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White paper

Pharma 4.0 – A Vendor's Perspective

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John Mack – Head of Perceptive APC, David Lovett – Chief Strategy Officer,
Ewan Mercer – Principal Technology Consultant, Matthew McEwan - Principal Engineering Consultant

Applied Materials | Automation Product Group Pharma

Overview

Industry 4.0 is a concept originally developed by the German government in 2011 to promote the computerization of the manufacturing industries through the four main principals of interconnection, information transparency, advanced technical assistance and decentralization. Although driven by discrete manufacturing, it has built upon many principles and technologies developed in the process industries over the preceding decades.

The International Society for Pharmaceutical Engineering (ISPE) is leading the adoption of Industry 4.0 in the pharmaceutical industry, with the introduction of the Pharma 4.0 initiative (1). The pharmaceutical industry has traditionally been more conservative than other industries in the adoption of new automation technologies. Nevertheless, it now recognizes the manufacturing challenges posed by the move from "one-size fits all" blockbuster drugs to products for much smaller patient cohorts, moving towards personalized medicine.

The pharmaceutical industry is embracing Pharma 4.0, enabling the industry to be more agile, responding to changes in demand and manufacturing disruption, while enabling faster product development, flexible manufacturing, process optimization cost savings and increased productivity.

This move towards Pharma 4.0 can be seen in the new GAMP 5 2nd Edition, that has been updated to reflect the increased adoption of software and automation tools and now includes a specific Artificial Intelligence and Machine Learning appendix.

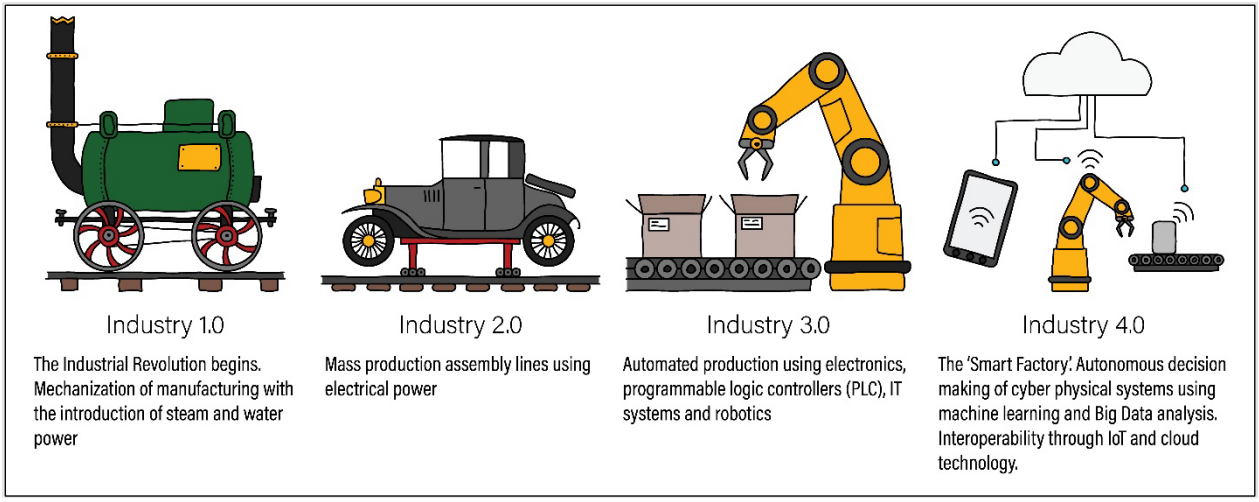
This white paper looks at the opportunities available to pharmaceutical manufacturing through the adoption of Pharma 4.0 and reflects on the potential pitfalls of "technology fatigue" from poorly implemented solutions. Examples show how SmartFactory Rx provides tools to allow the user to derive high-value actionable information from multiple data sources, rather than making the common mistake of implementing existing lower value tools in a new infrastructure.

Industry 4.0 Concepts and Technology

Pharma 4.0 is a term that encompasses the principles of Industry 4.0, introduced by the German Government's high-tech strategy in 2011, as applied to the pharmaceutical industry. The concept of Industry 4.0 is the adoption of four main principles: interconnection, information transparency, advanced technical assistance and decentralization. These requirements have largely been driven by industries, including the automotive industry, that have moved from traditional bulk manufacturing of identical products to increasing customization and personalization.

The principles of digitization build upon a central theme of manufacturing processes that are highly interconnected and able to employ Artificial Intelligence, particularly Machine Learning algorithms, to make decisions and respond to changing conditions without human intervention (2). These decisions can include the ability to anticipate, detect and repair faults. It also includes the ability to self-optimize based on changing production requirements, equipment status and environmental factors.

