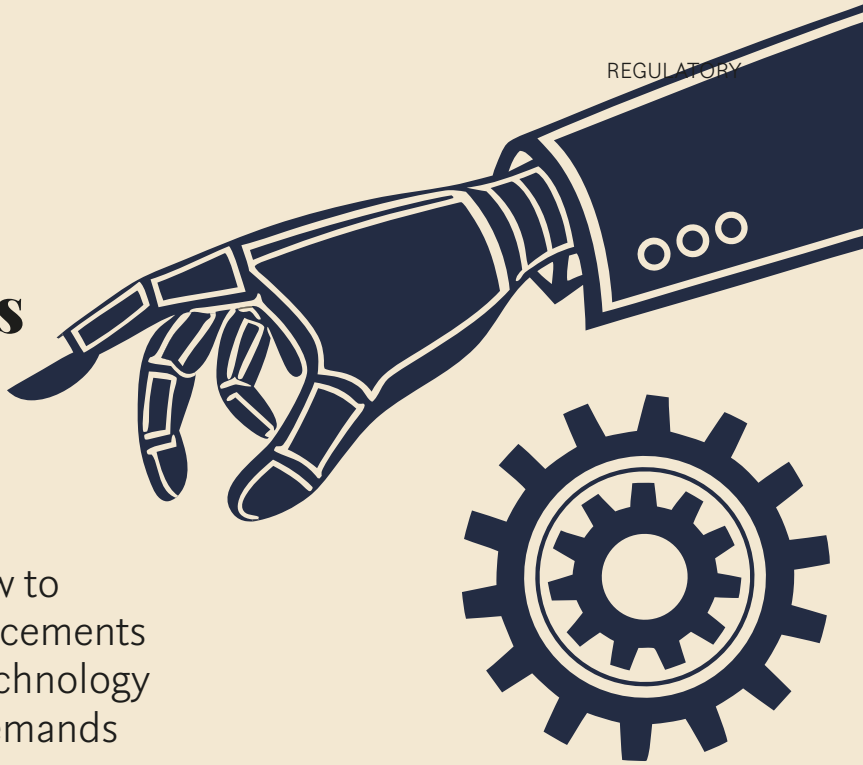
SMART DRUG MANUFACTURING:

Holistic approaches to digitisation and Industry 4.0



Steven Ng from AST explains how to balance capitalising on the advancements in manufacturing environment technology with meeting 2025's regulatory demands

Industry 4.0 began as an acknowledgement of the growing role of digital and automated tools for both the possibilities they presented and the way they transformed approaches to operations, processes, and data. First coined in 2011, the term spoke to the advent of a new era of innovative digital and data-driven technologies that would lead to new visions centred around agility, interconnectivity, and end-to-end holistic designs.

The evidence of the movement is seen across the life sciences industry: big data, machine learning, AI, robotics, and automation are all reshaping the conversations around operational infrastructure, efficiency, and best practices.

ISPE created the term Pharma 4.0 (trademarked) as a way to crystallise where the trends and innovations of Industry 4.0 intersect with the challenges and priorities of the life sciences Industry. They identified that the movement towards automation, digitisation, and comprehensive data frameworks should collectively work towards higher standards of drug product quality, where holistic, regulatory robust drug processes deliver innovative treatments to patients in the shortest time possible.

Comparatively, our industry has been slower than others in implementing Industry 4.0 practices and technology. And with good reason; the efficacy and quality of sterile manufacturing solutions take time to develop and validate. Regulatory bodies, to their credit, have played a pivotal leadership role by spearheading key initiatives to emphasise and support developing technologies (for example, the FDA's Emerging Technology Program and EMA's Quality Innovation Group).

So, where does the industry find itself currently? How do manufacturers balance the clear direction of our industry towards automation and digitisation with current operational and regulatory demands?

