



VOLUME 8

Pharma 4.0™

First Edition





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Preface

The challenge of implementing digital technologies and initiating successful digitalization projects is a common difficulty for many companies. Research indicates that a majority of organizations do not achieve their transformation goals, and those that do often find it hard to maintain their successes [33, 34, 164]. One of the main obstacles identified is insufficient preparedness.

In response to these significant challenges, the ISPE Pharma 4.0 Community of Practice aims to guide companies in overcoming their transformational hurdles. This Guide provides the framework for the structural capabilities necessary for successful transformations. Leveraging the extensive experience of our international and interdisciplinary author team brings the breadth and depth from years of experience to provide the reader with a strong overview, empowering readers to embark on, reinvigorate, or advance their transformation journey.

The effectiveness of a digital transformation is contingent on its alignment with a strategic business vision, ownership by every leader and employee, and the driving force of cross functional, cross sectoral leadership empowered by top management to cultivate a sustainable cultural shift towards a data-driven organization. This Guide serves as an educational lecture, actively fostering a shared understanding among all transformation stakeholders: encompassing industry leaders, suppliers, technology partners, and regulators.

As technology evolves and organizations develop, the ISPE Pharma 4.0 CoP will continue to offer support through further publications to benefit the life sciences industry.

We extend our heartfelt thanks and recognition to the continuous support of Dr. Thomas Zimmer, whose invaluable industry, regulatory, quality, and operational expertise significantly enhanced our Guide writing and reviewing processes throughout the development of this Guide.

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1 Principles of Pharma 4.0 and Focus of the Baseline Guide

1.1 Introduction

As the pharmaceutical industry matures, it needs to evolve in order to operate in a volatile, uncertain, complex, and ambiguous (VUCA) world efficiently and effectively. Applying emerging and digital technologies can lead to more robust and flexible manufacturing processes, which in turn can help the pharmaceutical industry respond to drug shortages, reduce interruptions in production and delivery of medicines, and ensure consistent clinical performance of products, among other benefits.

With the influx of new technologies on the plant floor and in the flow of work, the industry must think progressively about how organizations will work in the future. Organizations seeking to transform will embrace new technologies, move to a true end-to-end focus for their products and processes, and engage and utilize their people in new ways. Such an approach requires a systematic, systemic, and holistic transformation of the organization and its people.

The concept of Pharma 4.0 developed from Industry 4.0 (Industrie 4.0), which is “*the intelligent networking of machines and processes for industry with the help of information and communication technology.*” [1] The ISPE Community of Practice Pharma 4.0 North Star definition is:

We provide practical guidance, embedding regulatory best practices, to accelerate Pharma 4.0 transformations. Our 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.

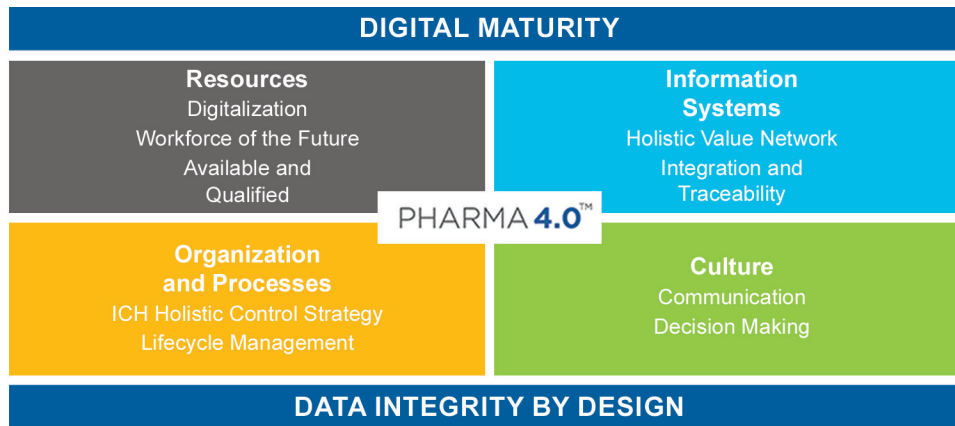
To aid life science organizations in starting, restarting, or continuing their transformational journey, the Pharma 4.0 Operating Model, shown in Figure 1.1, provides a framework for the prerequisite structural capabilities needed for a successful business-driven implementation of digital transformation. (See Appendix 2 for more information.) These capabilities are based on the Industry 4.0 elements and pharmaceutical-specific enablers:

Elements:

- Resources
- Information Systems
- Organization and Processes
- Culture

Enablers:

- Digital Maturity
- Data Integrity by Design

Figure 1.1: The Pharma 4.0 Operating Model – Elements and Enablers

The fundamental high-level principles are:

- Create and maintain a holistic view of all processes in the value network along the pharmaceutical product lifecycle
- Mirror reality using digital twins
- Sustain an interdisciplinary approach of all related functions
- Focus on data management
- Preserve compliance with regulations and incorporate industry best practices (e.g., EU [2] and US FDA GMPs [3, 4], ICH [5], *ISPE Advancing Pharmaceutical Quality Guide Series* [6], *ISPE GAMP® Series* [7])

Important prerequisites are furthermore:

- A business strategy should be available for the digital transformation related to the set operational business goals
- A maturity assessment of structural capabilities (refer to Appendix 3 – Pharma 4.0 Maturity Assessment) as a condition for the successful digital transformation is established for the respective business areas

1.2 Purpose and Scope of this Baseline Guide

This Guide presents the Pharma 4.0 concepts, benefits and challenges, recommendations, and examples to provide:

- A general overview for management
- A dialogue platform between industry experts and regulators
- A document for training experts in all functions of technical operations and related areas to align on the same principles and maturity levels

This Guide conveys the known Industry 4.0 digital technology-enabled transformational concepts to the specifics, codes, and terms (refer to the Glossary in Appendix 7) of the regulated pharmaceutical industry. This business-driven approach is called the Pharma 4.0 Operating Model.

The Guide describes areas of potential application for digital transformation and how to combine these with the high-level principles of Pharma 4.0. Namely, what to consider when implementing a holistic control strategy in supply chain, manufacturing and packaging, quality and validation, maintenance/engineering and automation, underpinned by a robust and flexible workforce.

The scope is the complete value network, and the approach is holistic.

Note that this Baseline Guide provides an overview or a broad view, the “what” of Pharma 4.0 but not a detailed roadmap for implementing a project or process in a certain area. This is planned to be provided in a series of Good Practice Guides, the “how.” In this way, the Baseline Guide has the character of a “textbook” with the Good Practice Guide similar to a “cookbook,” with a detailed, recipe-like sequence of how to do something.

1.3 Triggers for Pharma 4.0

The Industrial Digital Transformation is more than just an approach to implement digital technologies, it is a shift in mindset and a fundamental shift in the way companies operate their business to deliver value for patients and customers. This impacts all types of processes along the pharmaceutical product lifecycle and value chain. If reality is mirrored to a full extent, this is about a “metaverse” approach.

1.3.1 Challenges

There are numerous challenges to be addressed as the life sciences industry advances in the digital age, such as:

- Geopolitical and other shocks: Increasing geopolitical tensions will necessitate companies to build in greater resilience into the supply chain. Similarly, environmental (e.g., earthquakes) and other shocks (e.g., pandemics) also drive the need for companies to build in more resilience.
- Demand uncertainty: Uncertainties in demand add to the increasing complexity of manufacturing and supply.
- Sustainability commitments: Goals on sustainability require companies to design the future network (and supply chain) with the intent to minimize impact on the environment. Modular manufacturing, high productive cell lines and processes, and the application of Artificial Intelligence (AI) to optimize energy consumption can contribute significantly to sustainability.
- Raw materials: Shortages of raw material, which goes beyond the COVID-19 global pandemic, continue to be a challenge across the industry.

The COVID-19 global pandemic demonstrated companies’ ability to leverage digital, AI, and advanced technologies to accelerate, simplify, and invent new ways of delivering for patients.

Managing this complexity and uncertainty is the new “normal” and needs the entire industry to rethink the way of working and to adopt new analytical capabilities and technologies.

1.3.2 Opportunities

Manufacturers need to find new ways to identify and analyze problems and implement advanced technology to increase efficiency and effectiveness in meeting compliance requirements.

