such as whether accurate screw sizes and the right impellers are being used for that material. In addition, when refill materials are added to the system, it can create pressure that causes a loss in weight feeders, so it is critical you design an effective refill strategy. Potential technical issues or feeding risks can also be considered, again allowing an early look into the process. If any issues are identified early, modification or mitigation strategies can be put into place to overcome them. Since the materials and the feeders used for production are tested, it is possible to isolate their behavior and understand what the materials are doing without affecting the rest of the process.

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Thermo Fisher also completes compaction characterization studies, which utilizes a small amount of material to assesses potential compaction risks, such as capping, crack formation, high ejection forces, speed sensitivity, etc. A compaction simulator is used to estimate the various compaction properties and how the materials were compacted relevant to tablet press speeds. This helps estimate the critical quality attributes offline and produce ranges for extrapolation or exploration during larger studies. It also allows Thermo Fisher to determine the likely maximum throughput of the system. Usually, the regulating step in a process is a tablet press; therefore, by determining the highest speeds that a tablet press can run at while still producing quality tablets, it provides an upper range on the process throughput, which has a significant impact on the economics of production. Typically, the faster you can run your manufacturing line, the less expensive it is going to be to produce a given amount of material. This is a major factor in understanding what it is we can do with the process and offers insight into the ranges that can be expected during a continuous process as a client moves into future studies.

The deliverables from a compaction study include a report summarizing experiments, compaction property measurements and risk analysis and an assessment of material properties against materials of known behavior. It also includes recommendations on tablet press configuration and capabilities (i.e. maximum speed) as well as study conditions to be carried out in a proof of concept study or a larger designs of experiment (DoE) study.

Continuous manufacturing benefits during product development

There are several key benefits to using a continuous manufacturing process over batch processes. The first is that pilot scale quantities can be produced with a manufacturing scale process. Experiments can be performed during a continuous manufacturing run by changing set points and waiting for the change to propagate through the system. Individual experiments will consume somewhere between 3 and 15 kilograms of formulation, depending on the process, which is in line with what it is for small scale batch development. The exact amount of material per set point comes down to the goal of the study and the number of hard to change factors in that study. During the DoE, the system is run without stopping and the settings are changed. The product is allowed to flow through the system, and the process reaches a steady state at each experimental condition where samples and data are collected. This offers information about process performance at the right scale with the appropriate manufacturing equipment

Continuous manufacturing also allows powder to be transformed into product in minutes to hours, rather than days or weeks. This is because the continuous transformation of ingredients into products eliminates the need for material to be staged between batches, excluding the need for work in progress as well as reducing the time it takes to produce a batch. Small scale development batches typically take weeks to months to proceed through the steps while continuous manufacturing can produce the material within days. It is also much faster to perform studies in continuous manufacturing while simultaneously generating a significant amount of data compared to a batch process. This allows for more knowledge gained in a shorter amount of time, and that knowledge generation is what drives development forward.

Finally, with traditional batch manufacturing, processes are typically scaled from the scale at which clinical material is manufactured up to an acceptable manufacturing scale. However, many things can change when you go from a scale of one kilogram to a production scale of 500 to a thousand kilograms. There is a strong possibility that the knowledge gained at the small scale does not help predict behavior at the larger scales, especially since fewer studies are done during scale up of a batch manufacturing process. The scale-able nature of a continuous manufacturing process, though, means there is no need for scale-up, and instead, the way you produce a larger batch is simply by running the equipment for a longer period of time. The connection between batch size and time allows knowledge gained from studies where you are running for relatively short periods of time for each study point to be utilized for the larger batches. This can lead to material savings in the millions of dollars.

Other benefits of continuous manufacturing include:

- **Speed to clinic (and market)** – Because the time required for development can be significantly reduced with continuous manufacturing, it also shortens the time to market and creates a more flexible development cycle. Studies can also be pushed until more clinical data is available.

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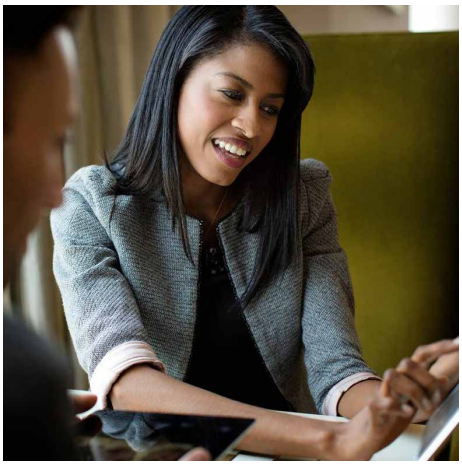
- **Robust, simplified formulation** – In the past, batch processes would require granulation, leading to a more complex formulation. Because continuous manufacturing enables direct blend processes, a simpler process formulation may be possible.
- **Reduced use of active pharmaceutical ingredients (API)** – API usage can be reduced, especially when considering data from the studies is generated at a manufacturing scale.
- **Greater assurance to quality** – Continuous manufacturing produces a large amount of data, which enables more tightly controlled processes and a stronger assurance of high product quality.
- **Scale-up efficiencies** – Once a process is developed in continuous manufacturing, there is no scale up work like in batch. The process is simply run longer if more volume is needed.
- **Regulator preference** – Continuous manufacturing offers a higher potential for quality, which has led to overwhelming support from regulators of its implementation.



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The table in Figure 1 outlines the possible costs associated with development of a batch versus continuous processes. The columns from left to right include: the type of study, the scale of the study (number of kilograms), number of expendable points carried out at each scale (rough estimate), the total amount of material estimated for those studies at that scale, and then the estimated cost for only the materials.

Traditional development scale up scenario				
	Mass	n	Total material	Total material cost
R&D	1.5	30	45	$90,000
Pilot	15	15	270	$540,000
Sclae up 1	150	6	1170	$2,340,000
Scale up 2	600	6	4770	$9,540,000
Total	766.5	47	6,255	$12,510,000

Continous manufacturing scale up scenario				
	Mass	n	Total material	Total material cost
R&D	1.5	30	45	$90,000
CM pilot	15	24	405	$810,000
Tech batch	60	3	585	$1,170,000
Total	766.5	47	6,255	$12,510,000

Figure 1: Scale-up efficiencies in development can lead to significant material cost savings

With batch processing, most studies, such as material characterization, take place at the smallest scale. The number of studies performed decreases at each scale up, reflecting the reduced opportunities to learn about the process as the scale, the material cost, and the level of risk increases. In continuous development, the primary studies are done on the manufacturing equipment and a larger number of study points are collected at the pilot scale than they are in the batch process. The scale increases only as the process is run for a longer period of time. Therefore, without the scale up requirement, continuous manufacturing can offer significant cost savings, which is only one of the many benefits this approach can offer your program. Overall, a thorough evaluation using the methods outlined in this paper will give you the information you need to make important decisions about the future, thereby creating the most efficient path to market.

1. Berezow, Alex. (June 2020). American Council On Science And Health. Clinical Trial Success Rates By Phase And Therapeutic Area. Retrieved from https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845

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