2011

Industry 4.0 term is first coined

Source: AST

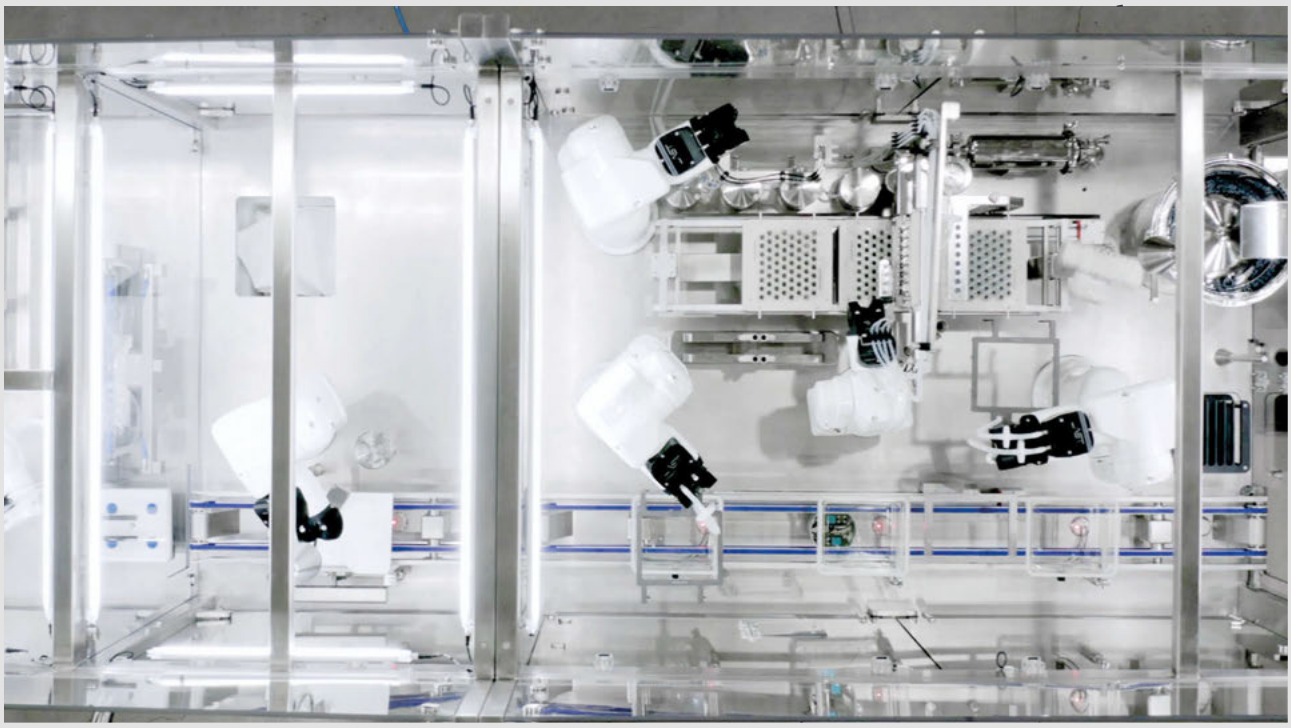
Digital evolution of fill-finish solutions

The engine of Pharma 4.0 is the principle and methodology ascribed in the concept of the Internet of Things (IoT), a transparent, interconnected network of broadly applicable advanced and smart technologies.

The capabilities presented by IoT applications are what makes a holistic vision of pharmaceutical manufacturing possible. IoT references the previously unconnected facets of an operation—people, data, robotics, functions, processes, and monitoring—enabling them to work together. IoT empowers and augments these factors in a unified fashion where data is tabulated, accessible, and comprehensive, and monitoring and feedback can occur in real time.

A central aspect of the IoT relationship in the context of pharmaceutical manufacturing is the role of the operator. Human input will always be a valuable part of the manufacturing process. Ideally, Pharma 4.0 solutions should focus on practical ways to empower operators by removing risk and streamlining or altogether eliminating time-intensive procedures. In practice, this enables an approach to quality previously not accessible to pharmaceutical manufacturing, which has paved the way for many of the innovative medicines we see today.

Figure 1 A fully automated, robotic fill-finish system. *Image credit: AST*



Evaluating approaches to digitisation and automation

Drug product manufacturers should consider the following questions when evaluating the possible implementation of Pharma 4.0 solutions.

Are you utilising a modular, multi-product approach?

The emphasis on Pharma 4.0 has a clear correlation with the rise of modular, standardised technologies. The expectations surrounding new drug products and, in many cases, the necessary processing requirements are contingent on faster time to market and ultimately quicker delivery time to patients. As such, there's been movement away from static, single-product operations to flexible, multi-product approaches that leverage standardised, modular technology. These modular solutions almost exclusively utilise automation, advanced programming, data retention, and process monitoring.

Are you automating high-risk processes?

The regulatory migration towards automation and other advanced solutions centres around the demonstrable reduction of risk, and specifically the continued elimination of human intervention. Where human operators lack (the single largest source of contamination, aberrant repeatability, and varying accuracy), robotics and automation excel with aseptic builds, low-particle operation, high repeatability, and high accuracy. This is particularly important for interventions in grade A spaces, like material transfers, container handling, and environmental monitoring interventions.

Are you utilising sensor and feedback technology?

