FERRING
PHARMACEUTICALS

Ferring Prototypes Continuous Manufacturing with Advanced PAT and Closed-Loop Control, Potential for Dramatically Lower COGS

aspentech | Case Study

"The combination of Aspen Unscrambler™ and Aspen Process Pulse™ enabled Ferring to prove the concept of transitioning from batch to continuous manufacturing at development stage, by providing real-time product quality measurements for closed-loop control. This solution gives us the tools to build robust models that are deployed and managed seamlessly online."

- Samd Guizani, Process Scientist Manager
Ferring Pharmaceuticals

ESTIMATED UP TO

25%

REDUCTION Cost of Goods Sold

CHALLENGE

Needed a solution that would enable faster commercialization, more cost-efficient production and reduced supply lead time while maintaining product quality in support of digitalization initiatives.

SOLUTION

AspenTech's Advanced Process Analytical Technology (PAT) solution—which includes Aspen Unscrambler and Aspen Process Pulse—delivers real-time, online product quality measurements to guide closed-loop control for continuous manufacturing while paving the path for real-time release testing (RTRT).

VALUE CREATED

- PAT-enabled closed-loop control ensures on-spec product quality in continuous manufacturing
- Significantly smaller footprint (continuous vs batch) saves expensive clean room space
- Real-time release testing greatly reduces delay and cost compared to offline laboratory testing
- Continuous manufacturing empowers production agility and avoids the need for equipment scaleup

Introduction

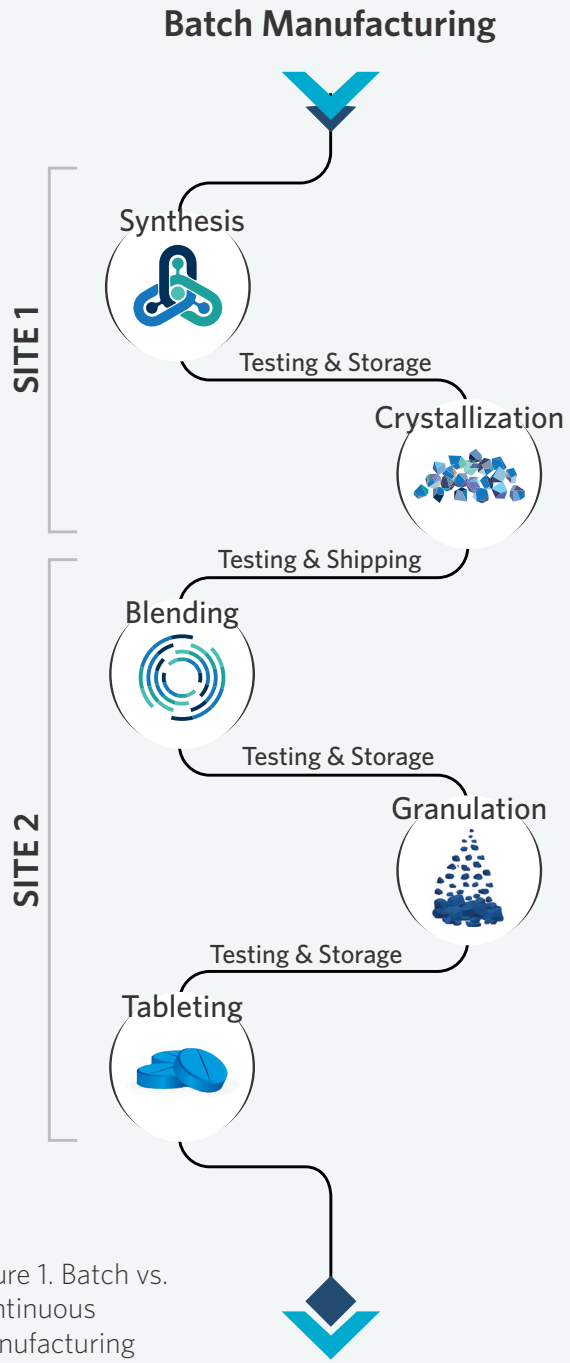
Ferring Pharmaceuticals is a multinational biopharmaceutical company with a longstanding track record of innovating therapeutics to support the growth of healthy families. The company's research-driven approach extends beyond drug discovery to include new innovations in manufacturing.