Digital transformation is not a purpose in itself. It aims at addressing current challenges in the development of drug manufacturing processes as well as large-scale commercial manufacturing and supply chains by leveraging new technologies and analytical capabilities. Over the last decades the biotechnology and pharmaceutical industry has gone through a number of challenges that led to learning and improvements to avoid disruptions in drug delivery and increased cost or time to market.

Digital transformation is a fundamental driver of business evolution, enabling the adoption of next generation data-based business models and additional contributions to provide various benefits:

- Deliver faster to patients: Optimize time to market, improve launch times and reduce overall development and manufacturing lead times
- Improve constant level of product quality and process robustness: Ensure an increased business resilience and consistent delivery of products to patients, while reducing end-to-end product and process variability
- Ensure and promote efficient and sustainable operations: Optimize processes across the value chain, maximize yield and titer, improve productivity and worker experience, and reduce overall product costs

1.3.3 **Pharmaceutical Innovation**

Although the pharmaceutical industry is constantly evolving, there have been many changes in recent years that have had a significant impact on the industry:

Advances in Biotechnology: Advances in biotechnology have resulted in the development of new and innovative treatments for diseases. For example, advances in genetic engineering have led to targeted therapies that are more effective with fewer side effects than traditional treatments, especially in the oncology and immunology spaces.

Personalized Medicine: The emergence of personalized medicine has enabled the development of treatments tailored to the individual needs of the patient. This is made possible through the use of sophisticated genetic and genomic technologies that allow for a better understanding of the underlying causes of disease, and the development of treatments targeting specific genetic mutations.

Digitization and Digitalization: Digitization is the movement from paper (analog) to digital records as a basis for Digitalization, which is better process integration and data analysis and has a profound impact on the pharmaceutical industry, enabling the collection, analysis, and use of vast amounts of data to support decision-making, i.e., Real-World Data (RWD), Real-World Evidence (RWE). This has led to improved efficiency in Research and Development (R&D), manufacturing, and distribution, facilitating a better understanding of the unmet needs of patients and healthcare providers.

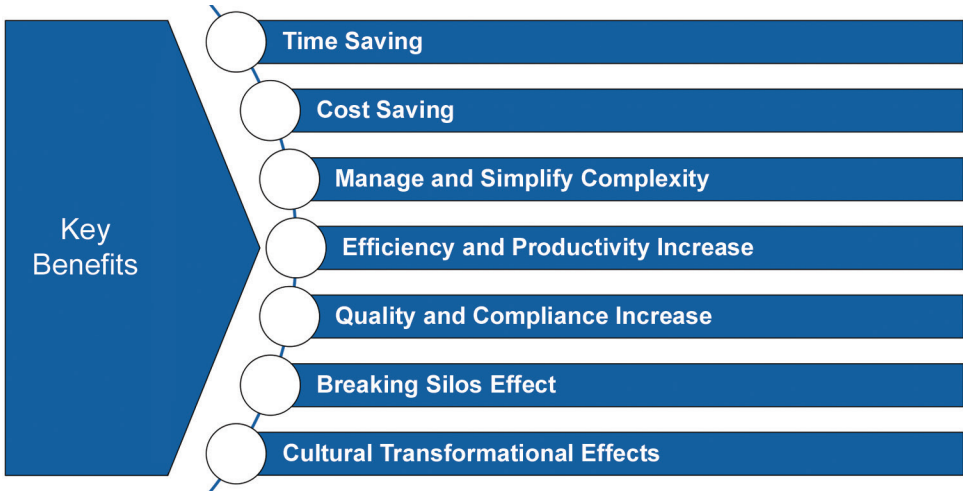
Furthermore, increased globalization has had a significant impact on the industry providing companies with expanded access to new markets and a wider patient population. This has led to increased competition around the world for market share and access to resources.

1.3.4 **Corporate Benefits**

When developing business strategies, the Pharma 4.0 technologies provide support by delivering the benefits listed in Figure 1.2 and developing new business models where data and digital technology can be used as a new source of revenue.

Defined case studies and related business cases, derived from a corporate strategy can bring the following benefits:

Figure 1.2: Key Benefits of Implementing the Pharma 4.0 Operating Model



In the strategic approach, one observes top-down determinations, e.g., in the construction of a fully digitized factory, and bottom-up approaches in which individual production areas are digitalized. Here it is particularly important to create good business cases that define goals and metrics for goal achievement.

1.4 The Pharmaceutical Industry Benefits of Pharma 4.0

Because of the regulated nature of the pharmaceutical industry, certain structural requirements are needed to successfully implement a digital transformation in a pharmaceutical company. As Industry 4.0 evolves into Industry 5.0 to incorporate sustainability, human centricity, and resilience aspects, the Pharma 4.0 Operating Model holistically integrates and describes these additional aspects. [8] Figure 1.3 shows how the Pharma 4.0 approach includes the principles of Industry 4.0/5.0.¹

Figure 1.3: Pharma 4.0 Adds the Pharmaceutical Industry-Specifics to Industry 4.0/5.0 Principles



¹ In the regulated pharmaceutical industry, special wording, codes, and terms are used. See the glossary in Appendix 7.

1.4.1 Holistic Control Strategy

Classical control strategies as described in ICH Guidelines [5] form the core of a holistic control strategy that has an extended scope and integrates, monitors, and reports risk management.

Firstly, the structural capabilities, as described in the Pharma 4.0 Operating Model, can also be measured here. Secondly, the performance parameters of daily operations, which were previously recorded in numerous isolated production dashboards, are also recorded. Lengthy analyses in the context of root cause analysis in the case of deviations in production or Quality investigations can be shortened. Finally, the risk parameters of the supply chain are included.

Monitoring, controlling, and reporting grow together in a single data room available for evaluation.

Since many pharmaceutical manufacturers today have international supply chains, it makes sense to align themselves not only with local regulations but also with regionally and nationally applicable GxP regulations and international standards.

Regional regulations include FDA [9], European Commission [10], European Medicine Agency (EMA) [11], World Health Organization (WHO) [12], and Pharmaceutical Inspection Co-operation Scheme (PIC/S) [13]. International standards include ICH Guidelines [5], ISO [14] and ASTM [15]. These lists are not exhaustive.

1.4.2 Stakeholder Based Culture and Ecosystem

Networking all data sources creates transparency that enables data-based decisions. Existing functional silos, e.g., between development and production, and between supply chains and internal factory logistics, are bridged. The market and patients are included. The classic supply chain becomes the consideration of an entire “value network.”

1.4.3 End-to-End Integrated Supply Chains

Today's global supply chains require an end-to-end integrated planning, execution, and distribution process. By leveraging advanced digital technologies, such as AI, Internet of Things (IoT), cloud computing, and data analytics, pharmaceutical companies optimize their planning, execution, and overall distribution processes. With the effect of improved efficiency, cost reduction, enhanced customer satisfaction, and better risk management capabilities throughout the entire supply chain.

1.4.4 Computer Supported Decisions

A particular area of tension for the pharmaceutical industry arises from the requirement for quality oversight when computers are making decisions or preparing key decisions. The inspector not only wants to see the result of a quality check, but also how the result came about. Therefore, the ultimate quality governance and overall responsibility remains with the Qualified Person (EU) or Quality Manager, Quality Head, Pharmacies Responsable, Director Technico, etc. (other countries).

Thus, requirements for algorithms are expected when computers are self-learning and prepare or make decisions based on that.

For the person performing batch release, the question is what knowledge of Information Technology (IT) will be needed in the future. The same question applies to inspectors performing GxP inspections.

1.4.5 Integrated and Applied Risk Management

The two main risks for patients are the unavailability of their drug and quality defects in their drug. Networked data makes it possible to identify potential shortages of materials ahead of time and take appropriate countermeasures or establish contingency plans.

Another example is unforeseen unknown impurities due to changes in synthesis or the use of newer, more accurate analytical methods of active ingredients and excipients. The result of long-term medical studies can classify excipients previously considered harmless as a cause for concern, so that major redevelopment and replacement programs become necessary.

The most dangerous are falsified/counterfeit medicines, which either do not contain any active ingredient or have been manufactured with hazardous substances, but do not differ externally from the genuine product. Here, too, networked data from the supply chain and digitally recordable safety features can create greater drug safety.

