Speeding Time to Market for Orphan Drugs with Pharmaceutical Continuous Manufacturing

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Pharmaceutical Continuous Manufacturing (PCM) has been touted to transform the pharmaceutical industry for many years. Even as adoption has not progressed as widely as anticipated, large-cap innovator companies have successfully applied PCM to new drug entities (NDE) in the major markets. PCM technology has been used successfully for decades as part of development and commercial activities to manufacture small quantities of highly reproducible drug product for early development and clinical supply. PCM's framework is a natural fit for small volume drug therapies providing the capability to deliver smaller volume rare disease applications faster to market. This article focuses on how PCM can accelerate time-to-market for innovative new medicines that are vital for those in need.

Orphan Drug Act

During the 1970s and early 1980s, patient advocacy groups and individuals raised awareness about the lack of available treatments for rare diseases and lobbied for legislative support. In response to these efforts, the U.S. Congress passed the Orphan Drug Act (ODA) in 1983 to incentivize pharmaceutical companies to develop drugs for rare diseases. In addition to tax incentives the Orphan Drug Act grants seven years of market exclusivity to the first sponsor of an orphan-designated drug that receives FDA approval. During this period, the FDA cannot approve a similar drug for the same indication, reducing direct competition and allowing the company to potentially recoup its investment. As most new drug products are developed by small-cap innovator companies with little or no commercial manufacturing footprint, PCM represents a cost-effective alternative to batch processing because it eliminates the complexity and cost of intermediate bulk release and storage with the potential for real time release of the product.

In January 2023, the NIPTE pathfinder workshop pointed out that using advanced manufacturing processes can indeed reduce time to market for new drugs. The article (Futran, et al., May 2024) published later that year reiterates PCM's ability to deliver faster, more detailed information that shortens development and CMC process timelines and time-to-market for new drug modalities destined for critical ill patients. Rare disease drugs are a critical segment because patient groups are small. The FDA's Orphan Drug Act (FDA) defines a rare disease as a condition that affects less than a population of 200,000 people (U.S.) and fewer than five in 10,000 patients in the EU (Agency). Although the ODA does provide incentives the capital and investment considerations can make orphan drugs less attractive than other disease therapies. The intent behind the ODA was to incentivize drug sponsors to address a small, underserved patient population. PCM represents an attractive platform to assist drug sponsors in serving these underserved populations while reducing the investment and risk associated with conventional drug development and commercial manufacturing markets. The NIPTE workshop and corresponding paper highlight solutions that industry showcased during COVID when products were safely and quickly developed and delivered to a global patient group. The advantages of PCM for the orphan and rare disease markets can be seen in its successful application in the manufacture of a rare disease drug treatment for cystic fibrosis, a disease affecting approximately 40,000 patients in the U.S. and 100,000 patients globally.

Business Case for PCM

The latest market research shows that the treatment for orphan- and rare diseases has become a sizable market comprising almost 300 BN USD within a 1.5 TN USD market and is expected to grow with a CAGR of 11.6 percent. This is considerably better than the overall market with is projected to grow at a CAGR of 7 percent *(*excluding generics) (Evaluate, 2023).

Vertex made the jump to PCM for its cystic fibrosis treatment segment. Their lead product, Trikafta™ has enjoyed retail sales of 8.9 BN USD, and was listed as number 13 among the top 200 drugs in 2023 (Ryan E. Willimas).

With the switch from batch to PCM (Hurter, 2023), Vertex reduced the development timeline by 18 months versus the traditional batch approach, estimating that the reduction in time to market translated to 4.5 billion USD in additional sales per annum. The savings in terms of API required was reported at 77 percent. The development timeline for Trikafta™ using the PCM approach was three and a half years (Hurter, 2023) from discovery to approval in October 2019. Retail sales are projected to continue to grow to 10.5 BN USD in 2024-2028. Vertex could accommodate this rapid growth partially because of the flexible output capability of the PCM process, without additional capital investment to build capacity. According to the same source, it is one of the two fastest-growing small molecules in this segment (Evaluate, 2022).

A big part of this success story is attributed to a bold entrepreneurial business decision in the early days of development for cystic fibrosis treatment when PCM principles were not widely known and few products could be reported (Thomas, 2014). Vertex's first product, called Orkambi™, was launched in 2015 a mere three years after their first continuous development and launch equipment (DLR) was commissioned at their Boston facility;

this was followed by Symdeco™ in 2018. One year later, in October 2019, Trikafta™ was approved. On a time scale, and using terminologies from higher physics and today's politics, this was a "speed of light" undertaking when compared to traditional product delivery.

