# A Roadmap for Pharma 4.0

## ISPE Accelerates Digital Transformation with Pharma 4.0 Initiative

*Despite the transformational potential of digitalization, the pharmaceutical industry has historically been slower than other sectors in adopting digital tools and in making associated changes in strategic priorities and workplace culture. Now, however, the Covid-19 pandemic may be accelerating the pace of change. The International Society for Pharmaceutical Engineering (ISPE) and its members are developing the roadmap to introduce Industry 4.0 at the pharmaceutical industry. Pharma 4.0 is defined as an operating model based on the Industry 4.0 elements, resources, information systems, organization/processes and culture. The pharma-specific enablers "digital maturity" and "data integrity by design" are added. Michael Reubold and Ralf Kempf asked industry experts Thomas Zimmer, Wolfgang Winter, Christian Woelbeling and Josef Trapl — all members of ISPE's Pharma 4.0 group — about the idea behind this initiative and the challenges on the way to realize the digital transformation of the pharmaceutical industry.*

**Thomas Zimmer** is ISPE Vice President, European Operations. He previously was Senior Vice President of the Corporate Division Safety, Quality & Environmental Protection at Boehringer Ingelheim, where he worked from 1981 to 2013 and held several positions in pharmaceutical development and manufacturing as well as in management operations. Zimmer was also chair or member of several industry associations and scientific institutes. He studied pharmacy at the Goethe University in Frankfurt/Main, Germany, and holds a PhD in pharmaceutical technology.

**Wolfgang Winter** is OpenLab Platform R&D Director in the Software & Informatics Division at Agilent, based out of Waldbronn, Germany. His primary focus is on re-usable components, connectivity and data standards to enable the digital lab. He joined the industry in 1989 as a software engineer with a Master's degree in Electrical Engineering / Biomedical Devices. Winter joined ISPE in 2003 and currently co-leads the Pharma 4.0 Plug and Produce workgroup. Since 2021, he is also a chair-member of the Pharma 4.0 group.

**Christian Woelbeling** is Executive Industry Advisor & Senior Strategic Account Manager at Körber Pharma Software in Lüneburg, Germany. He holds a Master's degree in mechanical engineering. Working in life sciences manufacturing IT for 30 years, Woelbeling has great experience in all GMP related processes. He is Founder & Chairman of ISPE's Special Interest Group "Pharma 4.0", ISPE "GAMP MES Special Interest Group" Co-Chair, ISPE GAMP Member at large of the European Steering Committee, and "PAT & Lifecycle Control Strategy" CoP Steering Member.

**Josef Trapl** is Global Head of MSci Innovation within the Global Manufacturing Supply Organization (GMS) at Takeda Pharmaceuticals in Zürich, Switzerland. He joined Takeda in 2015 and, in his current role, supports the Takeda network with innovation in manufacturing. Trapl is a chartered chemical engineer (MChE) and has an MBA degree from Mannheim Business School, Germany. Since 2010, he is an active ISPE member and currently co-leads the Pharma 4.0 Plug and Produce team and is a chair-member of the Pharma 4.0 group.

***CHEManager: Why is the digital transformation in the pharmaceutical industry happening slower compared to other industries?***

*Thomas Zimmer:* Historically, the uptake of innovation in the pharmaceutical industry takes longer than in other industries. It is often explained with high regulation and long-lasting subsequent change management processes in this sector. This is only part of the explanation. Many pharma companies started very small with low margins. There was no environment to engage in technological innovation on an industrial scale. Products had very long lifecycles, some over decades, there was no pressure to change them, thus, pharma companies are lacking this sort of change culture. In contrast, this situation created a certain culture of hesitance to go new ways. In addition, generic pharmaceutical products have low margins, which do not support investment in innovation. Use cases sometimes miss to provide — or prove — convincing business targets or company strategies.

> *"Change management is seen as a burden and not as an opportunity."*
> Josef Trapl

*Wolfgang Winter:* Sometimes, low-margin products such as generics may not be candidates for innovation at first sight, but they can be candidates for other process improvements that improve efficiency and decrease cost or risk, e.g. faster QC methods that are more robust based on better product understanding. This eliminates technical failures that may have previously been out of trend or potentially out of specification and required lengthy investigations and regulatory scrutiny.

