AsahiKASEI BIOPROCESS

The Ongoing Pursuit of Manufacturing Digitalization

Stefan Hyde
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Stefan received his Master of Science (M.S.) in Mechanical Engineering with a field of study on controls and an Engineering Management Minor from Northwestern University.

Asahi Kasei Bioprocess America, Inc. (AKBA) firmly believes that Oligonucleotides are one of the most promising therapeutic modalities for today and the future. Already, the industry is struggling with the exponentially growing demand for Oligo drug substance – and as the race to keep up continues, adding/onboarding knowledgeable resources becomes increasingly difficult. This means that the solution to the supply problem may very well require an evolution of the industry's manufacturing facilities to employ Pharma 4.0™ concepts to support not only the growth of the workforce but also increased per-head productivity. New digital technologies must be implemented to reduce testing and installation time, ease training for new operators and scientists, streamline production, and deliver real-time batch results for clearance and approval. Pharma 4.0 factories will become predictive and even adaptive in their operation, heading off risks and issues before they impact production. But before we begin to employ any of these concepts, we must first understand the fundamentals of just what defines Pharma 4.0.

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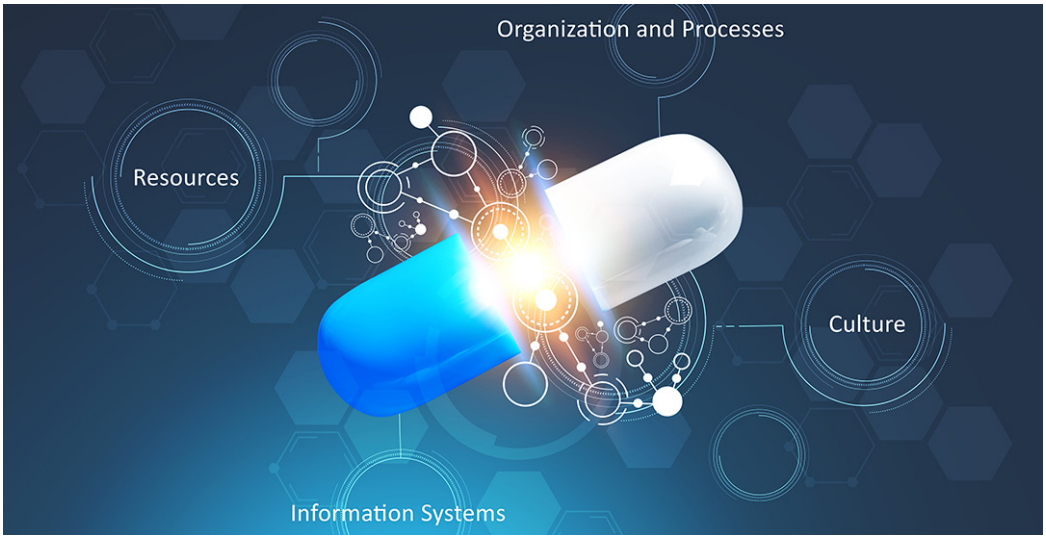
INDUSTRY 4.0

Pharma 4.0 (as coined by the International Society for Pharmaceutical Engineering – ISPE) is a specific introduction of "Industry 4.0" concepts to the pharmaceutical industry. The term "Industry 4.0" refers to the so-called "fourth industrial revolution," which is preceded by the first, second and third industrial revolutions.



The boundaries of these periods are defined differently by different groups, and they often overlap since adoption times varied drastically by region. But it is generally agreed that the first industrial revolution is defined by the steam engine and the weaving loom (early mechanization), the second with the adoption of electricity and assembly lines, the third with the introduction of computers and automation, and the fourth (current) industrial revolution with the Internet of Things (IoT) and large networks.

PHARMA 4.0 OPERATING MODEL

Pharmaceutical production based on Industry 4.0 factory design becomes "Pharma 4.0" when these same ideas are applied to GMP compliance, validation, and GAMP® requirements.