Recently, Ferring implemented a project at development stage to transition from batch to continuous manufacturing, assisted by the combination of closed-loop control and advanced process analytical technology (PAT) that uses predictive multivariate analysis. This directly supports the FDA's vision for QbD[1] in the context of continuous manufacturing, as articulated in the ICH Q13 draft guidance[2] and the ISPE's Pharma 4.0 initiative, as it builds resiliency into the Pharma Value Chain Network.

Closed-loop control technology automatically adjusts the critical process parameters (CPPs) to continually steer the critical quality attributes (CQAs) to their target values—even as the critical material attributes (CMAs) and environmental conditions change.

This behaves much like an autopilot that keeps an airplane on course despite atmospheric disturbances.

Batch Manufacturing vs. Continuous Manufacturing[3]



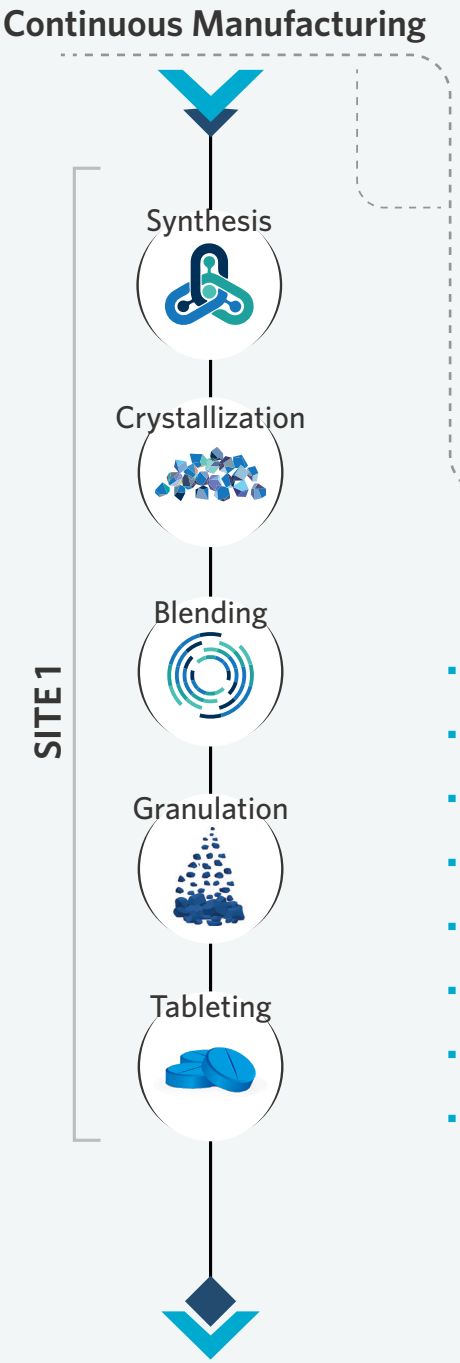


Figure 1. Batch vs. Continuous Manufacturing

All Steps Occur Simultaneously on a Single Process Line

Benefits of Continuous Manufacturing

- Reduced Processing Time
- Lower Operating Costs
- Reduced Waste
- No Manual Handling
- Smaller Footprint
- Consistent Quality and Uniformity
- Continuous Monitoring of Quality
- Increased Production Volumes

Continuous Manufacturing Drives Better Patient and Business Outcomes

Continuous manufacturing technology is gaining traction in pharma since it consistently demonstrates compelling benefits, including faster product commercialization, more cost-efficient production and reduced supply lead time (see Figure 1).

The continuous process that Ferring designed dissolves an API powder inline into a buffer solution to produce the finished pharmaceutical product (FPP). The two critical quality attributes (CQAs) are API concentration and the concentration of a key preservative, previously measured offline alongside the original batch process using time-consuming and costly HPLC.