***The intention of ISPE's initiative Pharma 4.0 is to transform industry-generic 4.0 models for pharma operations. What is the concept behind Pharma 4.0?***

*Christian Woelbeling:* The key concept behind the ISPE Pharma 4.0 Operating Model is to combine operational excellence with the requirements which are specific to the pharmaceutical industry, for example regulatory and validation requirements. From the beginning, the goal was not to reinvent the wheel, but to use and apply best practices for the manufacture of pharmaceutical drug products to the benefit of the patients.

The Operating Model is a holistic approach to each, the pharmaceutical development and pharmaceutical delivery supply chain — end to end — from the raw materials or patient cells up to the final drug and along the ICH Q10 pharmaceutical lifecycle from development via tech transfer to commercial manufacturing. We call this the holistic control strategy approach, as the ICH Control Strategy plays a key role in the lifecycle of a drug.

***How can the digital maturity, id est, the level of digitization and digitalization at pharmaceutical companies, be assessed and compared?***

*T. Zimmer:* There are a number of maturity models, e.g., from BioPhorum Group and also from the ISPE Pharma

4.0 working group "Impact and Maturity" which describe basically six levels of maturity: computerization, connectivity, visibility, transparency, predictability and adaptability. In addition, the Pharma 4.0 working group has described barriers, which work as an obstacle to achieve the next level of digital maturity: misalignment, distrust, weak business objectives, low respect and inflexibility. It is interesting that the hurdles are primarily not of technical nature but liaise with behavior and culture.

***Where do you see the biggest areas for improvement or development?***

*T. Zimmer:* One of the biggest development areas is quality management. It starts with the development of technical standards for electronic data. In parallel, regulatory standards for data integrity have to be implemented. The next step is to create a computerized systems landscape and architecture. Systems need to be connected to enable interoperability, and a harmonized and holistic view on all parameters is needed to make quality and compliance related decisions.

> *"Pharma 4.0 is not a one-size-fits-all approach."*
> Thomas Zimmer

On a managerial level and complementary to this, there is the need to define a holistic control strategy and to define digitalized setpoints for monitoring and control. The Pharma 4.0 oriented Holistic Control strategy has an extended scope to the full value network, from suppliers for starting materials to the patients and all stakeholders in pharmaceutical products on the market.

There are a number of conceptual questions to resolve, e.g. how to enable systems to make or prepare decisions, and the role of humans in such a process. How can regulators get a mechanistic understanding of a computer-driven decision in order to develop confidence with the new processes? Where is it wise to install computer-driven decisions? How do algorithms for predictability of results look like? What does validation 4.0 look like?

As shown in the Pharma 4.0 Operating Model, technology and IT are just one element among others like culture, behavior, readiness to leave traditional silo-thinking behind. Integration of all relevant functions including a good risk and issue management is key to success for smooth and reliable operations in future.

***How can the pharmaceutical industry overcome the obstacles to digitalization?***

*C. Woelbeling:* Pharma 4.0 needs a strategic approach. It is needed to gain insight to benefits of digitalized operations. Mechanistic understanding is needed for cause and effect chains: how does digitalization accelerate the implementation of regulation; how does it improve quality oversight and facilitates GMP inspections; how does it help to improve patient safety, how to improve productivity and optimize cost; how does it support drug availability in the market and help to avoid drug shortages; and last but not least, how does digitalization reduce time to market for new medications.

Just as an example: The conventional thinking of automation coming with the two-years ROI is not appropriate. Pharma 4.0 and digitalization are enabling new business models and business processes, for example, for integrating contract manufacturing organizations into the marketing authorization holder organization or for real-time release and continued process verification or demand planning based on direct patient feedback. Still far away from this broad usage, at least singular use cases are available for first exploration. Also, established change management practices require significant evaluation prior to implementation. While change management practices are necessary to maintain product quality, they are often seen as a burden instead of an opportunity.

