Merck Leverages Data and Analytics to Support New Continuous Drug Manufacturing Processes

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Overview

While moving from batch to continuous manufacturing may not be new in many other industries, it is in pharmaceutical and biotech manufacturing. According to Laura Wareham, Senior Scientist, Engineering, at Merck's man-

Pharma, a highly regulated, science-based, and largely batch-oriented industry, is relatively new to continuous manufacturing. Continuous manufacturing can lead to innovative pharma and biotech products and processes and help pharma companies resolve cost, quality inspection, and supply chain challenges. This report discusses how Merck is using OSIsoft and Seeq technologies to support drug development and commercial production using continuous manufacturing.

ufacturing division, while continuous manufacturing may be well-established in other high-volume industries with well-known processes, it is relatively new to the pharma industry. That's because pharma is a highly regulated, science-based, and largely batch-oriented industry with a large installed base of batch manufacturing equipment.

However, despite the upfront capital expense required to replace legacy equipment and perceived regulatory hurdles, continuous manufacturing can lead to innovative

pharma and biotech products and processes and help pharma companies resolve long-standing cost issues related to development and scale-up and delivering high-quality products with flexible batch sizes to meet changing market or customer demands.

Over the past couple of years, the European Medicines Agency and US Food and Drug Administration gave a handful of approvals to pharmaceutical companies to manufacture drug products using continuous manufacturing processes. In February 2019, the FDA released a draft guidance that defined continuous manufacturing as a process in which input materials are

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continuously fed and transformed within the process and the output materials are continuously removed from the system.

Merck is using the OSIsoft PI System data infrastructure and piloting Seeq's analytics to optimize its product and processes to support continuous manufacturing.

Merck's Continuous Manufacturing Challenges and Goals

As ARC Advisory Group learned from Ms. Wareham's end user presentation at the recent OSIsoft PI World Conference in San Francisco and subsequent discussions, Merck has initiated a project to qualify the company's first GMP (good manufacturing practice) continuous manufacturing equipment modules and actively develop new products at the company's facility in Cramlingon, UK. Line of site for its validation batches and filing is scheduled for later this year.

Merck's goal for the continuous manufacturing pilot is to minimize the traditional scale-up challenges when moving from pilot production to commercial manufacturing. To reduce its equipment footprint, the company wants to be able to use the same equipment to both develop new products and produce them commercially. Compared to traditional batch processes, continuous processing would reduce the costs associated with scale-up and transfer between equipment and site. This applies for active pharmaceutical ingredients (APIs) in particular. The project would result in flexible run times with volumes that could be adjusted to meet changing product demands. The company knew that the data-rich continuous manufacturing environment would provide opportunities to enhance both its product and process knowledge.

The Technology

Merck is combining data from its OSIsoft PI System with Seeq's analytics solution to encourage collaboration across the company and optimize its processes and products. The solution works with the company's existing PI System data, PI Data Link, and PI ProcessBook and incorporates Seeq technology for analysis, trends, visualization, and knowledge management from the product development stage through to commercial manufacturing. The objective is to enable a highly automated, agile, integrated, and optimized process.

Seeq, an OSIsoft partner, easily integrates with the OSIsoft PI System data and applications. In this application, Seeq's advanced analytics provide decision makers with improved insights from the PI system data. The PI System is the source of record. In the future, the company plans to capture process data through PI Asset Framework and PI Event Frames to enable the Seeq advanced analytics. Users will then be able to act upon the knowledge and information using PI Notifications and PI Vision.