With the increased momentum around patient-centred medicine, ensuring product quality is crucial. Advanced technologies are designed to provide a level of stewardship and control required by higher standards of processing and production. Functionally, this means that throughout production, the process, environment, and product are carefully monitored and reinforced end-to-end. This is accomplished by outfitting your facilities and equipment with Smart technology and robust sensor and feedback instrumentation. This includes AI-assisted cameras and visual technologies for quality checks and necessary failsafes, vibration and load sensors, safety sensors to guard aseptic environments, and comprehensive in-process analytical technology.

How are you approaching decontamination?

A key point of emphasis in Annex 1, beyond the general guidance to pursue automated

solutions, is specific guidance on utilising automated decontamination technology. A cycle application should be fully automated, with the method well understood and clearly validated. Additional designs should be implemented to ensure proper aeration, personnel safety, and, where possible, faster machine startup after decontamination procedures have been executed.

Working in concert with cleanroom design

When applied to drug product manufacturing solutions, the principles and advancements espoused in Pharma 4.0 work in concert with efficient cleanroom design. Optimised filling systems, specifically utilising isolator technology, reduce the aseptic burden and environmental and utility demands of the cleanroom, leading to a decrease in risk and cost over the life of the operation. Isolators should be outfitted with 4.0 technology, such as leak sensors, temperature and humidity sensors, environmental detection and monitoring, data feedback, and automation for routine maintenance.

And because the aim is the same—a carefully controlled and monitored environment—similar types of technology and strategies utilised on aseptic processing equipment can be applied to the cleanroom at large. Improving operator workflows, preventative maintenance, real-time monitoring, and even measuring and improving utility efficiencies can all be addressed through digitisation and automation.

As we've covered, improving the day-to-day efficiency and workload of personnel has been a major area of focus as 4.0 technologies have gained traction. In addition to the operational and time-saving advantages of automation, other innovative solutions, such as remote monitoring and control (reducing ingress instances for entering a cleanroom space), CFD analysis, and virtual reality tools, should all be explored as design and operational solutions. One of those exciting cutting-edge tools being utilised at AST and growing in application across the industry is digital twin technology.

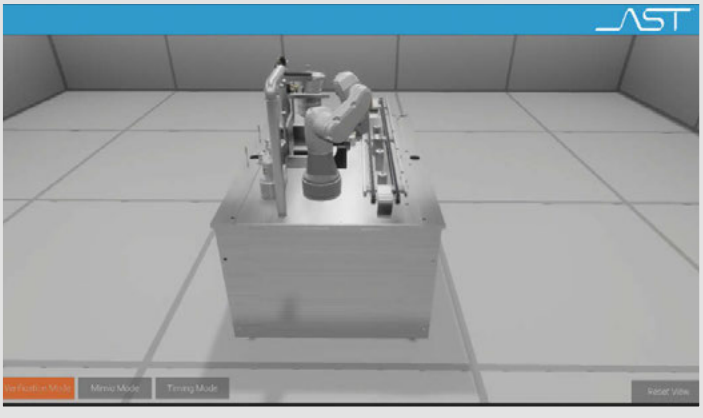
Spotlight: Digital twin for manufacturing

A digital twin is a dynamic virtual model that synthesises real-time data, physical operations, and virtual environments in an exact digital replica of a machine, system, or complete manufacturing operation. It consists of three parts: The physical machine, all data and parameters that influence or are generated by that machine, and the digital environment where the "twin" – the exact digital replica - exists. This virtual duplicate can run alongside the physical system in real-time (mirroring), offering an enhanced level of monitoring. It incorporates real-time data and parameters into the twin model, enabling complete integrated diagnostics and record-keeping. This virtual combination of the digital, data, and physical spaces also enables accurate simulations for a variety of pharmaceutical manufacturing purposes, including formulation and process development, error detection, predicted production outcomes, and scale-up strategies for operations and facilities. Tools like these will play an important role in the full realisation of automation and digitisation across our industry.

Finally, in order to make advanced solutions feasible and practical within the holistic vision of Pharma 4.0, there must be a clear path to integration. Complete alignment across technical platforms with digital infrastructure that can store, access, synthesise, and delineate immense amounts of data is the building block for real-world pharmaceutical manufacturing operations.

The future of sterile product manufacturing lies in the implementation of these innovative concepts and solutions.

Figure 2 AST's digital twin tool is a dynamic, predictive virtual model that synthesises real-time data, physical operations, and virtual environments in exact digital replicas of AST fill-finish systems. *Image credit: AST*



For more information
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