1.5 How to Use this Guide

This Guide serves as a comprehensive resource for professionals at all stages of digital transformation, from novices to experts. The authors recommend starting with Chapters 1 and 2 to build a solid foundation before diving into specific topics of interest (as outlined in Figure 1.4). Chapters 3-10 elaborate on the multifaceted aspects of the Pharma 4.0 Operating Model, covering the cross-functional areas essential for end-to-end transformation across the pharmaceutical lifecycle and supply chain. The appendices provide supplementary practical insights, case studies and a maturity model to help companies gauge their progress.

Figure 1.4: Guide Structure



Chapter Highlights:

- **Chapter 2: Digital Transformation – Pathways to Success**

This chapter outlines various starting points, prerequisites, governance structures, and strategies for achieving transformational success, tailored to an organization's size, risk tolerance, flexibility, and maturity level.

- **Chapter 3: Holistic Control Strategy**

This chapter expands on the control strategy as defined by ICH [5], presenting a comprehensive approach to managing the pharmaceutical product lifecycle and supply chain.

- **Chapter 4: Quality Management in the Digital Age**

Explores new digital opportunities for managing the increasing complexity in product lifecycles and global supply chains through enhanced process understanding.

- **Chapter 5: The Human Element: People, Organization, and Culture**

Understand the profound impact of digitalization on organizational culture, collaboration, and knowledge management.

- **Chapter 6: Navigating Regulations in a Digital World**

A review of pertinent regulations, guidelines, and industry standards, focusing on their implications in the context of digital transformation technologies.

- **Chapter 7: Process and Data Management**

Learn about the systematic creation, definition, and documentation of processes that serve as the foundation for interconnected plant architecture.

- **Chapter 8: Plug & Produce: Principles and Challenges**

This chapter discusses the architecture of an interconnected plant, focusing on the principles and challenges of its implementation.

- **Chapter 9: Engineering Design and Construction**

Discover how simulation, virtualization, and holistic control strategies are revolutionizing facility design.

- **Chapter 10: Technologies Enabling Digital Transformation**

This repository chapter provides definitions, technical principles, and real-world case studies to guide organizations exploring similar digital transformation opportunities.

Appendices:

- **Appendix 1: Case Studies**

Real-world examples illustrating approaches, procedures, technologies, benefits, challenges, and learnings

- **Appendix 2: In-Depth Overview of the Pharma 4.0 Operating Model**

Detailed description of the model's elements and enablers

- **Appendix 3: Pharma 4.0 Maturity Model and Assessment Tool**

A tool for ongoing monitoring of an organization's progress in its transformation journey

- **Appendix 4: Reporting Schemes**

Describes the reporting processes to be followed in a Pharma 4.0 model-driven organization

- **Appendix 5: Roles and Responsibilities**

Recommended roles and responsibilities for establishing and operating a Pharma 4.0-driven organization

2 Digital Transformation – Pathways to Success

2.1 General

Business transformation enabled by a digital approach (also known as digital transformation) must be governed and managed as an organizational and business change that goes beyond the implementation of IT. Business transformation enabled by a digital approach (also known as digital transformation) must be governed and managed as an organizational and business change that goes beyond implementation of IT.

Effective digital transformation is linked to a business strategy and subsequently owned by all leaders and all employees. Furthermore, it requires cross-functional and cross sectoral leadership empowered by top management to drive a sustainable cultural change to a data-driven organization.

2.2 Governance

“Corporate governance’ describes the processes, structures, and mechanisms that influence the control and direction of corporations.” [16]

Regarding the digital business transformation, the following principles for governance should be considered:

- Holistic approach
- Pharma 4.0 Operating Model Maturity Assessment
- Data orientation and acknowledgement of data as single source of truth
 - Data integrity by design
 - Data structurization, standardization, and availability
 - Data contextualization
 - Data interoperability
- Process orientation
- Digital twins (Metaverse – interconnected ecosystem of digital twins/between real and virtual)
 - End-to-End data and process transparency
 - Simulation of scenarios
 - Predictions
 - Prescriptions
- Foundation of IT and Operational Technology (OT)
- Vertical and horizontal communication culture to overcome silo mentality in business units and in functions

2.3 Define the Vision, Goals, and Priorities

Corporate Vision

The corporate vision, especially in the context of managing digital business transformation, is not merely a statement. It is an essential compass that aligns the organization's strategy, initiatives, and resources towards a unified digital transformation objective. At its core, the vision should reflect the company's overarching ambitions in harnessing digital capabilities and technologies to stimulate and encourage innovation, growth, and success, all while emphasizing sustainability.

Key Aspects:

1. Stakeholder Engagement and Value Delivery

- **Patients:** Beyond being mere consumers, in a digitalized environment patients are now more active participants in their healthcare journey.
- **Healthcare Professionals:** Engaging with doctors, nurses, and other healthcare providers ensures that Pharma 4.0 solutions are practical, effective, and address real-world challenges.
- **Regulatory Bodies:** With the increasing complexity of pharmaceutical processes and products, as well as the use of new technologies, maintaining open channels of communication with regulatory agencies is crucial. This ensures compliance and fosters trust in the industry's commitment to safety and efficacy.
- **Partners and Suppliers:** Pharma 4.0 is characterized by interconnected systems and collaborations. Engaging with partners and suppliers ensures a seamless flow of information, materials, and innovations.
- **Employees:** As the backbone of the industry, employees need to be equipped with the skills, knowledge, and tools to thrive in a Pharma 4.0 environment. Their insights, feedback, and well-being are crucial for sustainable success.

By emphasizing stakeholder engagement and value delivery, Pharma 4.0 companies can ensure that their innovations and initiatives resonate with all involved, fostering trust, collaboration, and a shared vision for the future of healthcare.

2. Agility and Innovation Culture

- **Agility:** In the Pharma 4.0 landscape, agility translates to the capacity of pharmaceutical companies to swiftly adapt to evolving regulatory environments, emerging patient needs, and rapid technological advancements. This agility allows for quicker responses to clinical findings, patient feedback, and market shifts, ensuring that the drug development and delivery processes remain efficient and relevant.
- **Innovation Culture:** Pharma 4.0 is characterized by its emphasis on data-driven insights, personalized medicine, and interconnected processes. An innovative culture in this context means fostering an environment where interdisciplinary collaboration is encouraged, where data is harnessed for continual improvement, and where novel solutions are sought to address complex healthcare challenges. This culture of innovation ensures that pharmaceutical companies can harness the full potential of digital transformation, from R&D to patient engagement.

Together, agility and an innovation-driven mindset position pharmaceutical companies to lead in a Pharma 4.0 era, ensuring they not only adapt to but also shape the future of healthcare.

3. Collaboration Platforms (Internal and External)

- **Internal Collaboration:** In the context of Pharma 4.0, internal collaboration platforms are essential for interdisciplinary teamwork and systematic knowledge management. As pharmaceutical processes become more integrated with digital technologies, seamless communication between departments such as R&D, clinical trials, manufacturing, and marketing is crucial. Platforms that enable real-time data sharing, project tracking, and collaborative problem-solving can expedite drug development and ensure consistency in decision-making. [17]
- **External Collaboration:** Pharma 4.0 emphasizes the importance of expanding the ecosystem beyond the company's walls. External collaboration platforms facilitate partnerships with biotechnological start-ups, research institutions, patient advocacy groups, regulatory agencies, and even other pharmaceutical companies. In an era where personalized medicine and patient-centric approaches are paramount, these platforms can also provide avenues for direct patient engagement, gathering invaluable feedback and insights.

4. Data-Driven Decision-Making

- **In Pharma 4.0, data is essential:** The vision should emphasize the importance of leveraging data analytics to make informed decisions, ensuring efficiency and accuracy.
- **Real-time Insights:** With the integration of IoT devices, sensors, and advanced analytics in Pharma 4.0, companies can access real-time data from various stages of the drug development and manufacturing process. This allows for immediate adjustments, optimizing efficiency and quality.
- **Personalized Medicine:** By analyzing patient data, pharmaceutical companies can tailor treatments to individual needs, leading to more effective and safer therapeutic solutions.
- **Predictive Analytics:** Utilizing Machine Learning (ML) and AI, Pharma 4.0 companies can predict potential challenges in drug development, manufacturing, and distribution, allowing for proactive measures.
- **Regulatory Compliance:** Data-driven approaches ensure that all processes are documented and traceable, simplifying regulatory reporting and ensuring adherence to global standards.

