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THE DEVELOPMENT OF A DIGITAL PLANT MATURITY MODEL TO AID TRANSFORMATION IN BIOPHARMACEUTICAL MANUFACTURING

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INTRODUCTION

The concept of a 'digital plant' is a hot topic among biologics manufacturing companies. However, there is no consensus of what this means. How does a digital plant relate to initiatives such as 'paperless plant', 'fully automated facility', 'factory of the future', etc., and what is its relationship to technology advances such as the Internet of Things and big data analytics?

Surely, we cannot consider a manufacturing plant in isolation but need to see it in its context of a seamless, end-to-end value chain from suppliers, through an internal and external manufacturing ecosystem, and all the way to the patient. This is not just about technology but also the need for people and processes within companies to adapt to the needs of the market. Companies will find themselves on a continuum, they are at different starting points on their digital journey and have different visions and aspirations of where they need to be and by when.

An industry collaboration accepted the challenge of developing a single 'Digital Plant Maturity Model' (DPMM) that describes the stages of maturity from simple paper-based plants through to the fully automated and integrated 'adaptive plant' of the future. The model will allow companies wanting to transform their manufacturing capability to address questions that are currently difficult to answer, such as:

- How do I define the concept of a digital plant in a way that describes how capabilities can be transformed step-by-step, and in a way that can be easily understood and measured?
- Against these capabilities, how mature is my environment today?
- How do I compare against industry benchmarks?
- What are my transformational aspirations in the next 3, 5 and 10 years?
- What are the prerequisites for moving up the maturity levels?

The collaboration comprised 20 industry experts from 11 major biopharmaceutical companies (see Appendix). This multifaceted team has expertise in manufacturing, IT, automation and analytics and is a mixture of senior engineers, strategists and operational managers. They have a unique view across the industry and its technology and understand both the evolving biologics market and the innovations that will enable it.

The DPMM was consciously developed to cover not just what is possible today, but also to define an advanced-level adaptive plant that, although not in the realms of fantasy, is beyond the capabilities of current manufacturing and IT technologies. The content of this model was developed with the BioPhorum Technology Roadmap work (which is publishing a strategic road map for biopharmaceutical manufacturing technology) as well as input from some key IT vendors and initiatives such as Industry 4.0.

This paper introduces the DPMM and its use – both as a tool for companies to plot their digital journey and to identify the common challenges for companies wishing to rise up the maturity levels. This will lead to further targeted collaborations between the industry and its technology providers to address the challenges and to develop a common digital roadmap.

INDUSTRY CHALLENGES AND OPPORTUNITIES

A combination of industry challenges and opportunities provided an impetus for change, and led to this initiative to define a vision for a digital plant:

Market access and price pressure:
Advances in medicine relieve human suffering and enable longer life, but increasing healthcare costs create economic challenges for individuals and nations. This leads to tremendous pressure on pricing, with market access often contingent on price negotiation and the emergence of pay-for-performance reimbursement models.

Biosimilars:
In 2015, the US FDA approved the first biosimilar medicine in the world's largest pharmaceutical market. Growth in biosimilars will lead to increased competition for established biopharmaceuticals as their patent-related periods of market exclusivity expire.

Evolution of biopharmaceutical manufacturing:
New technology will reduce biopharmaceutical manufacturing costs and accelerate the introduction of new medicines. Plants that were once dedicated to manufacturing a single product are evolving into multi-product facilities that may combine clinical and commercial manufacturing.

Regulatory compliance:
Biopharmaceutical manufacturers are subject to oversight from healthcare regulatory authorities in countries where their products are marketed. As regulatory standards become more stringent, manufacturers must reduce risk and variability and demonstrate higher levels of control.

Complexity:
Manufacturing of biopharmaceuticals is highly complex due to the intrinsic variability of biological processes and the need to meet the highest standards of product quality and safety. Increasingly, plants function as part of a complex integrated supply chain of internal and external (third party) plants.

Analytics:
In recent years, new capabilities have emerged to integrate and analyze huge volumes of data. Computer algorithms are increasingly able to generate insights and predictions that would not otherwise be available. Application of these new capabilities to biopharmaceutical manufacturing can be transformative.