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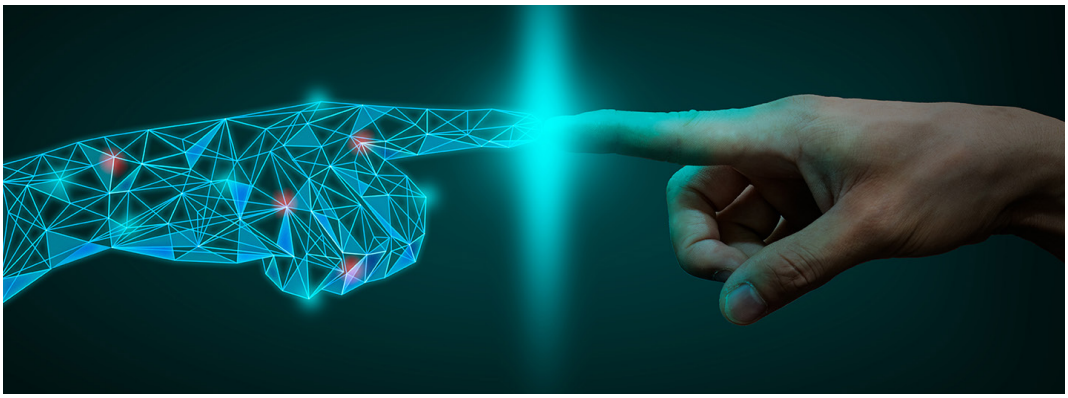
Pharma 4.0 is not a product, but rather a framework. ISPE has developed an operating model to apply the concepts of Industry 4.0 to the pharmaceutical industry. This operational model is a methodology for processes from product development all the way up to commercial manufacturing. It is summarized in a graphic[1] consisting of Elements – Resources (Digitalization, Workforce of the Future, Available/Qualified), Information Systems (Holistic Value Network, Integration/Traceability), Organization and Processes (ICH Holistic Control Strategy, Lifecycle Management, and Culture (Communication, Decision Making); as well as Enablers – Digital Maturity and Data Integrity by Design.

ICH Q10

These terms, Elements and Enablers, come from the International Council for Harmonisation of Technical Requirements for Human Use (ICH)'s Q10 guidelines. In the ICH Q10 model[2], elements and enablers are shown in grey (e.g., CAPA System, Change Management, etc.) and are quite familiar in the pharmaceutical industry. New elements made possible by digitalization (see Pharma 4.0 model) are shown in blue. When these elements are combined with the new enablers (Digital Maturity and Data Integrity by Design), they form a holistic control strategy for the complete product life cycle.

We must maintain a vision of the future to ensure that we are on the right track today, but this perfectly digitalized, adaptive, Pharma 4.0 plant can sometimes feel like a pie in the sky.

It's important to note that this digitalization effort is not an IT project – it is a project for the entire organization. This model requires information exchange both vertically and horizontally throughout the plant, meaning that all departments and stakeholders need to collaborate to enable Data Integrity by Design. Broad collaboration is imperative to properly Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), which are tenants of ICH Q10.



DIGITAL PLANT MATURITY MODEL

Of course, all these guidelines are helpful to achieve industry alignment, and we must maintain a vision of the future to ensure that we are on the right track today, but this perfectly digitalized, adaptive, Pharma 4.0 plant can sometimes feel like a pie in the sky. It can be difficult to understand where we stand today and what the next incremental steps are to get there. To support this evaluation process, the BioPhorum IT Collaboration Group (BPIT) created a "Digital Plant Maturity Model" (DPMM)[3]. This DPMM can be helpful in evaluating where a plant currently stands and what a reasonable next step might be, while keeping the end goal in mind.