The Process and Equipment

Merck's manufacturing equipment consists of four loss-in-weight feeders that accurately dose and mix the API with three other ingredients to be mixed in the first of two linear blenders and then transported to the other linear blender and mixed with two other ingredients. This blend is then delivered
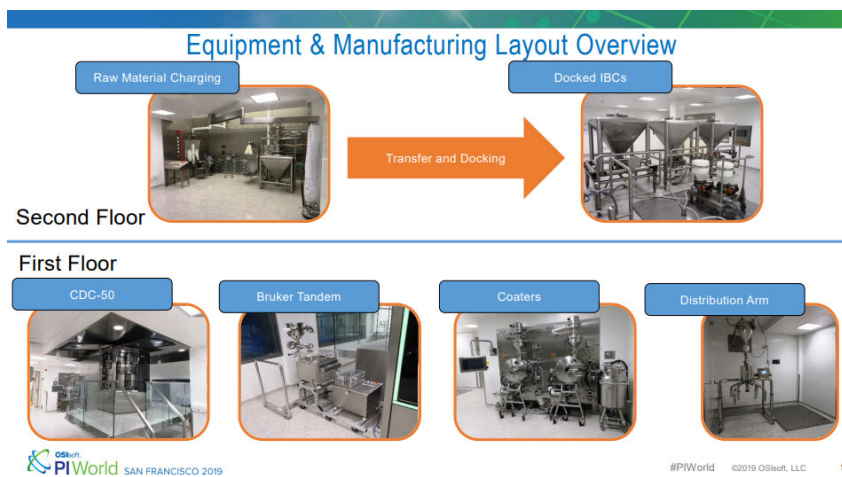
Equipment and Manufacturing Layout for Continuous Manufacturing

to a rotary tablet press that compresses the blend into tablets. The core tablets are conveyed either to an automated tablet tester that determines tablet attributes (e.g., weight, hardness, thickness) and spectra or to a film coater. After film coating, the tablets are conveyed to a distribution arm and then discharged into finished product containers.

Process Development Use Cases

Merck is employing the data and analysis technology to support several use cases for converting batch manufacturing processes to continuous manufacturing as well as supporting new product development.
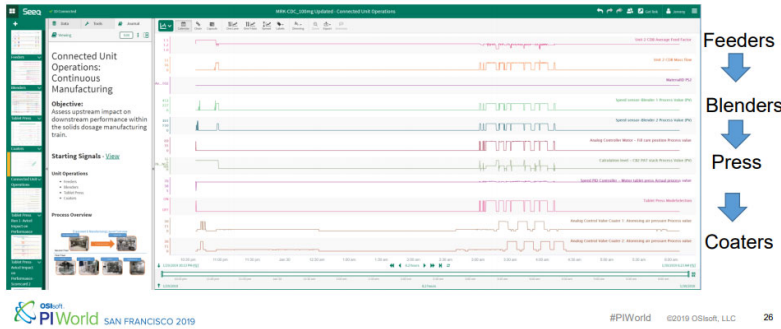
Tableting Process Pilot

Traditional batch manufacturing includes multiple unit operations executed separately and sequentially. The pilot process for this tablet manufacturing application was to develop the compression or transfer of a powder or blend into a tablet in a continuous process and integrate the feeding, blending,

compression and film coating operations to the upstream and downstream processes.

So far, the company has encountered no problems in compression development. Seeq can be used to analyze the relationship between multiple compression parameters as well as for upstream inputs (such as feeding parameters) and downstream outputs (such as tablet attributes). The user can quickly and easily isolate the data using Seeq's Capsules. Once isolated, the user can review raw material characteristics and tablet metric data using a dashboard that highlights standard deviations and process models.

Process Analysis of Merck's Data

The data can be filtered to remove false zero signals (e.g., when the tablet press is off, in maintenance, or in different operation modes). This makes the data appropriate and set up for further analysis.
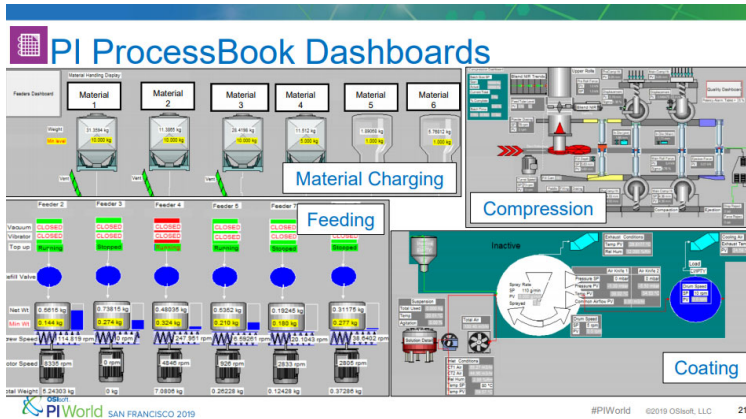
Reducing Product Release Time