Personalized medicine:
Medicines are increasingly targeted at specific combinations of disease conditions, and patient's biological and genetic characteristics. This leads to smaller manufacturing batch sizes and a greater need for flexibility in manufacturing plants. In some cases, a medicine is manufactured using a patient's own cells, i.e. a batch size of one.

Patient centricity:
Patient preferences and experiences have a greater influence on product scope, design and delivery. In the future, the industry must not only ensure medicines are available in the supply chain, but also provide the best overall patient, payer and physician experience and outcomes. This includes the patient's digital experience and is a fundamental shift in the industry operating model.

Digital value chain:
The concept of 'digital value chain' is emerging, where patient data may flow into the manufacturing plant, and patient experience and outcome data may flow back to healthcare providers and manufacturers. The product provided to patients may not only be a medicine, but also sensors and applications to capture patient-specific data.

Digital transformation:
Across many industries, new digital capabilities such as social media, analytics, mobile applications, smartphones, virtual reality and Internet of Things are reshaping the competitive landscape and enabling the emergence of disruptive business models. Digital transformation is on the agenda for CEOs and boards of directors and it has become essential for companies to have a digital strategy.

These challenges, trends and opportunities provided the impetus for BioPhorum IT member companies to collaborate to develop the DPMM.

BENEFITS OF THE DPMM

During initial discussions, BioPhorum IT group (BPIT) member companies shared the above challenges facing the industry and discussed how it is reacting to this evolving landscape. It became clear that we are all:

- **facing similar barriers, both internal and external**
- **taking similar actions to confront these barriers**
- **communicating a digital vision to our partners, both internal and external.**

The DPMM was created to help describe the technological evolution at a manufacturing plant as well as to communicate the industry's vision of a future state-of-the-art digital plant. The DPMM provides the following insights and benefits to BPIT member companies.

Internal and external benchmark:
Each BPIT member company is structured similarly as they have small and large molecule plants, fill/finish and active ingredient manufacturing sites, legacy products vs. commercialization and new product launch sites. As expected, it is inevitable that this results in variability in technology at sites. The DPMM template produces an assessment on the level of technological maturity at the plant providing a benchmark. A comparison between all sites, or more specifically 'sister' sites, is now achievable. Similarly, this benchmark not only applies internally, but across BPIT member companies, which enables shared learning and provides a common evaluation that can be shared with software vendors.

IT roadmap development:
By applying the DPMM, the IT organization can evaluate the state of its technology at all manufacturing sites, those within a network or at specific 'sister' sites. This evaluation can provide either a global roadmap spanning all manufacturing sites (e.g. a common gap for all IT) or a roadmap for specific sites (e.g. where there is no laboratory execution system). The IT roadmap shows the investments needed to improve manufacturing operations, enable future manufacturing processes and capabilities, and capitalize on the potential value of manufacturing data and analytics. At the highest maturity levels, significant value can be achieved through data integration and analytics, linking manufacturing data backwards into product development, and linking forward with clinical and patient experiences and outcomes.

Strategic alignment with manufacturing:
The DPMM is aligned with the BioPhorum manufacturing technology roadmap currently in devlopment. This illustrates the aspirational future state of biologics manufacturing, while the DPMM shows the IT advances that are needed to enable the plant of the future.

Influence software suppliers:
The DPPM can be used to inform software suppliers about the capabilities that the biopharmaceutical industry needs and thus can help influence the future direction of software products.

Transformation planning:
In conjunction with the technology roadmap, a multi-year transformation plan can be created, including the required future capabilities and deemed magnitude of capital investment.

Investment justification:
For IT to enable the transformation towards a digital plant, support and funding must be provided by the business. The deliverables generated by this model (e.g. internal and external benchmarks, technology roadmap, transformation plan) help provide context and business deliverables. It also allows for decisions about where NOT to spend capital; for example, there may be insufficient incremental business value to justify the investment to make a specific site fully digital. However, it will highlight those sites that are lagging behind in their digital investment.

Dependency mapping:
The structure of the model outlines core 'business capability' dimensions as well as supporting 'enabling capability' dimensions. The model connects these two dimensions, identifying the maturity required in both to achieve the digital plant vision for that level.

STRUCTURE OF THE DPMM

The five levels of digital plant maturity are:

1. **Pre-digital Plant**
2. **Digital Silos**
3. **Connected Plant**
4. **Predictive Plant**
5. **Adaptive Plant**

A conscious decision was made to make the highest maturity level aspirational to inspire the development of new technologies and capabilities and to enable the plant of the future.