5. Sustainability

- **Eco-friendly Manufacturing:** Advanced analytics and automation can optimize manufacturing processes, reducing waste and energy consumption.
- **Supply Chain Optimization:** Digital platforms can monitor and optimize the supply chain, ensuring minimal waste, efficient transportation, and a reduced carbon footprint.
- **Ethical Sourcing:** Data transparency ensures that raw materials and ingredients are sourced ethically and sustainably.
- **Circular Economy Integration:** Embracing principles of the circular economy, Pharma 4.0 companies can focus on recycling, reusing, and reducing, minimizing environmental impact.

6. Future Readiness and Adaptability

- **Continual Learning:** With the rapid evolution of technology and medical science, Pharma 4.0 companies must foster a culture of continual learning, ensuring that their workforce is always equipped with the latest knowledge and skills.

- **Scalable Digital Infrastructure:** As digital transformation progresses, companies need infrastructure that can scale and adapt to new technologies and increased data volumes.
- **Proactive Risk Management:** Leveraging predictive analytics, companies can foresee potential challenges, from supply chain disruptions to market shifts, and prepare accordingly.
- **Openness to Innovation:** Embracing an open innovation mindset, Pharma 4.0 companies can collaborate with external partners, from tech start-ups to academic institutions, ensuring they remain at the cutting edge of both technology and medical research.

7. The Role of Leadership in Shaping Vision

- **Leadership:** Inspire, guide, and drive the digital transformation vision, ensuring alignment across all levels of the organization.
- **Visionary Thinking:** Leadership in Pharma 4.0 must not only understand current industry trends but also anticipate future shifts, ensuring the company's vision remains forward-looking and relevant.
- **Stakeholder Engagement:** Leaders should actively engage with all stakeholders, from patients to regulatory bodies, ensuring the vision aligns with broader industry and societal needs.
- **Cultural Transformation:** As digital transformation reshapes operations, leadership must also drive a cultural shift, fostering an environment of innovation, adaptability, and continual learning.
- **Workforce Readiness:** Prioritize training programs, workshops, and seminars to ensure that the workforce is equipped to handle new technologies and methodologies.

8. Bridging the Gap between Vision and Execution

- **Actionable steps:** Delve into strategies to translate the corporate vision into execution, ensuring that the organization moves cohesively toward its digital transformation goals.
- **Strategic Roadmaps:** Create clear roadmaps that break down the vision into actionable milestones, ensuring every department and team understands their role in the larger transformation journey.
- **Resource Allocation:** Ensure that the necessary resources, from cutting-edge technologies to skilled personnel, are available to execute the vision.
- **Feedback Loops:** Establish mechanisms to gather feedback from all levels of the organization, ensuring that the execution remains aligned with the vision and can be adjusted as needed.

9. Measuring the Impact of Digital Transformation

- **Metrics:** Explore KPIs that can be used to gauge the success of digital transformation initiatives, ensuring that the company remains on track.
- **Operational Efficiency:** Monitor improvements in drug development timelines, manufacturing efficiency, and supply chain optimization.
- **Patient Outcomes:** Utilize data analytics to track the impact of personalized medicine on patient health outcomes.
- **Innovation Indicators:** Track the number of new patents, research publications, and collaborative projects as indicators of a thriving innovation culture.

- **Employee Engagement:** Measure employee satisfaction, retention, and upskilling rates to gauge the internal impact of digital transformation.

10. Challenges and Roadblocks

- **Cultural Resistance:** Employees accustomed to traditional methods might resist digital changes. Addressing this requires targeted change-management strategies.
- **Setting the Affordable Budget:** Investment approvals typically rely on traditional Return on Investment (ROI) expectations.
- **Budget Allocation:** Determine the budget based on the priorities set, ensuring that critical areas receive adequate funding.
- **Cost-Benefit Analysis:** Regularly assess the ROI to ensure that funds are being utilized effectively.
- **Integration with Legacy Systems:** Many pharmaceutical companies operate with older systems. Integrating these with new digital solutions can be complex.
- **Data Security and Privacy:** With increased digitization comes the challenge of ensuring data security, especially patient data.
- **External Suppliers and Technology Providers:** Use of different proprietary systems and technologies often do not integrate easily with a company's existing infrastructure. This can lead to compatibility issues, data silos, and operational inefficiencies. In addition, limited industry-wide standards are available.
- **Regulatory:** As digital technologies introduce new processes and products, navigating the different regional regulatory landscapes can be challenging.

2.4 Positioning Your Organization/Stepwise Implementation

The following step-by-step approach on how to start and apply fundamental principles applies a Pharma 4.0 maturity assessment in specific functions or across the organization. Based on a corporate strategy and need and identified problem statements, the following steps are proposed:

Step 1: Understand Pharma 4.0 principles and familiarize key stakeholders with the core principles of Pharma 4.0, emphasizing connectivity, data analytics, automation, and digital technology integration throughout the product lifecycle.

Step 2: Develop a common understanding and language to promote effective communication and alignment across the different functions and areas to:

- Apply definitions and examples for each digital maturity level (e.g., Initial, Developing, Advanced)
- Prevent misinterpretation and confusion by fostering a shared vocabulary

Step 3: Conduct the Pharma 4.0 Maturity Assessment (see Appendix 3) to set the baseline in order to understand the current state of the organization.

Harmonize maturity level assessments to ensure consistent assessments across functional areas and sites by:

- Applying standardized assessment criteria relevant to each area's unique characteristics

- Defining common metrics to facilitate meaningful cross-comparisons related to the business needs and cases
- Conduct an “as-is” assessment as evaluated according to the maturity grid to position the functional areas and sites on a Level 1–5 digital maturity scale. This also evaluates each area’s integration level using the positioning approach (Initial to Optimized).
- Define the “to-be” situation to set target maturity levels and transformation initiatives. It is important to outline the digital transformation initiatives, technologies, and practices required to progress from the current to the desired states

Step 4: Set clear objectives for digital initiatives and define quality benchmarks. Formulate a well-defined framework for planning digital initiatives, incorporating identified gaps and opportunities.

Step 5: Start operational implementation by defining an implementation roadmap considering the following subjects:

- Streamline processes, empower people, and install project organization with the goal of optimizing processes for digital readiness and engage employees in the transformation journey.
- Establish Key Performance Indicators (KPIs) to measure progress and success. (Refer to Appendix 4.)
- Perform the regulatory check and risk assessments to be applied based on Industry/Pharma 4.0 principles and on ICH Q9 [18] where necessary.
- Implement technical considerations and new technologies to address data management, systems, monitoring, controlling, and reporting. (Refer to Chapter 10 and Appendix 1.)

By integrating these basic steps, companies can ensure a structured and comprehensive approach, positioning the organization for digital transformation, from understanding foundational principles to operational implementation. This approach will empower organizations to stay focused on their business needs and navigate the complexities of digital change while staying aligned with industry-specific regulatory requirements.

2.5 Different Approaches to Execute the Transformation

There can be a more project-driven short-term approach as well as a broader mid long-term program-based approach. The following sections present the definitions, advantages, and disadvantages for each one.

2.5.1 *Project-related Approach (Short-Term)*

- Classical project organization: Project goal, project organization, project plan, reporting
- Structural capabilities are considered only when in direct relation to the project

Advantages

- Buy-in of short-term ROI possible
- Easier to get budget
- May result in faster proof of concept

Disadvantages

- Lighthouse effect: After the pilot, only limited scalability has been achieved, as transfer to other applications needs a holistic approach

2.5.2 Program-related Approach (Mid Long-Term)

- Digital Transformation is part of the business strategy and not only a technical effort
- Leading idea is that digitalized companies are faster and better
- Data is the prerequisite to adapt new technologies
- Structural capabilities such as culture, organization, processes, resources, and IT are considered in a holistic approach
- The whole value network is subject to the strategy
- The value network is the classical value chain including suppliers of suppliers, all market stakeholders, regulators, and sustainability needs
- Governance is made by creating transparency from data to decision

Advantage

- Company's structural capabilities allow a jump start for many business projects as defined in the strategy

Disadvantages

- Short-term ROI often cannot be construed for infrastructural investment
- High activating energy costs discourages decision-makers from investment

2.5.3 Brownfield versus Greenfield Assets

For brownfield and greenfield assets, different approaches are applied to address digital transformation.

