APPLIED MATERIALS | Applied SmartFactory®

Go green or go home

APG Pharma Applications Team

Overview

Pharmaceutical manufacturing leaders, like all organizational leaders worldwide, are facing increased pressure to meet sustainability goals and reduce their negative impacts on the environment and human health. Many are asking similar questions about whether and how implementing sustainability measures will improve their bottom lines. This white paper details how SmartFactory Rx® can help achieve both organizational and sustainability goals, exploring areas such as continuous biomanufacturing, energy efficiency improvements in the drying process and the management of wastewater.

Introduction

Sustaining humanity by addressing the most pressing climate challenge in modern history is critical for all industrial manufacturing and pharma is no exception. Driving ambitious sustainability goals to fruition can benefit from ways to improve energy, raw material, packaging and water utilization throughout the development, manufacturing, and supply chain. Come and learn more how Smart Factory Rx can aid to achieve these ambitious goals faster. In the journey of making products that save life and promote wellbeing we cannot accept production processes that negatively affect health. To this end, a go green or go home mentality is increasingly adopted by all pharma and other process industries to achieve ambitious sustainability goals. Moreover, regulatory licenses to operate - and an increasingly important social license to operate - virtually mandate a “go green or go home” mentality. We at Applied Materials are not only talking the talk but walking the walk. We are committed to very ambitious sustainability objectives and leading in the industries where we operate. Enabling the success of our customers in this herculean effort motivates and drives us forward [1].

What more can be done to support the sustainability drive within the pharmaceutical industry? In a recent blog, “Are you well eQYPt” we emphasized the questions leaders in pharma manufacturing should ask themselves. A few aspects come to mind when thinking about improving the sustainability metrics, see Table 1.

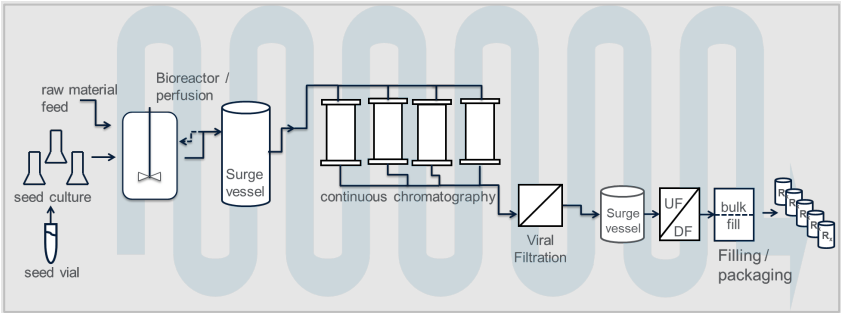
Table 1. Questions that Pharma Leaders are asking to **e**nhance **Q**uality, **Y**ield, **P**roductivity, and **t**ime to market while improving their sustainability footprint

	**Quality-related Questions** ▪ Will automating "QC by Inspection" with vision systems reduce my labor costs and quality risk? ▪ Can I minimize contamination risk by employing digital tools to alert for action?	**Sustainability Benefits** ▪ Most certainly will aid in minimizing lost batches and by that, lowering resources use ▪ While improving quality, manufacturers can benefit from reduced off specification material, loss batches, raw material consumption, energy, and water usage"
	**Yield-related Questions** ▪ Is there a way for my process scientists and operators to collaborate in a single data-connected workspace to reduce batch failures? ▪ Can I leverage my existing process data systems to reduce waste and improve Overall Equipment Efficiency (OEE) and supply predictability?	▪ Batch failure = Increase waste. With a single, data connected workspace, waste reduction goals can be achieved ▪ What more can one ask to leverage the "more for less/same" mentality while driving sustainability risk KPI lower?
	**Productivity-related Questions** ▪ Can I employ adaptive scheduling to optimize assets and other resources to satisfy production demands with significant improvements? ▪ How do I improve Return on Capital Employed (ROCE) and apply it across all my manufacturing plants? ▪ If I improve my process variability, can I reduce my inventory costs?	▪ Yes, optimizing asset utilization, minimizing raw material, energy, transportation, water etc. usage ▪ Maximizing uptime while minimizing resource utilization is in our DNA and key for your success. ▪ Less inventory = less raw material, storage & energy need as well as potential waste mitigation
	**Time-related Questions** ▪ Will the right Design of Experiment (DoE) platform reduce my process development time? ▪ After I define Critical Process Parameter (CPP) and critical process quality (CPQ) during development, can I transfer and verify them at manufacturing scale in less time?	▪ Clear reduction of number of experiments = less raw material, equipment, and people time ▪ Robust, consistent, and reproducible accelerated process tech transfer equals less resources and time usage

Whilst this provides a few examples there are several more. Specifically, wastewater management, energy intensive processes like crystallization, granulation and spray drying as well as the immense benefits of continuous, smaller footprint, distributed manufacturing to drive sustainability-by-design success.