Figure 1 provides a high-level characterization of a digital plant as it advances through the five levels of maturity from a predominately manual and paper-based facility to a fully automated, adaptive, collaborative, self-optimizing, autonomous plant that is also fully integrated to the end-to-end, internal and external value chain.

Figure 1: *DPMM: Definition of levels*

Level 1 Pre-digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant 4	Level 5 Adaptive Plant
Primarily Paper-based processes Predominately manual processing. Low level of automation. Basic PLC controls. Applications are stand-alone 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 interfaced to PLCs Site-specific systems; limited integration across functional silos Analytics on demand, "why did it happen?" high manual effort Plants operate independently with little "real-time" supply chain visibility	Vertical Integration ERP, LES, MES and Automation layer are fully integrated to support digitized 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 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 collaborations (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-n-play everything" from an instrument to a production scale or a CMO Zero system down-time (including upgrades) – 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; 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.

To assess a plant's maturity level, two categories of dimensions have been established.

Business capability dimensions – This category includes the primary business capabilities required to design, build, operate and maintain the digital plant and its role in the end-to-end enterprise value chain. These capabilities are:

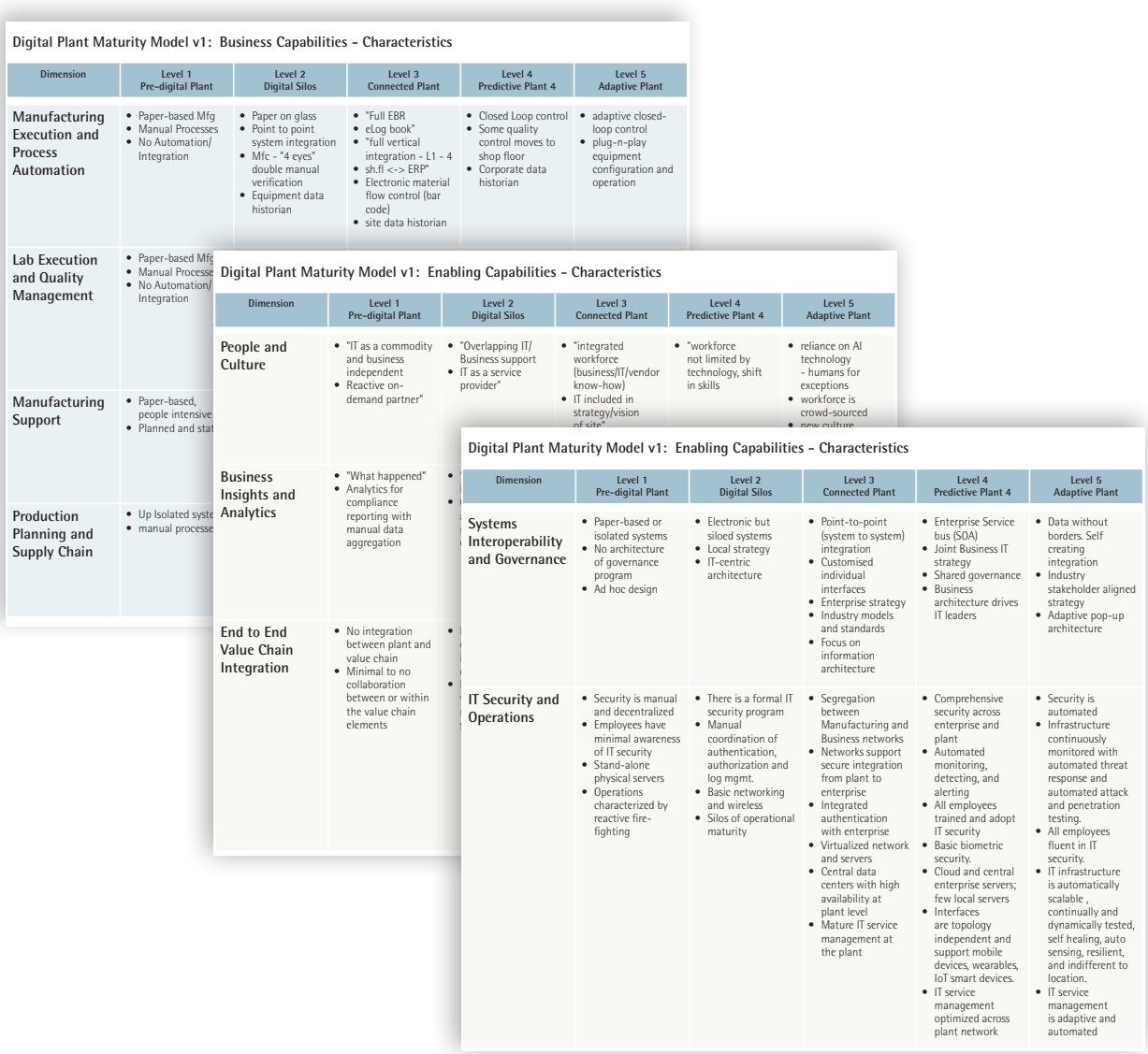
- **Manufacturing Execution and Process Automation** – Includes drug substance and drug product manufacturing execution, packaging, labeling, weighing, cleaning, change-over, batch records, data capture and historization, process control and analysis.
- **Manufacturing Support** – Includes all required support functions, including maintenance and calibration management, plant and facilities engineering, environmental monitoring, plant security, health and safety, building automation, utilities, energy management, process development, knowledge management, remote monitoring and collaboration, and learning management.
- **Lab Execution and Quality Management** – Includes QC/QA, product monitoring and testing, raw materials testing and inspection, batch release, laboratory methods execution, laboratory scheduling, certificate of analysis generation, data archiving, stability, change management, CAPA, audit and inspection management, document management, customer complaint management, in-line/at-line testing and process verification.
- **Production Planning and Supply Chain** – Includes production planning and scheduling, warehouse, logistics, dispatch, transportation, materials management, serialization track and trace, components management, supplier integration, distribution center and cold chain management.