In a traditional batch manufacturing process, samples may be taken manually with in-process checks and then tested offline. For a representative four-hour compression run, 10 to 15 samples may be taken per batch to establish uniformity for the tablet compression. Offline testing in the analytical lab would then often take up to two weeks before the batch was tested and released. For continuous manufacturing, Merck is collecting more than 1,600 tags a second.

Continuous manufacturing will generate more data in real time and enable process adjustments to be made based on trends. Innovative data analysis tools are needed to be able to take advantage of all data and to enhance visibility into the process performance. The company expects to be able to complete release testing in about a day, compared to a week for a comparable product that does not use real-time release testing.

All continuous manufacturing-related equipment at Merck's Cramlington facility is connected to the PI System. Other standalone feeders and pilot

equipment for continuous manufacturing are either connected to PI, another data historian, or not at all. There is an opportunity to collaborate and standardize analysis of the data.

Merck wanted to be able to connect the subject matter expert to interactive, intuitive dashboards and decided to use Seeq's advanced analysis and PI

PI Vision for Continuous Process Stages

ProcessBook to highlight, document, and connect the team to data-driven insights. To determine the impact of performance on operations (such as the compression of tablets) it was important to be able to view the data holistically, rather than just by individual unit operations.

Merck brought the equipment online in January and is working actively with Seeq to analyze development data and study equipment performance. It is using the technology to identify early warning indicators and opportunities that can prevent downtime and support preventive maintenance. The software enables the company to use data to predict equipment failures before they happen so processes can perform robustly and help prevent downtime losses. In the future, Merck would also like to use the software to set up a preventive maintenance program that could help it determine optimum timing for maintenance, rather than relying on calendar- or rule-based maintenance.

Impact of Raw Material Variability on Tablet Press Performance, Tablet Metrics, and Process Robustness

Merck is using the technology to experiment with raw material variations, simulated disturbances, and process parameter performance to determine the impact on the product and help ensure product quality, consistency, robustness, and safety, and support the company's control strategy. The knowledge gained will be used to assess the robustness of each unit, robustness across all unit operations, and optimize the integrated process.

The Future: Knowledge Management

The company is also working with Seeq to identify additional application areas. The company will continue to use the technology to inform development and manage knowledge management as continuous manufacturing continues to develop and future products are introduced. The Seeq technology can be used to standardize data analysis, view the information in a single repository, and share knowledge with scientists, management, and partners to improve collaboration.

Other areas that Merck intends to explore include using the technology to enable predictive strategies for standard and unified analysis, collaborating and managing across sites and operations, integrating with process analytical technology (PAT) and automating the tablet spectral analysis, and automating development and analysis of the residence time distribution model.

Recommendations

Seeq analytics, combined with the OSIsoft PI System technology, lend themselves well to the data-rich environment at Merck and in the pharmaceutical industry in general. Both a challenge and an opportunity, continuous manufacturing requires collecting, analyzing, interpreting, and acting on thousands of process and analytical tags collected every second on the production floor. Continuous manufacturing will generate significantly more data, but also enable more opportunities to respond in real time using the newer technology tools.

Based on ARC research and analysis, we recommend the following actions for owner-operators and other technology users:

- Process understanding is important to speed plantwide decisions. The solution can start with either a diagnostic approach to determine why something *is* happening, or a predictive approach to determine what *will* happen. For continuous manufacturing, it is equally important to monitor the process proactively to determine what is happening and get more prescriptive and descriptive understanding so the user knows what should happen and better understand what did happen.

- Data and advanced analytics technology can help users analyze and develop knowledge to standardize their processes for continuous manufacturing.

- Work with technology partners that understand your industry, science, processes, regulations, and applications.

- Better knowledge management and real-time collaboration can help enable scientists, engineers, managers, and partners optimize continuous processes across the enterprise.

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