- **Brownfield Assets:** These refer to older facilities or sites that may require upgrades or modifications to accommodate new technologies or processes. They often come with legacy systems, infrastructure, and sometimes cultural practices that need to be considered during digital transformation.
- **Greenfield Assets:** These are new facilities or sites that are built from scratch. They offer the advantage of designing with the latest technologies and processes in mind, without the constraints of legacy systems.

3 Holistic Control Strategy

One of the basic principles of the Pharma 4.0 Operating Model is the holistic approach, especially to the control strategy.

3.1 Rationale for Implementation

There are several issues affecting the supply chain that cause shortages or risks, for example:

- *Force majeure* events damaging the supply chain
- Production problems at API and material suppliers
- Falsified and counterfeit medicines
- Diversification and higher complexity of the supply chains

Added to this are situations in product lifecycle management with the potential for improvement, such as:

- Isolated operating functions at inbound logistics
- Slow reaction time to changed conditions leading to long lead times
- Isolated units or silos between functions for product change management
- Long lead times for product Corrective and Preventive (CAPA) and improvement

The application of emerging and digital technologies may help organizations address these issues by creating more robust and flexible manufacturing processes. This provides the pharmaceutical industry with several benefits, including quicker responses to prevent or address drug shortages, reduce interruptions in production and delivery of medicines, and ensure consistent clinical performance of products.

For example, organizations may receive the benefit of shorter production times from **real-time** process control and product release. However, establishing a process for product realization that is **fully digital and connected** requires real-time data availability for real-time decision-making and continual improvement. Not only must the manufacturing process be digital to ensure all process and product data is available to control the process downstream, but the **supporting processes** such as GMP, Quality Control (QC), and Quality Assurance (QA) processes must also be digital and interconnected with the manufacturing execution control process. Supporting processes include deviation management, change management, and batch review and release. This requires a holistic understanding of how the product is being realized, based on data acquired across the **entire product lifecycle**. The holistic control strategy provides this overview and is therefore an important enabler for establishing novel processes based on emerging and digital technologies.

By digitally mapping the supply chain in the form of a **digital twin**, risk assessments can become robust and less error prone. The digitalization of processes in manufacturing and operations management can provide considerable support in gaining an overview of activities that are sometimes running in parallel or uncoordinated. To avoid this, digitalization should be embedded in the holistic control strategy. Some examples of this are:

- Elements of information can be given by **end-to-end track and trace** and data access to a single source of truth in real time, with digital interconnectivity (gun, Radio Frequency Identification (RFID), e-catalog, vendor managed inventory, customs software, etc.). Blockchain technology can be used to reliably trace **entire supply chains**, preventing counterfeit drugs.

- Enterprise Resource Planning (ERP) link to Building Management Systems (BMS), Manufacturing Execution System (MES), Supervisory Control and Data Acquisition (SCADA) provide “real-time monitoring” to optimize the production process and support the critical supply chain planning and scheduling process.
- Managing biological transports with short shelf life or high cost of damage using GPS follow-up, QR codes, bar code labels/tags of equipment, e-platforms
- Environment, Social, and Governance (ESG) goals can be supported by a transparent view of the overall chain of supply/production/storage/delivery steps and monitor their impact on the environment.

3.2 The ICH-Based Control Strategy

ICH Q10 [19] defines “control strategy” as:

“A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.”

ICH Q8 [20] states:

“A control strategy is designed to ensure that a product of required quality will be produced consistently.”

ICH Q11 [21] continues:

“Every drug substance manufacturing process, whether developed through a traditional or an enhanced approach (or some combination thereof), has an associated control strategy.”

The control strategy is essential as it defines how a product must be manufactured and controlled in line with the Quality Target Product Profile (QTPP) expectations. Control of product and processes are therefore the main focus.

3.3 The Pharma 4.0-based Holistic Control Strategy Definition

3.3.1 Integrated Approach from Development to Market

The Pharma 4.0 term “holistic control strategy” is derived from ICH Q8 [20] and Q10 [19] definitions. The term refers to an integrated approach to product and process lifecycle management, including ongoing change management, to understand all aspects that must be controlled to ensure product acceptability. This approach covers both the development chain where initial Critical Process Parameters (CPPs), Critical Material Attributes (CMAs) and Critical Quality Attributes (CQAs) operating ranges are defined as well as commercial manufacturing with the control strategy at scale and operation in a GxP controlled environment.

The holistic control strategy also covers activities of the process equipment, utilities, supply chain and facility. These activities typically relate to product protection and are defined through a set of GMP requirements including those to minimize the risk of product contamination (contamination control strategy), equipment control and instrument calibration, operator actions, etc. Also support of preventive and even predictive maintenance is in focus.

The holistic control strategy can be refined further for commercial manufacturing as new knowledge is gained. The gained knowledge can be captured from numerous sources such as open-source information, literature, changes, new technologies, and manufacturing history. These changes could include acceptance criteria, analytical methodology, or the points of control (e.g., introduction of real-time release testing). Internal and external signals should be considered, such as feedback from the market and all stakeholders using the medication. The knowledge is improved over the lifecycle of the product as more information becomes available such as trends over time.

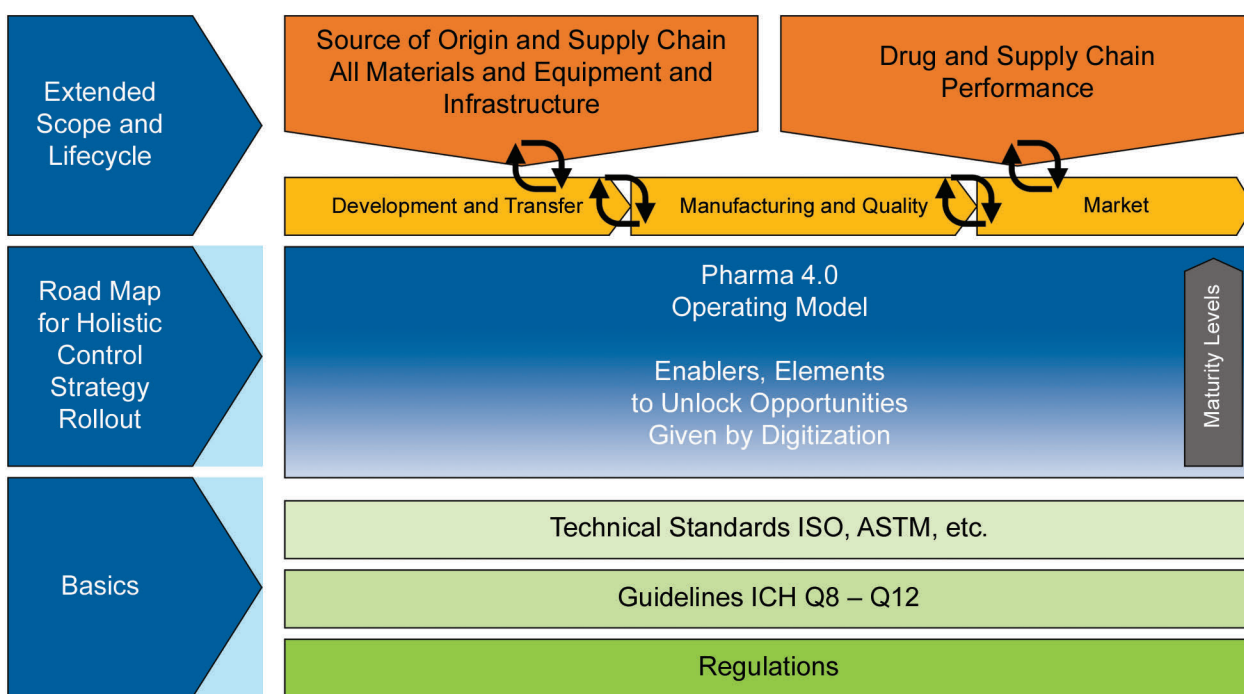
Continuous process verification enables monitoring of the process in real-time and adjusting the process and/or the control strategy as appropriate. When multivariate prediction models are used, systems that maintain and update the models help to ensure the continued suitability of the model within the control strategy.