***Which industry 4.0 automation and digitalization technologies can be applied to pharmaceutical manufacturing and which challenges are companies facing?***

*Josef Trapl:* In the current world of digitalization, Industry 4.0 means automation and data exchange in pharma manufacturing. A smart pharma factory in the framework of Industry 4.0 is the new wave of digital transformation driven by recent technical development in cloud computing, AI, analytics, IoT, and application programming interface (API) technologies, which are needed when data must be exchanged between software applications and no defined interfaces are available. There is yet good progress in the adoption of modern operation and information technologies toward intelligent and connected machinery, automated processes and the use of predictive analysis. The three main challenges are well known from our legacy production sites:

- isolated and monolithic systems,
- interoperability and adaptability between machinery and systems,
- lack of harmonized standards and complexity of technical integration.

> *"Pharma 4.0 is a philosophy of driving a data-driven business model!"*
> Christian Woelbeling

In our Pharma 4.0 journey, the intention is to help to overcome these barriers by enabling a seamless flow of information with the use of APIs that secure integration between systems and devices in a standardized way. The use of APIs allows to develop a microservice-based architecture, which can be combined with other systems as a component without impacting the backend, enabling the reuse of components and delivering new features and applications.

***What is the best way to achieve the flexible and maintainable integration of IT systems for data-driven pharmaceutical manufacturing?***

*W. Winter:* So far, our investigations and prototype developments clearly identified several key success factors for Plug & Produce, like a vendor-agnostic and machine-type-independent approach that is not locked into specific commercial platform products as well as an extensible, service-oriented architecture that enables transactions between systems — i.e., processes, machines, subsystems, components — with built-in mechanisms for security and data integrity.

In the earlier stages of the workgroup, we learned that the number, variability and complexity of use cases is growing faster than the implementations. This means that Plug & Produce needs an information metadata model that allows us to model the interactions that occur between level 2 and level 3 in the ISA-95 model. It also needs an abstract concept of services and transactions that are designed to transport any set of data, without defining the "what" by mandatory service or variable names or structures. This way, the Plug & Produce concept is not locked into specific use cases or machine types. And thirdly, we need to take provisions for

> *"Dinosaurs will be left behind, and we all know what happened to them."*
> Wolfgang Winter

### The 12 Theses for Pharma 4.0

1. Pharma 4.0 extends/describes the Industry 4.0 Operating Model for medicinal products.
2. In difference to common Industry 4.0 approaches, Pharma 4.0 embeds health regulations best practices.
3. Pharma 4.0 breaks silos in organizations by building bridges between industry, regulators and healthcare and all other stakeholders.
4. For next generation medicinal products, Pharma 4.0 is THE enabler and business case.
5. For the established products, Pharma 4.0 offers new business cases.
6. Investment calculations for Pharma 4.0 require innovative approaches for business case calculations.
7. Prerequisite for Pharma 4.0 is an established PQS and controlled processes & products.
8. Pharma 4.0 is not an IT Project.
9. The Pharma 4.0 Operating Model incorporates next to IT also the organizational, cultural, processes & resources aspects.
10. The Pharma 4.0 Maturity Model allows aligning the organizations operating model for innovative and established industries, suppliers and contractors to an appropriate desired state.
11. Pharma 4.0 is not a must, but a competitive advantage. Missing Pharma 4.0 might be a business risk.
12. When moving from blockbusters to niche products and personalized medicines, Pharma 4.0 offers new ways to look at business cases.

GxP compliance and data integrity already in the design. For instance, we made sure that metadata is included in the design. This is necessary for the trustworthiness and reliability of critical data, e.g. through user IDs, timestamps or physical units of measure.

***What is your strategy to achieve an accepted understanding of readiness and maturity in the industry?***

*W. Winter:* We structured the Plug & Produce workgroup as a dialog platform where documents, guidelines, principles are collaboratively created and shared in knowledge exchange forums and conferences. During the pandemic crisis, we replaced face-to-face interactions with virtual events. Since 2019, we established a steering team and an advisory board and maintain a roadmap for Pharma 4.0. We deliver on the Pharma 4.0 roadmap with our ISPE Pharma 4.0 knowledge sharing calls, publication of peer-reviewed concept papers, articles, training sessions, virtual conferences, expert exchange webinars and networking events. All the deliverables are created by the volunteers in the Pharma 4.0 communities of practice and workgroups — all of whom are experts in their field. It is important to note that all our workstreams are cross-organizational and cross-functional by design, with experienced contributors from biotech/biopharma, automation, software, validation, consulting, academia, including ISPE Young Professionals, who helped "rock the boat" through their invaluable energy and fresh mindset demonstrated in various hackathons.