Enabling capability dimensions – This includes the people, process, technology and information capabilities required to enable the above business capabilities. These enabling capabilities are:

- **People and Culture** – Includes managing talent to support and evolve the digital plant across both shop-floor personnel and professional staff. Skills include automation, IT, architecture, delivery, data science and service ownership. Also includes maturity of culture and skills shift (due to more advanced technologies), integrated and complex systems, increased focus on data and analytics, and integration of people metrics into digital plant monitoring and control systems.
- **Business Insights and Analytics** – Analytics to drive insights from aggregated data to improve decision making and enable business transformation. Includes reactive, proactive and predictive analytics such as native system reports, shop-floor visual management, ad hoc self-service visualization and reporting, predictive modeling, simulation, big data analytics, text analytics and machine learning.
- **End-to-End Value Chain Integration** – The information flow in and out of the digital plant is integrated with, and available in, the greater ecosystem of the end-to-end value chain from raw materials to patients. Value chain examples include product lifecycle and variation management from R&D to commercialization, technology transfer, enterprise recipe management, planning to shipment and in-market release.
- **Systems Interoperability and Governance** – The overall digital plant strategy and governance that is linked to the business strategy and investment model. Includes global standard information architecture blueprint, data governance, platforms and roadmaps aligned with business capabilities. Also includes business process automation through key systems that are integrated horizontally and vertically across the enterprise blueprint. Includes data integration and aggregation across the plant as well as the integration with the end-to-end value chain.
- **IT Security and Operations** – Use of enabling information security and infrastructure technology in digital plant evolution. Includes secure manufacturing and business networks, DMZs, firewalls, wireless, virtualization, backups, monitoring and alerting, cloud, mobile, wearables and augmented reality infrastructure. Also includes lifecycle management of digital assets, such as application run and build management, continuous improvements, GxP qualification and compliance, data integrity management, configuration management, technology platform management, long-range planning and reinvestment program management, supplier management, service management, innovation frameworks and roadmap execution.

The DPMM framework further characterizes the maturity levels for each business capability and their supporting enabling capability dimensions as shown in Figure 2.