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LEVEL 1 Pre-Digital Plant	LEVEL 2 Digital Silos	LEVEL 3 Connected Plant	LEVEL 4 Predictive Plant	LEVEL 5 Adaptive Plant
Primarily paper-based processes	Islands of automation	Vertical Integration	Enterprise Integration – internal integration of plant value chain	Full end-to-end value-chain integration from supplies to patients
Predominantly manual processing	Some manual processes	ERP, LES, MES, and Automation Layer are fully integrated to support digitized processes	Integration of Product Development and Manufacturing (PLM)	Modular, mobile and collaborative Manufacturing Environment
Low level automation	Batch records may be semi electronic or paper on glass	Full Electronic Batch record with review by exception	Advanced production technologies start to be used	Advanced production technologies used as standard
Basic PLC controls	Local batch-recipe system interfaced to PLCs	Industry standards such as ISA 88 (recipe) and ISA 95 (material, equipment and personnel) have been adopted	End-to-end supply chain visibility with limited external collaborations (supplies / CMOs)	"Plug-n-play everything" from an instrument to a production scale or CMO
Applications are stand alone with minimal or no interaction	Site specific systems; limited integration across functional silos	Standard application platform adopted across plant network	Enterprise Recipe Management (ERM) in place	Zero system down-time (including upgrades) – continuous evolution
	Analytics on-demand "Why did it happen?" high manual effort	Analytics semi-automated; "Where else can it happen?"	Online/At-line quality testing with Real Time Release	In-line, real-time continuous closed loop, process verification and control with automated real-time quality release
	Plants operate independently with little "real-time" supply chain visibility	Issues if real-time process analytics	Proactive analytics across plant and internal value chain "What can happen and when"	Self-Aware, continuously adaptive, "Autonomous" plant; exception conditions handled by remote experts
			Simulation used for process modeling and improvements	Advanced simulation used across value chain for modeling, testing and improvement of manufacturing and supporting business processes
				Trusted information insights are freely and securely available
				Pervasive use of adaptive analytics and Self/Machine learning across value chain

Source: BioPhorum IT Collaboration Group (BPIT) "Digital Plant Maturity Model."

It is equally common that technology already in place can be used in a more connected or predictive way – allowing the benefits of Pharma 4.0 digitalization to be enjoyed almost immediately and not necessarily with major capital expenditure.

Levels 1, 2, and 3 of this model are quite recognizable to those in the industry. As such, it may not come as a surprise that BPIT conducted a survey upon completion of the DPMM and found that most Pharma companies are at level 2 or 3, with some incorporating level 4 concepts.

BENEFITS OF DIGITALIZATION

While a "Level 5 – Adaptive Plant" may not be immediately within reach, incremental steps are often easy to define and have a big impact:

- *Real-Time Reporting:* Quick access to data supports critical management decisions
- *Technology Supports the Workforce:* Digitalization can help operator training, reduce human error, identify issues, and give feedback to users and maintenance teams to minimize downtime
- *Prevent Data Loss:* robust backup technologies and data/power redundancy prevent discard of good product
- *Prevent Equipment Obsolescence:* Support Continuous Process Verification (CPV) with adaptable equipment that can be easily configured for different products by the end user
- *Reduced Waste:* Process Analytical Technology (PAT) can be used control blend composition, detect deviations, and make product decisions based on CPPs and CQAs

Some digitalization efforts may carry a significant cost and require large-scale buildouts; but it is equally common that technology already in place can be used in a more connected or predictive way – allowing the benefits of Pharma 4.0 digitalization to be enjoyed almost immediately and not necessarily with major capital expenditure.

Questions?

Email me at
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[1] https://ispe.org/initiatives/pharma-4.0

[2] https://ispe.org/pharmaceutical-engineering/july-august-2018/pharma-40tm-hype-or-reality#footnote3_3tsx327

[3] https://www.biophorum.com/wp-content/uploads/bp_downloads/BPOG-DPMM-Best-Practice-for-Plant-Assessments-May-2018.pdf

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