A journey through a Digital Pharmaceutical Plant

"Big Data is becoming as important as chemistry or biology for us," said Merck Group CEO Stefan Oschmann in a video interview[1].

Such a strong statement from one of the most important global pharmaceutical companies indicates the role that digitalization will be playing in the life sciences sector in the near future. This is exactly what was discussed at length at the ISPE Pharma 4.0 conference held in Manchester over November 19-21, 2019.

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(1) https://www.cnbc.com/video/2017/01/18/big-data-becoming-as-important-as-chemistry-for-us-pharma-ceo.html

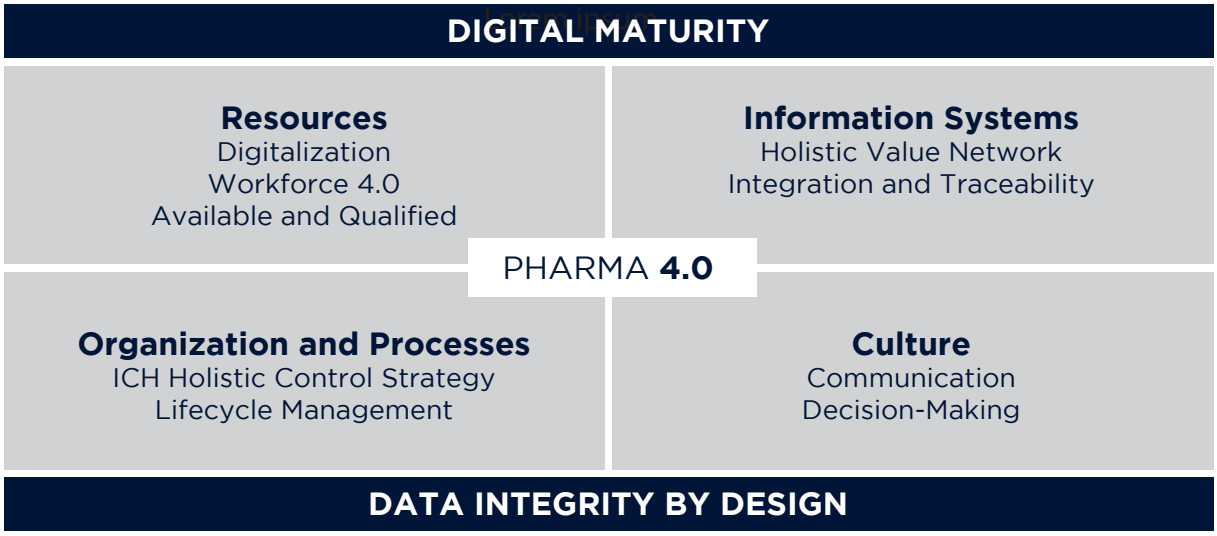

Figure 1: ISPE Pharma 4.0 Special Interest Group (SIG) operating model. Source ISPE [2]

The last ISPE Europe conference in Manchester was an interesting opportunity to dig into the Pharma 4.0 framework developed by ISPE[2]. This operational model, which starts from the valorization of human resources, includes information systems, organization and processes and culture (as illustrated in *Figure 1*).

The different speakers offered technological insights, ongoing studies and real use cases. In the many speeches, reference was often made to the concept of the "Digital Plant". It became obvious that, to date, there is no clear definition of what constitutes a digital plant. Some associate a digital plant with the introduction of the electronic batch record, others with the IoT and more still with the addition of an MES system. There were several mentions of work undertaken by BioPhorum towards a Digital Plant Maturity Model (DPMM)[3] that offers an interesting picture of the current situation surrounding digital systems in life sciences manufacturing.

DIGITAL PLANT MATURITY MODEL (DPMM)

With a clear focus on the life sciences industry, the DPMM describes the mature stages of a life sciences manufacturing plant, beginning from the traditional "paper-based" facility and extending all the way up to the fully automated and integrated "adaptive" plant of the future.

This is a useful instrument that uses a five-level classification to evaluate a plant's level of digital maturity. This way, steps that need to be taken to increase a plant's integration can also be identified.