With the continuous version of the process, Ferring reported a dramatic reduction in clean room space needed compared to batch manufacturing, significantly lowering capital and operating costs. In addition, the same continuous processing equipment could be run for clinical trial production as well as commercial production by simply extending the run length. This would markedly speed up product commercialization and reduce costs by eliminating the need for equipment scale-up.

Similarly, Ferring identified that by adjusting the duration of the run, the amount of production could readily be matched to market demand, boosting agility and reducing the need for safety stock. Logistics would be simplified and costs reduced. These outcomes simultaneously benefit both the patient and the business.

Continuous Manufacturing with Real-Time Quality Assurance

Continuous manufacturing does, however, introduce the challenge that parcels of product (product lots)—unlike from batch manufacturing—cannot be easily isolated for quality assurance. Ferring explored the combination of advanced PAT and closed-loop control to counter this challenge and make the continuous processing approach feasible.

Transitioning away from offline laboratory testing, Aspen Unscrambler and Aspen Process Pulse were used to build and deploy models that quantify the two CQAs (API and preservative concentrations) online every few seconds, from UV-Vis spectra of the product. This technology combination provides timely and frequent product quality inspection, which enables RTRT.

All product that is in-spec is sent to packaging while any out-of-spec product is automatically diverted. RTRT also greatly reduces the need for offline laboratory testing, delivering additional and significant cost savings.