Thus, the holistic control strategy targets all stakeholders, from the marketing and manufacturing authorization holders to the patient, from clinical to manufacturing to supply, and from regulatory to quality. The holistic control strategy is enabled by digitalization of processes (manufacturing and management) used for product realization, the necessary data are managed in real time, fully transparent, and available for sound real-time decision-making, improving quality and manufacturing process efficiency and accuracy. (See Figure 3.1.)

Therefore, the holistic control strategy ties regulators, industry members, and patients together in an overall holistic value network structure driven by the Pharma 4.0 operating model.

Figure 3.1: Scope, Basics, and Roadmap for a Holistic Control Strategy [22]

The parts of the supply network are connected in real-time and in iterative approaches.



3.3.2 Process Understanding, Data, and Digitalization as a Basis

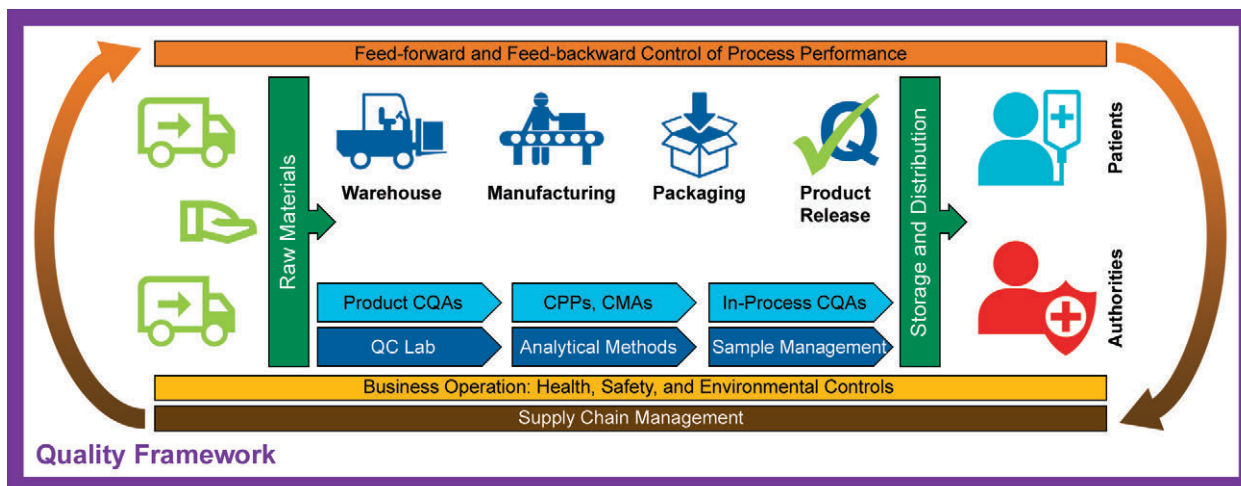
The holistic approach includes parameters typically decoupled from the understanding of process variability, going beyond the usual parameters considered during the development of a pharmaceutical product. An example is the impact on manufacturability and product quality of a change in the supply network. Specifically, the holistic approach addresses all events that happen throughout the lifecycle of the product, including the supply chain and patient needs and response to treatment and product quality.

A more detailed view of the classical supply chain is given in Figure 3.2. This figure shows all elements and processes that represent a source for generating measurable parameters to control product acceptability and product availability. Suppliers are fully integrated in the “upstream supply chain” as well as patients and all other stakeholders in the “downstream supply chain.”

Quality in this figure is understood in the sense of Total Quality Management (TQM), going beyond GMP, as well as in the understanding of Philip B. Crosby in the 1960s that “all work is process” and therefore measurable and therefore also controllable. [23].

Figure 3.2: Holistic Control in the Supply Chain [24]

In the supply chain, the holistic control strategy represents all controls across the entire supply network that ensure product acceptability, availability, and improvement.



3.3.3 Data-Driven Decisions

A holistic control strategy enables data-driven decisions on all aspects of the pharmaceutical product lifecycle while maintaining product safety, efficacy, and quality for the patient. It spans development, operations, supply chain, and regulatory systems, and addresses market surveillance, drug demand, and secure drug supply.

In a holistic approach driven by digitalization, a Pharmaceutical Quality System (PQS) becomes effective and efficient by creating and using real-time information for decision-making driven by data.

3.3.4 Use Cases

3.3.4.1 Supply Chain, Packaging, and Logistics

Systems for inbound logistics, available in the market, describe raising dormant potential through process management and process simulation. They describe decentralized decision-making processes, a suitable incentive system, and flat hierarchy as the operational framework condition.

The potential problems to be eliminated include:

- Identifying missing manufacturing components
- Preventing the buildup of excessive inventories
- Preventing capacity bottlenecks
- Preventing underutilization of equipment and staff
- Identifying impending bottlenecks in order-relevant resources such as personnel, equipment, and maintenance

The most important measures are:

- “What if” considerations detached from operational dispositions and control
- Synchronized preliminary review of all resources before primary needs are made real



- Integrated simulation of upstream work centers such as order processing, work preparation, document preparation
- Integrated simulation of interference and downstream workstations such as in-process control and QC, batch release
- Short simulation times of all bills of materials
- Identification of impending bottlenecks on all workstations, filtering of relevant information and data
- Programming of bottleneck elimination and focused resource identification over a chosen planning horizon (performance modeling)
- Inclusion of workarounds, special processes in manufacturing and distribution

Digital Twin as a Simulation Tool

A digital twin is a digital representation of a physical system. In the supply chain, for example, the following facts could be represented:

- Logistical and management processes
- Operational planning and line allocation
- Stock in-house and at suppliers
- Planning principles for demand allocation
- Inventory management
- Decision-making processes of planners and management

If the supply chain is digital, changes can be made based on testing the impact of the change determined from stress testing the model, for example:

- Fluctuations in demand
- Fluctuating material availability
- Increasing material or energy costs

By doing so, it is possible to see how the reactive and proactive countermeasures work and how best to mitigate risks.

Mitigation is managed in three steps:

1. **Network Planning of Ideal Scenarios:** A digital representation of the end-to-end network is used to simulate how the forecast demand for the next few years can be served, including the optimal allocation of demand or forecast including restrictions on production, transport, and inventory. Stress tests can be run against this ideal scenario.
2. **Stress Tests:** The impact of disruptions can be assessed by making critical resources and vulnerable processes visible. For this purpose, the disruptions of the supply chain processes are described in disruption profiles, where assumptions are made for capacity or delivery disruptions. It is then possible to see where countermeasures are needed and what effect they have on the entire network.

3. Mitigation Options: Using the knowledge gained from the stress test, a mix of preventive measures can be identified, for example:

- Dual sourcing
- Additional capacities in production and transport
- Stockpiling and risk levels
- Regulatory implications, e.g., change management
- Preparation of alternative scenarios, e.g., supply agreements, quality agreements

These functionalities should be mapped in the digital twin. Other functionalities in the digital twin may include [25]:

- Resource requirements
- Investment requirements

3.3.4.2 Digital Solutions for Master Data Management

Master Data Management (MDM) is the process of creating and maintaining a single master information set, or “single source of truth,” for each entity (resource, product, location, asset) actively contributing to the company value and supply chain. Master data is the set of identifiers and related attributes that describe the core entities of an enterprise including customers, suppliers, sites, resources, assets, raw materials, finished products and their key regulatory and quality characteristics. All this is managed in order to ensure the uniformity, accuracy, stewardship, semantic consistency, and accountability of the enterprise’s official master data.

These sets of data are traditionally managed by different organizational silos (Planning, Regulatory, Quality, Production, Supply Chain, etc.) with diverse digital applications and sources of truth, opening the risk of discrepancies and duplications. More and more pharmaceutical companies, also pushed by upcoming regulations, are working toward Identification of Medicinal Products (IDMP) by EMA [26] and introducing new digital solutions of MDM that allow adequate management of company-wide master data in a single point of truth.