### Pharma 4.0

ISPE and its members are developing the roadmap to introduce Industry 4.0, also called the Smart Factory, at the pharmaceutical industry as Pharma 4.0. The objective is to enable organizations involved in the product lifecycle to leverage the full potential of digitalization to provide faster innovations for the benefit of patients. Implementing new Industry 4.0-based manufacturing concepts in Pharma 4.0 requires alignment of expectations, interpretation, and definitions with the pharmaceutical regulations.

While Pharma 4.0 has been called a new industrial revolution, its implementation will more likely resemble an evolution in which digitalization and automation meet very complex product portfolios and lifecycles. It is therefore important to achieve an accepted understanding of readiness and maturity, starting with additional digital enablers and elements added to the ICH Q10: The Pharmaceutical Quality System along the product lifecycle.

Digitalization, an important component of Pharma 4.0, will connect everything, creating new levels of transparency and adaptivity for a digitalized plant floor.

***ISPE is not alone trying to propagate the Pharma 4.0 concept in the industry. Wouldn't it be good to also harmonize the efforts of different organizations?***

*W. Winter:* We realized quickly that we are working on solving a huge problem. Multiple initiatives and consortia operate in this space in parallel. Examples are Allotrope for scientific data exchange based on ontologies, NAMUR with Module Type Package (MTP), BioPhorum Group for single-use systems, Pistoia Alliance with the concept of e-methods, Spectaris with the coordination of a Lab Agnostic Device Standard (LADS), and OPC-UA, to name just a few.

The key take-away for all of us is: This is not a competition. The sum is more important than any individual piece. This only makes sense as a collaboration where each initiative covers a range of the spectrum. The trick is to put all the significant ones on the map and focus on how

we complement each other without reinventing the same wheel all the time.

As far as I can see, ISPE Pharma 4.0 is the only initiative with the explicit charter to cover the pharma- specific requirements, including the regulatory aspects, and "translates" them into the Industry 4.0 / Industrial Internet of Things (IIoT) context. If you asked me for a motto to achieve this standardization, maybe it should be "Reuse, Leverage, Augment".

***Which expertise is required to implement Pharma 4.0?***

*J. Trapl:* Successful implementation of Pharma 4.0 requires a lot of expertise from different functions. Teamwork and strong stakeholder engagement are key, with opportunities within the existing ISPE organization to utilize capabilities of established CoPs, workgroups including regulatory and GAMP community.

***Does a pharmaceutical organization need external experts to implement Pharma 4.0?***

*J. Trapl:* To drive Pharma 4.0, we understand that in addition to leveraging existing internal competencies, external collaboration is key. Pharma 4.0 provides the right forum to bring together the necessary stakeholders such as pharmaceutical companies, technology providers, consultants and regulators. In the dialogue with pharma companies, we define the business needs for Pharma 4.0 and discuss how the Workforce 4.0 should look like to support seamless end-to-end integration in the future.

Technology solution providers and consultants are playing an important role to consider upcoming technologies and ways to successfully apply them in the regulated environment. This gives us the opportunity to build the right capabilities to operate the manufacturing and to work on common harmonized standards.

***How can all stakeholders be involved in either stage of the process?***

*T. Zimmer:* It is essential for the success that experts from various functions collaborate in the same team. Also, regulators should be invited, some health agencies have offices for innovation. The ISPE Pharma 4.0 Special Interest Group founded several of these cross-functional teams.

When defining Pharma-4.0-related goals it is important to determine the strategic target. Pharma 4.0 is not a one-size-fits-all approach but has some common principles to apply, such as holistic view, digitalized data and a culture of trust and openness. In such a strategy the "what to do" and the "how to do" should be clearly explained, but most importantly, the „why" should be explained to get decision makers to buy in.

***Such a profound industry transformation does not come at zero cost. What can companies do to keep the price tag of Pharma 4.0 as small as possible?***

*T. Zimmer:* Companies should begin by defining an overall Pharma 4.0 strategy, i.e. the big picture, and the program elements that fit into the overall strategy including related business cases, benefits and financial returns. Successfully implementing pilots are key to building momentum and long term success of the overall strategy. Finally, an entrepreneurial spirit is needed to see advantages beyond business case return-on-investment calculations.

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