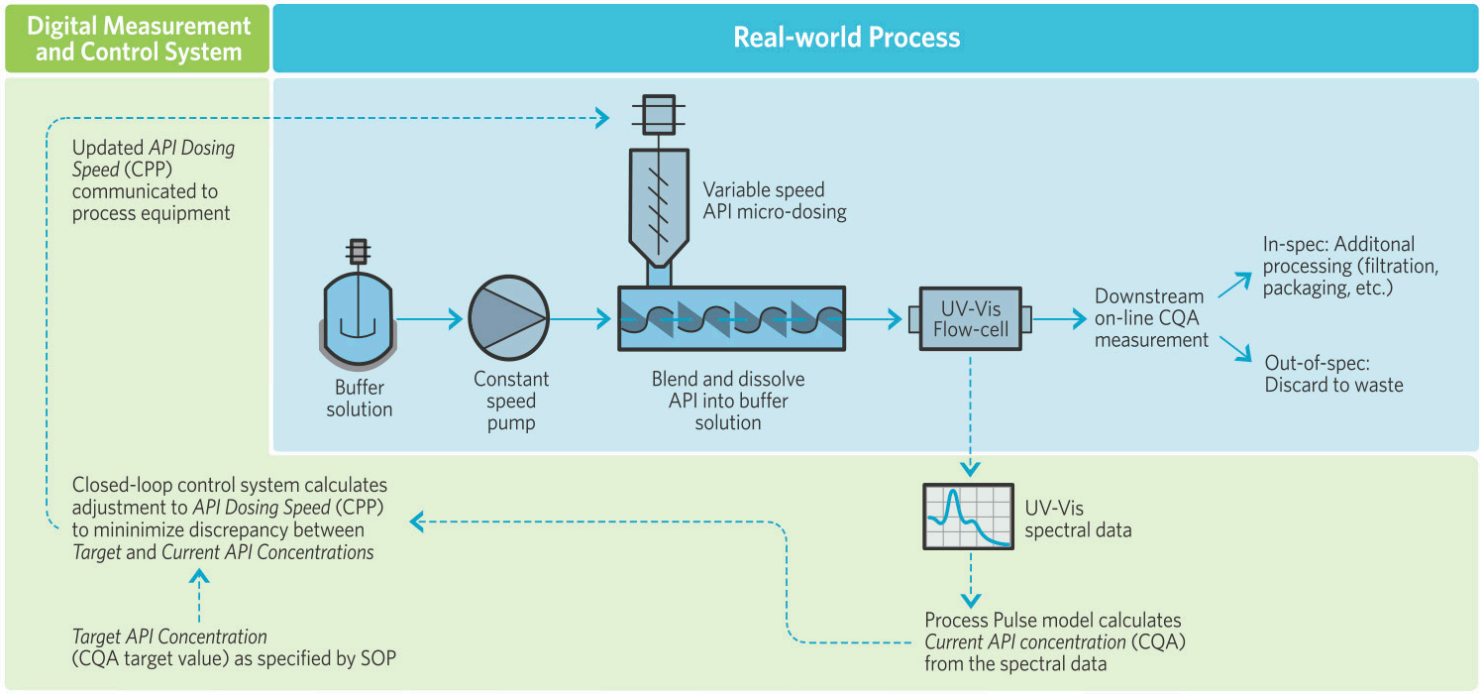


Figure 2. Closed-loop control system in production.

Abbreviations:

API	Active Pharmaceutical Ingredient
CQA	Critical Quality Attribute
CPP	Critical Process Parameter
UV-Vis	Ultraviolet-visible
Spectral data	Spectrum of light absorbance
SOP	Standard Operating Procedure

Enabling Closed-Loop Control

Ferring also demonstrated how this real-time advanced quality measurement system, empowered by Aspen Unscrambler and Aspen Process Pulse, enables closed-loop control. The rate of the API powder addition to the inline mixer can be adjusted. The real-time controller, implemented in a Programmable Logic Controller (PLC) in Ferring's case, compares the measured API concentration (calculated by Process Pulse) against its target value. If the measured concentration is below target, the controller automatically increases the rate of powder addition to bring it back to target and vice versa. Control of the CQA is continuously achieved for all production without the need for manual human adjustments (see Figure 2).

Over many past applications in industries adjacent to pharma, it is typical to see a twofold or greater reduction in quality variation by transitioning from manual to automated (closed-loop) control. In Ferring's case, the closed-loop control system ensured sufficiently tight quality control that the vast majority of all production was within specification limits.

By empowering both RTRT and closed-loop control, AspenTech's advanced PAT solution is a powerful enabler for monitoring and improving both process and product quality.

Conclusion

As demonstrated by Ferring, consistent quality from PAT-enabled closed-loop control, verified online with PAT-enabled RTRT, would support agile and reliable delivery of the scheduled amount of saleable product through continuous manufacturing — helping reduce supply pressures in the pharma Value Chain Network while accelerating Ferrings's digitalization journey, in keeping with the Pharma 4.0 vision. Equally valuable, through the combination of reduced clean room space, reduced offline laboratory testing and reduced safety stock inventory, Ferring reported their new design would reduce COGS by up to 25% compared to the incumbent process design that was batch and without RTRT. Ferring chose Aspen Unscrambler and Aspen Process Pulse for their PAT implementation due to the comprehensive tools for building robust models and the ease of deploying and managing these models online.

Citations:

[1] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding Pharmaceutical Quality by Design. AAPS J. 2014; 16(4):771–783. doi: 10.1208/s12248-014-9598-3.

[2] ICH Q13 Draft. **https://www.ema.europa.eu/en/ich-guideline-q13-continuous-manufacturing-drug-substances-drug-products**

[3] Pharmaceutical Manufacturing: Current Trends and What's Next – AIChE, December 2018. **https://www.aiche.org/resources/publications/cep/2018/december/pharmaceutical-manufacturing-current-trends-and-whats-next.**

About Aspen Technology

Aspen Technology (AspenTech) is a global leader in asset optimization software. Its solutions address complex, industrial environments where it is critical to optimize the asset design, operation and maintenance lifecycle. AspenTech uniquely combines decades of process modeling expertise with artificial intelligence. Its purpose-built software platform automates knowledge work and builds sustainable competitive advantage by delivering high returns over the entire asset lifecycle. As a result, companies in capital-intensive industries can maximize uptime and push the limits of performance, running their assets safer, greener, longer and faster.

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