FDA Approval

The FDA has embraced advanced manufacturing technologies such as PCM applications, resulting in faster approval and market authorization. The FDA (Adam C. Fisher, 2022) assessed the approval process between 2016-2020 by auditing the outcomes of submissions in the U.S., finding that PCM applications had a shorter time to approval compared to similar batch applications. The same audit estimated that faster approvals result in higher additional revenues for companies that have implemented PCM to manufacture new drug products.

What are the main reasons for faster time to approval with the regulatory agency? In his recent presentation at the ECA CM conference (April 16, 2024, in Portugal), the FDA's Sau (Larry) Lee mentioned that early interaction with the agency through CDER's Emerging Technology Team (ETT) was key to getting products to market earlier. The reference publication states that faster approvals are independent of existing breakthrough therapy designations that would lead to further acceleration for any rare disease case. Another important finding was that data provided for the filing was much more consistent and comprehensive due to the flexibility of PCM process equipment in the final adaption of the process to commercialization, whereas typical batch process see some changes at this stage. Mr. Sau highlighted that *"no substantial regulatory barriers for PCM, related to manufacturing changes and due to pre-approval inspections"* have been found ((FDA), 2024).

Gaining Market Share

A McKinsey study published in September 2014 (Myoung Cha, 2014), showed that a 12 percent gain in market share can be expected for a pharmaceutical company that gets to market faster than their peers in the industry. This confirms the Vertex Trikafta™ case, cited above. For the business case this indicates a considerable gain in peak sales and extended sales volume extending beyond the patent cliff. The effect on the business is illustrated in the following graph showing year-over-year sales and including an anticipated gain in market share, as follows (**Figure 1**). The sales projection leads to the following corresponding NPV scenario in the next graph with the addition if line CM_1 when the respective company does not have PCM assets and procedures in place.

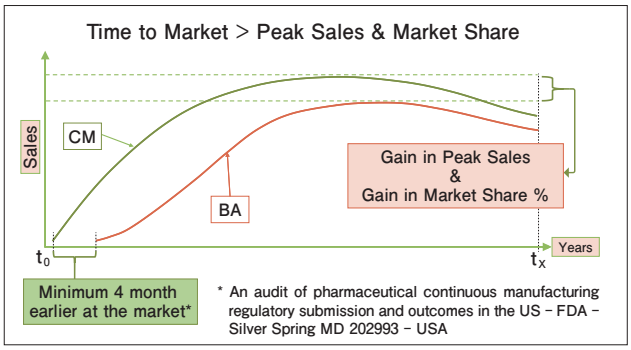

Figure 1 Sales projection over time - published during the PCM Summit September 2023 (Richard Steiner, 2023)

Figure 2 compares NPV for companies that have PCM (CM) and Batch equipment (BA) installed and ready for commercial use. The CM_1 line represents NPV over the time of depreciation (for example 10 years). When a company buys and installs a continuous manufacturing system at a later stage (CM_2), the years t_0 to t_3 indicate the expected timeline to build and install a continuous system (Steiner, 2023).

Why is this important for the rare disease case? Most companies start implementing continuous manufacturing in Phase II product development with lab scale equipment. Investment and procurement of a commercial PCM asset is postponed to a later date when the product demonstrates safety and efficacy in Phase 3. This can put drug sponsors 18 months to two years behind as they react to a positive clinical outcome and then procure a commercial PCM equipment train. The reality is that pharmaceutical companies struggle when a promising drug candidate approaches commercialization stage and there is not yet a commercial PCM unit ready within their supply chain. In such cases, pharmaceutical companies tend to switch back to their Batch equipment and established processes. Consequently, companies relinquish potential NPV surplus and profit gain demonstrated in Figure 2.