Figure 2: *DPMM: Characteristics of dimensions*



Digital Plant Maturity Model v1: Business Capabilities – Characteristics

Dimension	Level 1 Pre-digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant 4	Level 5 Adaptive Plant
Manufacturing Execution and Process Automation	• Paper-based Mfg • Manual Processes • No Automation/ Integration	• Paper on glass • Point to point system integration • Mfc - "4 eyes" double manual verification • Equipment data historian	• "Full EBR • eLog book" • "full vertical integration - L1 - 4 • sh.fl <-> ERP" • Electronic material flow control (bar code) • site data historian	• Closed Loop control • Some quality control moves to shop floor • Corporate data historian	• adaptive closed-loop control • plug-n-play equipment configuration and operation
Lab Execution and Quality Management	• Paper-based Mfg • Manual Processe • No Automation/ Integration				
Manufacturing Support	• Paper-based, people intensive • Planned and stat				
Production Planning and Supply Chain	• Up Isolated syste • manual processe				

Digital Plant Maturity Model v1: Enabling Capabilities – Characteristics

Dimension	Level 1 Pre-digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant 4	Level 5 Adaptive Plant
People and Culture	• "IT as a commodity and business independent • Reactive on-demand partner"	• "Overlapping IT/ Business support • IT as a service provider"	• "integrated workforce (business/IT/vendor know-how) • IT included in strategy/vision of site"	• "workforce not limited by technology, shift in skills	• reliance on AI technology - humans for exceptions • workforce is crowd-sourced • new culture
Business Insights and Analytics	• "What happened" • Analytics for compliance reporting with manual data aggregation				
End to End Value Chain Integration	• No integration between plant and value chain • Minimal to no collaboration between or within the value chain elements				

Digital Plant Maturity Model v1: Enabling Capabilities – Characteristics

Dimension	Level 1 Pre-digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant 4	Level 5 Adaptive Plant
Systems Interoperability and Governance	• Paper-based or isolated systems • No architecture of governance program • Ad hoc design	• Electronic but siloed systems • Local strategy • IT-centric architecture	• Point-to-point (system to system) integration • Customised individual interfaces • Enterprise strategy • Industry models and standards • Focus on information architecture	• Enterprise Service bus (SOA) • Joint Business IT strategy • Shared governance • Business architecture drives IT leaders	• Data without borders. Self creating integration • Industry stakeholder aligned strategy • Adaptive pop-up architecture
IT Security and Operations	• Security is manual and decentralized • Employees have minimal awareness of IT security • Stand-alone physical servers • Operations characterized by reactive fire-fighting	• There is a formal IT security program • Manual coordination of authentication, authorization and log mgmt. • Basic networking and wireless • Silos of operational maturity	• Segregation between Manufacturing and Business networks • Networks support secure integration from plant to enterprise • Integrated authentication with enterprise • Virtualized network and servers • Central data centers with high availability at plant level • Mature IT service management at the plant	• Comprehensive security across enterprise and plant • Automated monitoring, detecting, and alerting • All employees trained and adopt IT security • Basic biometric security. • Cloud and central enterprise servers; few local servers • Interfaces are topology independent and support mobile devices, wearables, IoT smart devices. • IT service management optimized across plant network	• Security is automated • Infrastructure continuously monitored with automated threat response and automated attack and penetration testing. • All employees fluent in IT security. • IT infrastructure is automatically scalable , continually and dynamically tested, self healing, auto sensing, resilient, and indifferent to location. • IT service management is adaptive and automated

Using the characteristics provided for each dimension of the model, an assessment can then be made of a plant (or a network of plants) against the five maturity levels within each dimension. Figure 3 shows an example high-level assessment of a plant against the model:

Figure 3: *DPMM: Example high-level plant assessment*

		DIGITAL PLANT MATURITY MODEL FOR: XYZ COMPANY					
		Trend	Level 1 Pre-Digital Plant	Level 2 Digital Silos	Level 3 Connected Plant	Level 4 Predictive Plant 4	Level 5 Adaptive Plant
Business Capabilities	Manufacturing Execution and Process Automation	Steady	Mature	Mature			
	Lab Execution and Quality Management	Up	Mature	Mature	Emerging		
	Manufacturing Support	Steady	Mature	Mature			
	Production Planning and Supply Chain	Up	Mature	Mature	Emerging		
Enabling Dimensions	People and Culture	Up	Mature	Mature	Emerging		
	Business Insights and Analytics	Up	Mature	Mature	Emerging		
	End to End Value Chain Integration	Steady	Mature	Mature			
	Systems Interoperability and Governance	Steady	Mature	Mature			
	IT Security and Operations	Up	Mature	Mature	Emerging		

THE DPMM JOURNEY

Under the auspices of the BPIT, the digital plant team was formed in early 2016 with manufacturing IT leaders from member companies. Within two months, the team completed the initial draft model and tested it by conducting an informal maturity assessment at one of the member company's biomanufacturing plants. Based on learnings from the assessment, the team revised and simplified the model, and developed a scoring tool to be used in future maturity assessments.