Sustainability benefit of E2E continuous biomanufacturing:

In the pharmaceutical industry, continuous manufacturing has been a focus point for top Pharma companies over the last 5 – 10 years. Advances in technology, as well as adoption of the Quality-by-Design (QbD) paradigm in the development cycle and Process Analytical Technology (PAT) [3] have made continuous manufacturing an attractive alternative to the conventional batch approach. Furthermore, this shift supports the USA's Food and Drug Administration (FDA) initiative [4] towards a highly efficient, agile, flexible manufacturing industry relying on risk-based decision making and latest technology advances. Indeed, continuous manufacturing has been adopted by major pharmaceutical companies such as Eli Lilly, Vertex, Janssen and Pfizer, to name just a few, for commercial products.



Conceptual continuous bioprocess

Research into this space has increased together with the industry's shift towards continuous manufacturing and the advantages are noticeable [3]:

- Process understanding and knowledge supported by PAT allows the manufacturer to implement Advanced Process Control (APC) strategies which will result in high-quality, on-spec product minimizing waste.
- Digitalization and new sensor technologies enhancing the process understanding and therefore identification of areas of risk which can be included in control strategies.
- Reducing plant footprints as scale-up bottlenecks are resolved by increasing throughput using the continuous process units.
- Time to market. In a world where demand pharmaceutical development and production has been in the spotlight over the past years, reducing the time-to-market is key.

The Smart Process platform has been used in several continuous initiatives, both in the small and large molecule space, from lab scale to routine manufacturing. The unique combination of a GxP-compliant platform, Industry 4.0 capabilities, support for PAT integration and Multivariate Analysis (MVA), Advanced Process Control (APC) and Optimization has been fully used to enable the implementation of continuous manufacturing.

In one recent application, our Smart Process Development platform has been used for end-to-end continuous bioprocessing in collaboration with Takeda. The platform has been used across the full line to meet the requirements and demands of such a process:

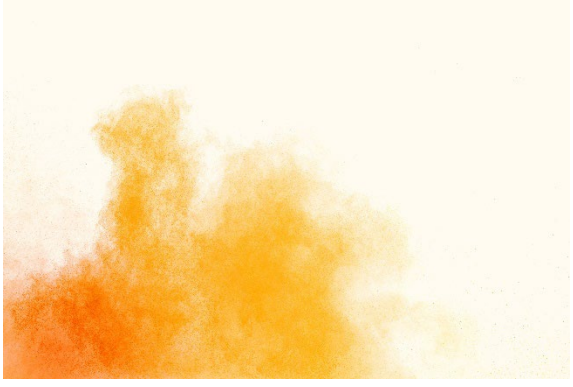
- A holistic view over a wide range of process units, PAT equipment, online/offline/at-line sensors
    - All data, univariate (process units, in-line/at-line/off-line sensor) and multivariate (PAT), centralized, time aligned and available
    - Process development using targeted Design of Experiments (DoE) - complete data sets including PAT predictions to better understand process behavior
    - Real-time process monitoring using in-depth, drill-down dashboards - faster time to react, minimizing downtime and waste
- A comprehensive set of alarms and events to support remote development and execution
- Multivariate models generating CQA predictions to enhance the process understanding, monitoring and control
- An APC strategy that combines multivariate and complex interactions across the whole process, whilst maintaining a stable and on-spec process
    - Controlled the line throughput – minimizing waste by 7% compared to open loop operation
    - Controlled CQA (Viable Cell Density) to target – reducing the standard deviation by 70%
- Enabling development and commissioning remotely during the COVID-19 pandemic. The majority of this project has been conducted remotely with limited presence on site due to lockdown restrictions.

The feedback from Mark Henson, Head of Sustainable CMC at Takeda, is:

"*We are extremely enthusiastic about the benefits already being realized through the application of Advanced Processing and Control strategy digitalization via APC. By improving Quality through reduced CQA variability while also reducing buffer usage with more highly automated and efficient processing, we are achieving net improvements in multiple sustainability measures.*"

Emphasis on manufacturing site footprints, waste, development cycles and use of resources is becoming more and more the center point of any decision around drug manufacturing. The implementation mentioned above is an example of how SmartFactory Rx can be used to support a pharmaceutical company in addressing those issues.