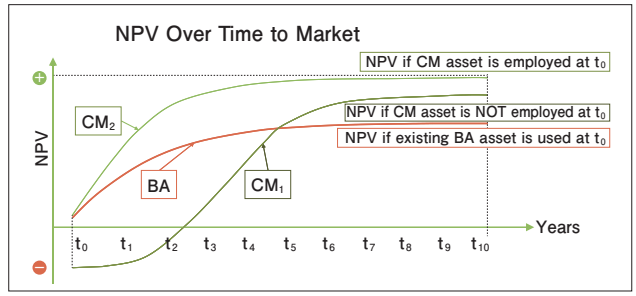

Figure 2 Graph with NPV over time - published during the PCM summit September 2023 (Richard Steiner, 2023)

PCM for Low Volume Low-cost Manufacturing

As to expected benefits of PCM, it was understood that deploying continuous manufacturing would save significant amounts of material, especially for expensive active ingredients (API). Equipment vendors offer small scale small volume equipment to process as little as 1kg to 10kg *per hour* for pharmaceutical products. Companies such as Bohle (Bohle, 2024), GEA (GEA, 2024), and Gericke (Gericke, 2024) have introduced equipment to manufacture low-volume products, thus making equipment widely usable in development, launch, and commercial manufacturing departments. In the Vertex case a so-called Development and Launch Rig (DLR) mentioned above was used to save tech transfer and scale-up time (Thomas, 2014). Pfizer has developed a Portable Continuous Miniature Manufacturing (PCMM) technology using the same principle to save time to market (Pfizer, 2019).

Supply Chain Agility

Supply chain agility is the second major benefit of PCM. Due to its flexible batch size capability, PCM opens the door to a lean manufacturing paradigm with the possibility of adapting faster to unpredictable market demands. ICH Q13 (ICH, 2022) chapters 2.2. (batch definition) and 4.3. (batch description and batch size) show how to define a batch and its range when it comes to flexible batch sizes. However, agility also means the option to adapt shift models and to increase shifts with the possibility of 24/5 if not 24/7 operations on the same asset.

With their PCMM project, Pfizer applied a similar rationale to Vertex to successfully with the product Daurismo™, an acute myelocytic leukemia treatment for an estimated 20,800 patient group representing about 1 percent of all cancer cases in the U.S. in 2024 (Society, 2024), (Technology, 2020). Pfizer used the same size PCM system to develop and commercialize new drug products and skip traditional tech transfer with scale-up facilities.

Scale-out instead of scale-up promises to save material and time to market: To apply PCM in this setup, economies of scale can be reached by employing multiple modules. For a global rollout the modules can be installed in different regions for a more regional supply which would help to reduce supply chain risk on a global scale. This type of rollout contributes to supply chain agility.

Onboarding PCM Expertise

CDMOs such as Hovione (Santos, 2024) and Thermo-Fisher Scientific (Torres, 2024), provide proactive services for PCM pioneers from development to commercial scale without the heavy investment required to start those ventures. Because their equipment is immediately accessible, this further shortens the timeline for innovators that do not have GMP facilities and PCM equipment ready to go. At the outset, CDMOs avail of PAT experts and PCM equipment operators and this can contribute to the decision whether to go continuous with a product or remain on existing batch processing equipment.

Another way to shorten timelines and the learning curve and reduce risk is close collaboration with PCM expert consultants and equipment providers for initial trials and process development, to take advantage of their expertise, firsthand experience, and trained SMEs.

The ACHEMA 2024 exhibition in Frankfurt Germany showed us that the pharmaceutical industry is in a comfortable situation. Reliable process equipment is available for drug substances and drug products. This includes many kinds of PAT sensors and control systems and analytic software solutions to drive toward real time release (RTR) testing. Real time release (RTR) concepts can be implemented at the same time as PCM in some cases, to save time and costs on product release procedures. We maintain that small volume and PCM are not a contradiction. Product and process simplification is the hallmark of PCM.

Summary

The major PCM business case for large-, medium or small-cap innovator companies is faster time to market for new drug candidates. PCM offers an opportunity to save time during the regulatory market approval process by skipping the typical technology transfer and commercial scale-up activities. Overall, PCM brings higher flexibility during the traditional Chemistry, Manufacturing and Control (CMC) product and process development.

In this light, PCM is a win-win for all parties involved. The critically ill patient or the patient with a rare disease will access new drug modalities faster. With PCM the pharmaceutical industry can gain competitiveness on many levels. PCM is part of the advanced manufacturing technologies supported by regulatory agencies like the FDA (Rapti D. Madurawe, 2024). Regulatory agencies can ensure that their constituents benefit from lifesaving medicines and reduced supply chain risks. Perhaps the greatest benefit of PCM is how it can enable the pharmaceutical industry to produce medicine for all.