Development of the DPMM is integrated with other BioPhorum initiatives, including:

- **Technology Roadmap (TRM):** This defines a shared industry vision for the future of biologicals manufacturing. Elements of this vision are embedded in the DPMM and realization of the future state vision in the TRM depends on delivery of the IT capabilities defined in the model.
- **Taxonomies and Data Reference Models:** The Taxonomies workstream is working to define standards to enable system interoperability, which is crucial for advancing to the highest digital plant maturity levels.
- **Compliance for the Digital Age:** The Compliance workstream operates at the intersection of emerging IT capabilities and health agency regulatory compliance. An efficient path to compliance is essential to enable the innovations required for the higher maturity levels in the DPMM.
- **Supplier Interactions:** The highest DPMM levels cannot be achieved with currently available IT offerings, so the model is being used to define scenarios to drive discussion and collaboration with technology companies and innovative suppliers.

Alongside the publication of this white paper, the team is seeking feedback from additional internal and external experts, and applying the DPMM internally to benchmark member company plants. The learnings from these activities will be used to further refine the model.

LEARNING AND INSIGHTS

In developing the DPMM, the BPIT members are learning and gleaning insights.

Current biopharmaceutical state:
It is clear that while all companies use a different set of vendors, have varied manufacturing organizations they support, and have plant sites at different levels of maturity, we are all similar in our levels of maturity. Informal use of the model suggests that the biopharmaceutical industry is predominantly at Level 2 (Digital Silos), albeit with numerous plants still at Level 1 (Pre-Digital), and a minority of plants approaching or at Level 3 (Connected Plant). Within a single plant, there can be varying levels of maturity. At the moment, best-in-class in the biopharmaceutical industry seems to align to Level 3 (Connected Plant). A brief examination of selected industries was undertaken and some highly advanced sectors have reached Level 4 (Predictive Plant). Level 5 (Adaptive Plant) is still aspirational in the biopharmaceutical industry and cannot be achieved with currently available technology (either IT or manufacturing technology).

Digital plant variability:
Not all plants need to be at a high maturity level, nor do all areas within a plant need to be at the same maturity level. For example, pilot plants and commercial plants manufacturing products that are late in the product lifecycle may need portions of their environment to be digital, but the cost of being fully digital can outweigh the benefits. Companies should use the model to make a conscious decision on where they need their plants to be, and to align target maturity levels with plant and product strategies.

Key to the success of this DPMM effort has been the expertise and varied perspectives of the participants from BPIT members and their willingness to challenge, adjust and adapt.

CONCLUSION

The collaboration provides a cohesive starting point for biopharmaceutical IT leaders to build on the insights garnered and to share their digital transformation plans and experiences. Importantly, it represents a uniting of minds and industry experts who are catalyzing the call to action within the broader ecosystem – IT developers and vendors, industry suppliers, thought leaders and external experts – to align and focus the development of capabilities, technologies, standards and know-how. In the DPMM, the industry now has a tool in which it can set ambitions and plot and measure its transformation journey. Extending the reach of the collaboration will enable a concerted effort for the BPIT member companies to achieve their industry aspirations and transformation goals — ultimately to the benefit of patients and to the wider healthcare ecosystem.

APPENDIX

The DPMM was developed under the auspices of the BPIT. The contributing members of the collaboration were:

NAME	COMPANY	NAME	COMPANY
Eric Anttonen	Eli Lilly	**Shawn Mullins**	Pfizer
Sonia Banerjee	MSD	**Mark O'Neill**	MSD
Harmik Begi	Amgen	**Nirav Patel**	BMS
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James Connaughton	Regeneron	**Christoph Pistek**	Shire
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Christian Hoferer	Roche	**Mike Tomasco**	Pfizer
Peter Iles-Smith	GSK	**Hernan Vilas**	Roche
Alexander Muffler	Janssen	**Dan Wasser**	BMS