Sustainability benefit of energy efficiency in the drying process:



Many upstream chemical, pharmaceutical and nutritional processes produce a liquid slurry that has to be dried into a powder form. Spray dryers are ubiquitous in this process - and from an energy intensity standpoint, of particular interest. The requirements of the spray drying step are multiple: achieving a desired particle size distribution, bulk density, moisture content and water activity without degrading functional properties. There are also process considerations, such as avoiding scorched particles, avoiding temperature and humidity conditions favorable to

microbial growth and avoiding glass transition / sticky regimes that cause powder caking on the walls of the dryer and cyclones, lump formation and blockages. Clearly this is a multivariable optimization challenge, for which we have a long-established solution.

Coming back to the energy angle, optimizing the energy consumption is often overlooked in the pursuit of throughput, yield, and quality. However, with multi-objective optimization, specific energy consumption can be included along with all other quality and operational objectives to achieve the most efficient outcome.

It is estimated that over a wide range of evaporation rates of 0.1 to 12 t/h, spray dryers have a specific energy consumption of around 3 to 20 GJ/t water evaporated, with the average at approx. 5 GJ/t. Estimates on the energy wasted in spray drying vary considerably, with losses of up to 30% reported when compared to ideal adiabatic evaporation. Nevertheless, it is a truth that there is energy wasted and it is true that some of this energy can be saved by optimizing the drying conditions.

Of course, we mustn't forget CO_2 reduction, which goes hand in hand with using less energy.

To give an indication of the savings that can be made in energy cost and carbon, the following example is a good guide with the dryer inlet temperature at 200 °C.

- Powder produced: 22,000 tons per year
- 5,000 hours of production per year
- Inlet and outlet temperature reduced by ~5 °C
- Energy saving $62K per year
- Carbon saving 215 tons per year

A similar thought process and analysis can be applied to other commonly used drying operations in pharmaceutical manufacture, for example fluid bed dryers and bowl granulators. If we consider an agitated granulation process that may include the following steps: dry mixing, wet mixing, pre-heating, and drying. The powder must be dried to below a regulated value for process completion and energy usage can be reduced through several steps. First, optimizing the drying process through agitation, vacuum, and heat transfer understanding. This may lead to changes in the operating space e.g., agitation duration, or improved maintenance monitoring e.g., online monitoring of pump performance to ensure optimal pressure conditions. Other strategies can be employed to ensure minimal energy usage on a batch-by-batch basis including deploying a soft sensor for moisture ensuring the process is stopped for sampling at the correct moment and reducing the amount of water being evaporated.

Sustainability benefit through wastewater management:

Pharma and other process industries suffer from process inefficiencies. With the gap between global water supply and demand to reach 40% by 2030 [2], manufacturers can benefit from a much better and more sustainable wastewater management.

For biological wastewater treatment, there is typically a primary challenge to maintain a stable process. This is because when continuous biological water treatment processes fail, the recovery times can be very long, with a corresponding cost in terms of non-compliance, regulatory penalties, and organizational reputation.

Secondary to maintaining stable operation is the challenge of optimizing the process. Biological wastewater treatment processes are typically large consumers

of both chemicals and energy. As with many processes there is a tradeoff between optimizing a process and maintaining stable operation. An analogy that has been used widely is that of "riding a bicycle along the edge of a cliff" – doing this might offer the best views (i.e., the best efficiency), but it also poses the most danger.

The advanced control and monitoring techniques available within the WaterMV solution offer a means of controlling and optimizing wastewater treatment processes in a manner that is both efficient and robust. This is achieved through a combination of robust model-based techniques and algorithms, tightly integrated within the one software solution.

The WaterMV solution considers quality intrinsically, focusing initially on the quality of incoming sensor data. This is critical for wastewater applications, as the operating environment is very harsh for sensors, and making operational decisions based on inaccurate data can have potentially catastrophic consequences. Above the data quality layer a fusion of data driven models and mechanistic 'first principles' models provide both multivariable data validation and model predictions in a highly non-linear solution space. Finally, advanced optimization and control algorithms are used to provide real-time control of aerators, blowers, air control valves, dosing pumps etc. to provide optimal control irrespective of influent load conditions.

The net result is typically an energy saving in the range from 10% to 30% and associated reduction in CO_2 emissions, across a wide range of different processes. Such an energy saving will typically contribute substantially to a site's carbon savings targets.

In our next blog we'll discuss how Smart Scheduling can help advance your productivity while improving your sustainability footprint. Stay tuned!

References:

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4. U.S. Pharmaceutical CGMPs for the 21st Century - A Risk-Based Approach. Maryland: Food and Drug Administration; 2004.

Ready to learn more about how SmartFactory Rx solutions can help address these questions?

Connect with us here.

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