Benefits of MDM digital solutions reside in:

- End-to-end track and trace and data access (single source of truth) in real time, with interconnectivity to digital solutions (gun, RFID, e-catalog, vendor managed inventory, customs software, etc.).
- Securing trust in master data by users in multiple departments
- Supporting quick and data-objective decision-making
- Avoiding duplication and increasing data quality and accuracy
- Reducing security risks and ensuring better compliance

An important part of these information sets, such as medicinal products and their raw materials, are GxP critical, so that MDM digital solutions must be designed, implemented, and tested under the established computer system validation principles (GAMP [7]).

Despite these important benefits, digital solutions for MDM are by nature complex as they need to break many technical and organizational silos. They usually require high integration and maintenance efforts to ensure the needed data accuracy is achieved, which can lead to high project costs and longer timelines than expected.

3.3.4.3 The Falsified Medicines Directive for the International Supply Chain

The Directive 2011/62/EU of the European Parliament and of the Council from 2011 [27] stated: *“There is an alarming increase of medicinal products detected in the Union which are falsified in relation to their identity, history or source. Those products usually contain sub-standard or falsified ingredients, or no ingredients or ingredients, including active substances, in the wrong dosage thus posing an important threat to public health.”*

For certain products, mass serialization with 2D barcodes, in connection with tamper-evident seals for the products has been introduced in the countries of the EU. This allows product authentication to be carried out along the supply chain. This was only possible using standardized product numbers, through the interoperability of data and their digital transmission to a centralized hub.

3.3.4.4 The ISPE Drug Shortages Prevention Model

Within the ISPE Drug Shortage Prevention Plan [28], three top priorities are identified (Figure 3.3) that can be realized with digital support:

- Transparency through connected communication with all stakeholders along the supply chain
- Stockpiling policies harmonized between suppliers and manufacturers
- Risk management planning between all connected stakeholders: suppliers, manufacturers, distributors, and regulators

Figure 3.3: ISPE Drug Shortage Prevention Operating Model [28]



4 Quality Management in the Digital Age

The purpose of this chapter is not to describe a new quality system. Rather, this chapter describes the opportunities opened by digital transformation in quality management following the Pharma 4.0 principles. The following areas are in focus:

- Digitalization and general principles of quality management
- Quality and performance monitoring
- New way of working with a digital, big-data driven quality management
- Quality culture in digitalized environment

The foundation for quality management that this chapter builds on are found in sources such as ICH Q10 [19], the ISPE APQ Guide Series [6], Quality Management Maturity (QMM) Initiative of FDA [29], and others.

4.1 Need and Opportunity

In light of the ever-increasing complexity and instability of global supply chains and new concepts for drugs and dosage forms in personalized medicine, ATMPs, and cell and gene therapy, new operational concepts for manufacturing, logistics, and quality management are needed. Here, digitalization offers an opportunity for the challenges of operations management. Digitalization can also bring benefits for traditional medicines in terms of efficiency, Operational Excellence (OPEX), and cost management.

4.2 Digitalization and General Principles of Quality Management

4.2.1 *Pharma 4.0 Principles in a Digitalized Environment*

In a digitalized quality management environment, the following principals are important:

- Compliance with regulations (the starting point must be an inspection-proof quality system)
- Real-time information (the right information at the right time to the right people)
- Connected systems and services
- Mature operating model (resources, information systems, organization and processes, culture)
- Holistic view of the lifecycles (product, process, data, environment, equipment, factory, etc.) and the operations value network. The operations network in this sense is all processes and all stakeholders along the supply chain, including process development, all subprocesses, and all sub-suppliers; it is a wider focus than the classical end-to-end supply chain.
- From a retrospective view to a prospective view of prevention, prediction, and adaptation
- From “documents orientation” to “data orientation” (quality requirements become targeted, executable instructions, managed as modular information units/structured content fully connected and transparent)

4.2.2 Strategic Goals

Often, the root cause of deviations is “human error.” Digitalized processes will provide better user guidance, which will reduce quality issues induced by misunderstanding, lack of education, and lack of training. Using a mechanistic understanding of processes and products through a holistic overview and digitally supported knowledge management, regulatory compliance can be sustainably improved.

To achieve this, organizations need a better understanding of deviation sources and to correct, prevent, and mitigate the root causes to reduce recurrence.

4.2.3 Digital Tools

The purpose of this Guide is to give an overview of where digitalization can be used and what are the leading principles to use it. Even if many of these elements in some companies are used in a more or less connected way, a systematic approach starting with data management and structural capabilities as described in other chapters of this Guide is needed before starting digital transformation.

A pure technical approach will not be sufficient.

Digitalization allows the principles of quality management, such as fact-based decisions, traceability of results, GMP-compliant documentation, monitoring of processes, and others, to be brought to a higher level of efficiency and sustainability, and a lower error rate. This higher level is achieved through real-time information and preventive and predictive elements. Technically, this is achieved through:

- End-to-end integrated systems and services
- Common work platforms for the people involved in the process
- Technical sensors that transmit real-time data from equipment
- Automated manufacturing processes taking over routine work from employees to free them up for higher-value activities
- Large amounts of data are processed by computers and stored in the cloud, accessible at any time and transparent for all decision-makers
- User-friendly devices that keep work instructions up-to-date and accessible to all relevant personnel at all times
- Simulations, e.g., of planning processes, can ensure rapid adaptations to the reality of production
- Digitalized processes can be standardized and used to harmonize manufacturing and quality between sites producing the same product, as well as improve technology transfer
- AI and data image analysis can capture potential breaches/risks of noncompliance from operations through surveillance

Using advanced data analytical approaches are by no means restricted to innovation in the QC space but are widely utilized as part of the digital transformation in many areas in pharmaceutical manufacturing, such as rapid root cause investigation, process development and optimization, planning and scheduling, etc.

Improvements utilizing digital solutions are available for other areas of QC. In terms of reducing lead times and eliminating waste, digital opportunities can be identified in sample and capacity management (e.g., scheduling tools), seamless data flow avoiding time-consuming reporting on paper (paperless lab), review by exception, and in the overall digital release process including country-specific aspects for the final quality approval decision.

4.2.4 The “Digital” Quality Manager

Digitalization will also shorten the time needed to complete many classical QA tasks, for example, resolving deviations and Out of Specification (OOS) (if they may occur at all in a digitalized world), and processing and/or handling CAPAs and changes.

This will have a huge impact on the job profile of a QA employee for the future. Today it is expected that QA personnel lead the company with their knowledge of regulations. In the future it may be important to have also a profound knowledge of statistics and the application of statistical methods. Additionally, QA managers may need to be knowledgeable in software validation methodology and the corresponding issues/limitations, etc., for specific applications.

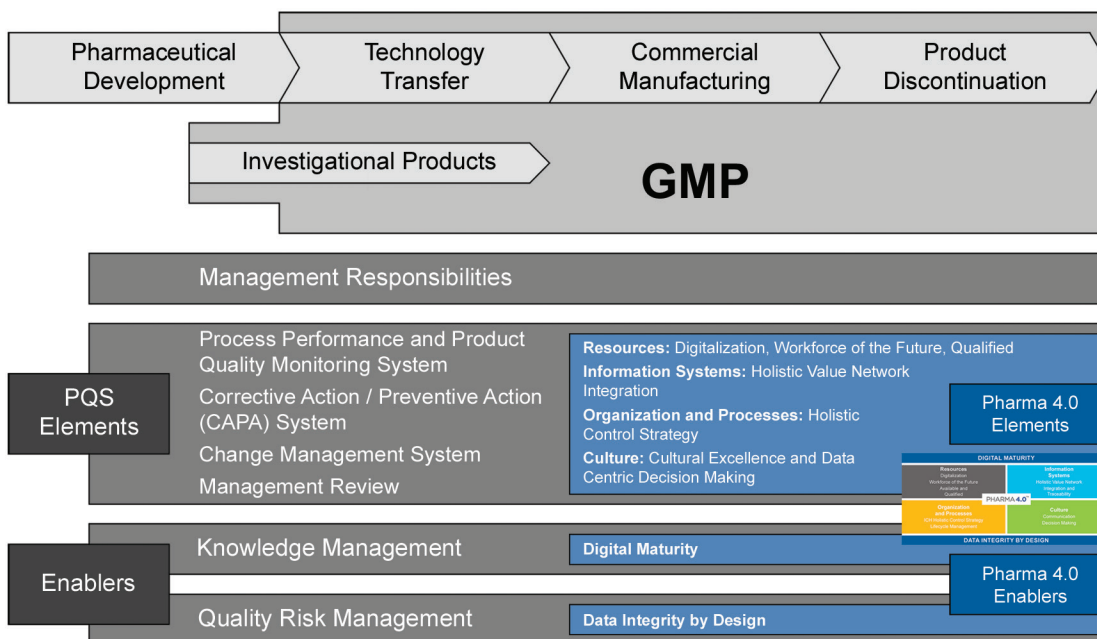
The “digital” Quality manager must think and act in a process-oriented manner. The Quality manager is part of the system, not its boss, coordinating experts and stakeholders, not only managing checklists.