Process automation prior to Industry 4.0 – a history lesson from other Industries



To understand the characteristics of an Industry 4.0 enabled process it is useful to review the production techniques adopted by other high-value manufacturing industries such as the oil and gas, nutritional powders, paper and chemical industries:

- Continuous manufacturing has been employed routinely, but not exclusively since the early 20th century.
- Production efficiency has steadily increased since the 1950s through the application of affordable instrumentation, automated actuators (e.g., valves, motors) and associated three-term process controllers.
- The advent of computer-based automation from the 1970s, in what is now referred to as "Industry 3.0" brought about sweeping improvements in production efficiency. Affordable computing power enabled the introduction of Distributed Control Systems (DCS), and Supervisory Control and Data Acquisition (SCADA) platforms. These platforms allow data from many hundreds or thousands of data points to be collected in either local or centralized data historians and used in highly distributed, highly automated failsafe process control strategies.
- Through the 1980s to the present day:

- The combination of Advanced Process Control techniques such as Model Predictive Control, Fuzzy Logic and Real-Time Optimization have allowed tight control of product quality while simultaneously responding to disturbances and maximizing economic efficiency.
- Neural networks and black box approaches have been applied for prediction and control of Critical Quality Attributes in real-time and Multivariate Process Monitoring has been used for early detection of process faults.
- Machine Learning techniques have been used successfully to update control models allowing "self-learning" control strategies.
- Initiatives such as lean manufacturing and six sigma methodologies have been employed to improve product quality and process efficiency.

The past decade has seen a renewed interest in Machine Learning, primarily driven from the IT sector, where the advent of elastic cloud platforms, proliferation of relatively low cost IoT (Internet of Things) devices, and the generation of Big Data with platforms offering Open Source software all create an environment that offers interesting productivity opportunities.

The need for change within pharmaceutical manufacturing

Historically, the pharmaceutical industry has taken a more conservative approach to the uptake of manufacturing improvements in comparison to other high-value industries. A steady pipeline of small molecule Oral Solid Dose (OSD) form drugs have been successfully manufactured in batch processes using paper-based records and offline testing for product release. Furthermore, manufacturing has traditionally represented a small proportion of the overall product life cycle cost, so there has been little incentive to maximize efficiency through process optimization and control. Nevertheless, improvements have been made through the application of Quality by Design, Process Analytical Techniques (PAT) and the adoption of continuous manufacturing.

Pharma 4.0 has arrived at a time of significant change within the industry. With the decline in the pipeline of new OSD small molecule products, pharmaceutical companies are turning to biotechnology and small-scale manufacturing to develop therapies that are tailored to ever smaller patient groups. Global drug shortages, increasing complexity and cost pressures have highlighted the limitations of traditional batch manufacturing. In addition, although there are isolated examples of "Industry 3.0" model-based systems in use for applications such as fault-detection, Advanced Process Control and scheduling, these best-in-class techniques have had limited uptake within the industry.

Challenges and Opportunities

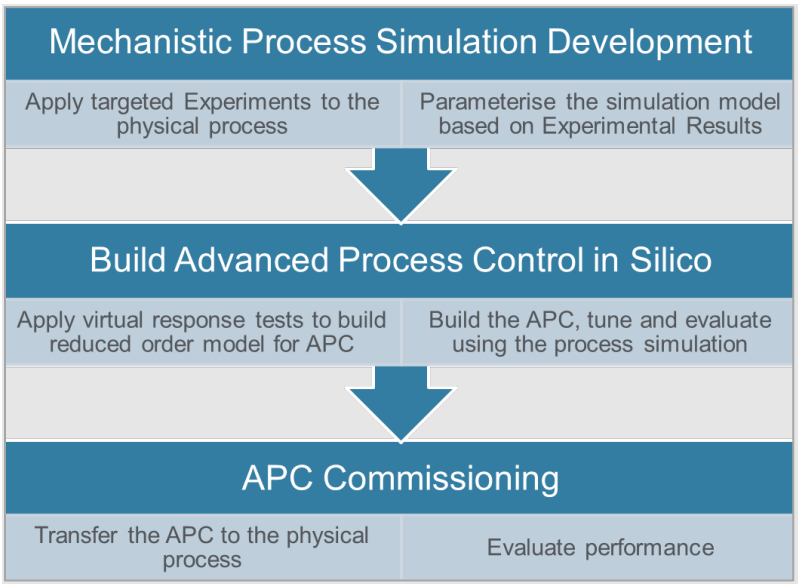
Pharma 4.0 presents both challenges and opportunities for vendors and industry alike. The four concepts and vision underpinning Pharma 4.0 are easily understood when considering the motivation to move from bulk to flexible manufacturing. However, a challenge for vendors is to promote Pharma 4.0 with a clarity of vision and avoid end-user "technology fatigue." In many cases, solutions are presented that draw upon Pharma 4.0 technology but do not necessarily add to the overall mission of digitization, which is improved manufacturing agility and flexibility. For example, deploying a Statistical Process Control (SPC) chart with associated alarm limits on a hosted, cloud-based server using an IoT protocol is not digitally transformative. Rather, it has simply moved a basic quality control approach to a different location. To be digitally transformative, the Machine Learning techniques should ingest data from many sources, evaluate a multivariate representation of the quality attribute and automatically pass/fail for real time release, thus achieving productivity improvements. These systems are in operation today, albeit in small islands in the pharmaceutical sector.