The DPMM diagram in *Figure 2* has been intentionally developed to cover not only what is possible today, but also to hypothesize a possible advanced (level 5) adaptive plant with the clear awareness that it is still beyond the level of current IT and manufacturing technological capabilities.

Let's now analyze this by focusing our attention, for the sake of brevity, on the field of pharmaceutical manufacturing.

A level 1 plant is characterized by the extensive use of manual operations at different levels. For example, all manufacturing activities are managed following paper-based procedures, while the processing parameters in the plants and machines are set manually. Therefore, while plant operations might be controlled by PLCs and DCS systems, there are no HMI systems with recipe management or integrated audit trail functions. Under these circumstances, meeting the regulatory requirements for data integrity can often be very complicated.

In a level 2 plant, automated production systems integrate user management, recipe management and an audit trail, and are able to generate an end-of-batch report. Nevertheless, each machine is an island. There is no data integration between operation (OT) and higher IT levels (e.g. MES, ERP) or horizontal integration, for example, between machines on a line. The operator has to move among the different machines and log in to select recipes and processing parameters. To supervise the operation of that line, the operator must have good knowledge of the process. The operating procedures and batch records are usually paper-based. Operating data that is essential for data integrity, such as audit trails or deviations from critical GMP parameters, remains at the machine level. This configuration complicates the management of GMP data storage and backup activities.

At level 3, data finally begins to flow more smoothly because the machines in the manufacturing line are

(2) https://ispe.org/initiatives/pharma-4.0
(3) https://www.biophorum.com/how-does-your-digital-plant-maturity-compare

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. Predominately manual processing. Low level of automation. Basic PLC controls. Applications are standalone with minimal or no integration.	"Islands of automation". Some manual processes. Batch records may be semi-electronic or "paper on glass". Local batch-recipe system interfaces with PLCs. Site-specific systems; limited integration across functional silos. Analytics on demand requiring manual effort: "why did it happen?" Plants operate independently with little real-time supply chain visibility.	Vertical integration. ERP, LES, MES and automation layer are fully integrated to support digitalized business processes. Full electronic batch record with review by exception. Industry standards such as ISA-88 (recipe) and ISA-95 (material, equipment and personnel) have been adopted. Standard application platform adopted across plant network. Analytics are semi-automated: "where else can it happen?" Islands of real-time process analytics.	Enterprise integration: internal integration of plant to value chain. Integration of product development and manufacturing (PLM). Advanced production technologies start to be used. End-to-end supply chain visibility with limited external collaboration (suppliers/CMOs). "Enterprise Recipe Management" (ERM) process in place. Online/at-line quality testing with real-time release. Proactive analytics across plant and internal value chain: "what can happen and when?" Integrated real-time process analytics. Simulation used for process modeling and improvements.	Full end-to-end value-chain integration from suppliers to patients. Modular, mobile and collaborative manufacturing environment Advanced production technologies used as standard. Plug & Play everything: from a single instrument to production scale or CMO. Zero system downtime (even for upgrades) and continuous evolution. In-line, real-time, continuous, closed loop process verification and control with automated real-time quality release. Self-aware, continuously adaptive "autonomous" plant with exception conditions handled by remote experts 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.

Figure 2: Digital Plant Maturity Model (DPMM) – definition of levels. Source BioPhorum IT [3]

managed by a line management system. The operator is able to manage and send recipes to the different machines, carry out operations and preliminary checks, start a production batch and supervise the operation of the line in a guided manner from a single workstation. The line management system acquires production data from the machines and sends any deviations from critical GMP parameters to an MES system in real time. The audit trail is centralized at a single point and can be sent to the plant's electronic batch record (EBR) system. The batch release phase is facilitated thanks to the "Review By Exception" (RBE).

Even isolated machines or other technical services such as production of water for injection (WFI) can be integrated through automation integration layer platforms, which can directly connect control systems and acquire critical GMP parameters, pre-process them and manage deviations by integrating all of this at higher IT levels.

From level 3, data integrity compliance is easily and effectively fulfilled. At level 4, we can finally focus on process optimization in terms of quality, efficiency and sustainability. Thanks to the extensive acquisition and archiving of production data, we can now, for example, take advantage of current machine learning and big data analytics techniques to predict quality problems and anticipate potential deviations.