A second major challenge exists in the application of these tools in GMP manufacturing. Recent developments in the regulatory guidelines have allowed models to be categorized by criticality, offering a path for Advanced Process Control to be used within the industry. ISPE's GAMP 5 guidance document provides a framework for GxP compliant computerized systems, and the recently published 2nd edition reflects the increased use of automation, including a specific appendix on the use of AI and ML models, opening the way for deployment of these tools in pharmaceutical manufacturing.

Finally, there is the challenge of merging platforms between IT and industrial automation; it is still unclear where the hierarchical automation infrastructure with well-developed safety and operational standards developed during the 1990s and 2000s applies going forward.

With the challenges understood, the opportunities for vendors and industry alike are significant:

- Increased uptake of technologies due to lowering complexity barriers through the application of Artificial Intelligence and Machine Learning.
- Designing and building technologies into production equipment, rather than retrofitting, helps de-risk the uptake.
- Standardization/centralization of data using cloud-based solutions allows more efficient roll-out and supports process monitoring at an enterprise level. Easier access to multiple sources/locations (process, business, quality) provides a richer data source for decision support/modelling. Fusion of disparate data combined with new sources of data provides a dramatic improvement in the level of understanding of process behavior - even if this understanding isn't always utilized to greatest effect.
- The process simulation or *digital twin* concept is a key feature of Industry 4.0, falling under the guise of "advanced technical assistance." The combination of mechanistic and higher order modelling approaches enables control strategies and operating scenarios to be developed "in-silico," generating savings through more efficient process development. While there are still significant gaps in understanding, and adoption is far from universal, the results have been impressive when the techniques have been used.



Example workflow: Rapid in-silico development of Advanced Process Control

Example Applications

Successful Pharma 4.0 applications will utilize these new techniques, platforms and technologies to build upon robust industry proven mathematical, Machine Learning, process monitoring and optimization tools. Examples of such applications could include:

1. **Self-Optimizing Processes in Process Development:** Machine Learning can generate “smart data” that can be simultaneously used for process optimization and the automated development of models for calibration and process control. The combination of sophisticated ML algorithms combined with “traditional” adaptive Advanced Control delivers a process that can update, correct and compensate for changing conditions.
2. **Anticipation and Detection of Faults:** Cost effective IoT enabled sensors aggregated in the Cloud with existing data sources from multiple pharmaceutical processes can employ Multivariate Analysis and/or Machine Learning to detect degradation in a unit operation as part of a predictive maintenance program.
3. **Flexible Manufacturing:** The automotive industry leads the way when considering how information about a discrete manufactured unit is retained all the way through the supply chain. The equivalent for many process industries is a minimal certificate of analysis for a raw material, but this is rarely used to drive process adjustments in a predictive manner. Typically, if a raw material is "within specification" then that is regarded as acceptable. With Industry 4.0 that data should be used to drive better outcomes.
4. **Scheduling:** Machine Learning and automated algorithms can collect and analyze real-time data feeds from across the operation bringing together inputs from material supply, equipment status, shop floor processes and changing market demand. The algorithms connect to and constantly monitor manufacturing data—providing automatic schedule updates whenever significant changes need to be made to operations. This brings speed, accuracy and a more agile approach to commercial manufacturing schedules, all with considerably less effort from operators, supervisors and schedulers.

Concluding Remarks

Industry 4.0 continues to introduce sweeping changes in many industries, enabling the transformation from bulk "one size fits all" manufacturing to processes that are customized, flexible and intelligent. Arguably the opportunity for the pharmaceutical industry is even greater as the manufacturing technology baseline is lower. Nevertheless, for the Pharma 4.0 initiative to maintain credibility, vendors and clients alike must strive to develop solutions that deliver business benefit through improved robustness, flexibility, intelligence and efficiency.

However this plays out we, as a vendor, are partnering with industry to adopt a common approach to standardize on techniques and work with tools that are supportable and maintainable. Together we can avoid creating thousands of "in house" bespoke systems and algorithms which historically have consumed vast amounts of time and resulted in costly failures, only to be replaced by commercial platforms (3).

SmartFactory Rx has been developed and continues to evolve in partnership with the pharmaceutical industry to deliver a flexible automation solution for process development and manufacturing. As an integrated platform for pharma analytics, it facilitates shorter time to market, increased product yield and responsive changes to demand.

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Contact

SmartFactory_Rx@amat.com

appliedsmartfactory.com/pharmaceutical

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