Up to this point, we find real applications in the life sciences sector. When we look beyond this to level 5, we enter the world of ambitions for the future. As can be seen from *Figure 2*, in the adaptive plant, digitalization extends horizontally from the supplier to the final patient. The new machines are integrated with the plant systems as plug-and-play solutions. The production processes are able to self-regulate. It is true that the path to level 5 is a long one and, at present, current technologies are not yet mature enough.

CURRENT STATE OF MANUFACTURING PLANTS

An initial analysis undertaken inside the biotech industry, which is likely representative of the entire life sciences sector, shows that many production sites are still at level 1 (pre-digital) but most plants are level 2 (digital silos). Some of these facilities are approaching or have reached level 3 (connected plant). Only a few highly advanced sites have reached level 4 (predictive plant). Meanwhile, level 5 (adaptive plant) is still a dream for the biopharmaceutical industry and cannot yet be achieved with today's technology.

This assessment has also been confirmed by a survey undertaken by the NNIT consultancy and presented at the conference in Manchester. The survey showed that it remains true that MES systems are not very widely used in life sciences. For example, just 21 % of respondents working in API (active pharmaceutical ingredient) manufacturing

(3) https://www.biophorum.com/how-does-your-digital-plant-maturity-compare

have implemented an MES. Only 36 % of packaging area in secondary manufacturing have integrated an MES system. The majority of respondents are thinking of a more modular and scalable approach to MES functionality as a result of a progressive pervasiveness of IoT in their companies.

We can, therefore, consider level 3 as a point of reference or a first objective to be achieved for the majority of production sites. For manufacturing, this becomes a question of adopting HW/SW technologies and solutions that have been available and consolidated for some time now.

THE PATH TOWARDS A MORE CONNECTED FACILITY

Which solutions could be adopted immediately to increase a pharmaceutical plant's level of maturity without replacing existing assets? Sticking with manufacturing, for the sake of the simplicity, let's look at a couple of examples.
Let's imagine we are at level 1. Our manufacturing assets are reliable and performing. They have significant economic value. However, they do not have the essential functionality for data integrity regulatory compliance. The adoption of a user interface that implements user access control, time synchronization, an audit trail, recipe management, data acquisition of critical GMP parameters and vertical data integration with higher IT levels is an excellent remedial intervention for data integrity that would preserve past investment and prepare for the next steps of digitalization.

Let's consider a level 2 company. Even though the machines are isolated (digital silos), it has an adequate level of compliance in terms of data integrity. The adoption of a management system for the line, such as a line management system or a line execution system, can simplify the setup of new batches (cleaning and changeover procedures via a digital device and recipe management throughout the line). The line execution system offers the operator a single control point for the line and it will generate a centralized audit trail, acquire and archive critical GMP parameters, and will promptly recognize any deviations. The electronic line report will, therefore, be available and can be vertically integrated into company workflows.

For all systems that are not included in a line in the level 2 company, a vertical data integration layer can be implemented. This is typically referred to as an IoT automation integration platform. Thanks to its high degree of connectivity, the platform will maintain bidirectional data exchange between the different devices. The platform will also acquire and store critical GMP parameters, allow centralized management of GMP deviations and will manage and send groups of settings (recipes) to the equipment. It can acquire data entered by operators through mobile devices (paper on glass). Thanks to its archiving capability, the platform will store the information needed to produce a batch record.

Thus, we would have reached level 3 manufacturing through vertical data integration infrastructure, using standardized, modular and scalable software solutions. We have adopted a software platform configurable as CAT.4 according to GAMP5 and we have laid the foundations for continuing our journey towards level 4.

Would you like to find out how to reach digital plant maturity level 4? Or would you like to know more about the solutions mentioned above? Connect with us and keep up with the next issues of Information Unlimited.

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Giuseppe Menin began his career in mechatronics engineering as an automation engineer and software developer. As project manager, he coordinated R&D projects for automating and monitoring manufacturing lines. In 2004, he joined COPA-DATA and is currently covering the role of Pharmaceutical Industry Manager at HQ. As a member of the ISPE Pharma 4.0 Special Interest Group and the Connected Machines working group within GAMP Italy, he is in regular contact with professionals of the life sciences industry.