Process thinking also emphasizes the importance of understanding and managing the interdependencies between different processes, which can help ensure that processes are aligned and working together effectively to achieve common goals. This can help prevent quality issues and ensure that processes are compliant with regulatory requirements.

4.2.4.1 Elements and Enablers of a Digitalized Quality Management System

The currently valid principles for quality systems, as laid down in legal regulations, form the starting point for the digitization of a Quality Management System (QMS). The QMS model described in ICH Q10 [19] is supplemented by additional enablers as well as additional elements in a digitized environment. (See Figure 4.1.)

Figure 4.1: Extended ICH Q10 Pharmaceutical Quality System (adapted from ICH Q10 [19])



4.2.4.2 New Enablers

In a digitized and “data-centric” approach, two additional enablers are necessary: digital maturity, as described in Chapter 1 of this Guide, and data integrity by design, that is, structured and standardized data suitable for transmission (interoperable). For more information on knowledge management, see Chapter 2.

4.2.4.3 New Elements

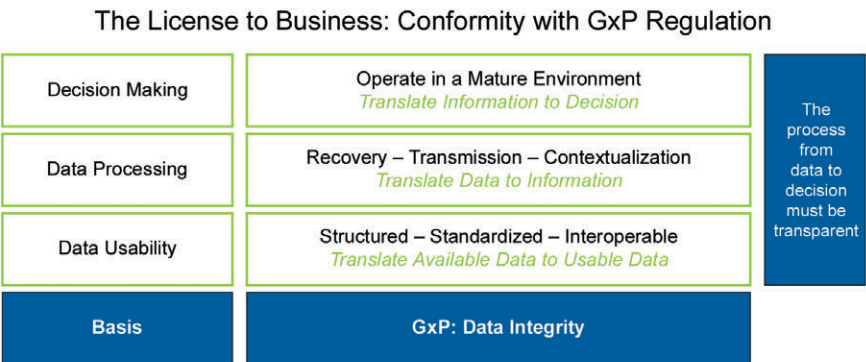
Digital transformation is not a “technical project” but a journey in which organizations routinely assess and advance/maintain their level of maturity to realize the benefits of technological enhancements and organizational cohesiveness. It requires a number of prerequisites described in the Pharma 4.0 Operating Model. Each quadrant in this operating model requires its own maturity scale to create the conditions for digital maturity. The old phrase of computer coding applies: “garbage in – garbage out.”

For quality management, this means that a quality system that meets regulatory requirements must be in place before going digital.

4.2.5 How Digitalization can Support the Implementation of ICH Guidelines

The primary source or starting point for the digitalization of a process is data and how data is utilized. To maximize the use of data and the efficient evaluation of data will be key in the future for the pharmaceutical industry (as described in Figure 4.2).

Figure 4.2: Principles of Data Management in Pharma 4.0



“Compliance” means the GxP principles not only with checklists.

Implementing the guidance presented in ICH Q8 [20], Q9 [18], Q10 [19], Q11 [21], and Q12 [30] can be enhanced and improved through digitalization.

ICH Q8 – Pharmaceutical Development [20]

ICH Q8 [20] describes how Pharmaceutical Development can take place in a systematic manner: the Quality by Design concept. This encompasses, among others, the identification of CQAs, CPPs, and CMAs to develop a control strategy. The control strategy supports the establishment of the Design Space, which is a “*multidimensional combination and interaction of input variables.*”

Establishing the design space may require complex mathematical modeling. For these operations, huge computing power with the appropriate software is needed to achieve a robust result, and for data that comes from different platforms, the interchangeability of data among these platforms must be guaranteed. Processing large amounts of data is the precondition for conducting the design space and moving toward higher process robustness.

ICH Q9 – Quality Risk Management [18]

Digitalization is also necessary for the application of Quality Risk Management (ICH Q9 [18]). Currently, risk assessments are usually conducted based on the experience of individuals. This is very subjective and relies on personal factors. Having the ability to assess large amounts of data can lead to a much more consolidated judgement than is possible for an individual.

Hazard and risk analysis protocols in risk management can also be digitalized.

ICH Q10 – Pharmaceutical Quality System [19]

The PQS described in ICH Q10 [19] lists Knowledge Management as one enabler.

Knowledge management will prove to be one of the most important factors in the future. Knowledge management is an approach to make data usable. Data as such is meaningless, just numbers and text. To turn it into usable information it must be put into context. When this information is correlated, it becomes knowledge. The more data that can be accessed and contextualized, the more consolidated and up-to-date knowledge is provided for (human or electronic) decision-making. This is the last step in the knowledge management cascade and leads to improved situations. Without a digital system it is extremely difficult to utilize the huge amount of available data to come to a consolidated conclusion.

Another item discussed in ICH Q10 [19] is the execution of the Management Review. Often departments use Excel sheets and slides to compile results for a management review, which, depending on the size of the company, may occur monthly. During these reviews, management decides where to distribute resources among the respective units. Digitalization will provide the company with the necessary data available on a real-time basis. There will be no need to wait until the next management review meeting; a decision can be made ad hoc with all involved.

ICH Q11 – Development AND Manufacture OF Drug Substances [21]

ICH Q11 [21] focuses on maintaining lifecycle management. *“The development and improvement of a drug substance manufacturing process usually continues over its lifecycle.”* This means that process performance and control strategy are routinely assessed and improved/adapted through the knowledge management cycle as shown in Figure 4.1. This leads to Continuous Process Verification (CPV). Therefore, a systematic approach to manage all the data (knowledge) through the lifecycle is needed. Lifecycle management comprises the provision of data starting in the development phase and throughout commercial manufacturing. It also includes experience with other products or new technologies. The “open-source” approach, as used by more and more companies, is very helpful in this respect. Overall, a repository is needed where all available data is pooled.

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management [30]

The interface between industry and regulators on one side and assessors and inspectors on the other side are discussed in ICH Q12 [30]. Besides effective communication between assessors and inspectors, a standardized interface of exchanging data/information between regulators and industry is needed. ICH Q12 provides the respective tools. Appropriate mechanisms to share knowledge and information between industry and regulators will facilitate communication between the parties. This interaction can be done by electronic systems and does not need to be based on human interaction.

Digitalized processes can be standardized and used to harmonize manufacturing and quality across sites.

Overall, the ICH Guidelines [5] provide encouragement for the pharmaceutical industry to move toward Pharma 4.0: the guidelines as of today enable the application of digitalization in the industry. In turn digitalization will enable industry to meet regulations (see ICH Q8 [20]) in a more sophisticated way (see also Chapter 6 of this Guide).

4.3 Validation 4.0

Generally, validation demonstrates that the manufacturer has control over products and processes. It must be done from the beginning (or “by design”), in an iterative manner, and needs as a prerequisite a profound understanding of the process.

The common goal of digital transformation and the creation of a state-of-the-art control system with *real-time control elements* is to achieve simplified and robust processes with a higher degree of automation and digitization targeting *less manual interaction*. Consequently, attaining this goal would reduce the chance of human errors, produce faster and more responses, reduce the number of deviations, and enable a higher and more robust level of quality assessment.

Currently, there is a shift from *check now and periodically recheck* to **continuous verification**, from **static and finite documents as records** to **live, dynamic digital records** that can provide real-time intelligence, from *need to know* to *visible and available to all*, enabling a broader ability to make informed decisions.

Validation 4.0 is the approach that there is a *continuous cycle* of development, risk assessment, risk control, and evolution. It is this continuous cycle that results in a growing knowledge base of interdependencies between the current operating state, the risks associated with that state, and the controls that provide good quality.

4.3.1 Basis of the Pharma 4.0 Operating Model

The Pharma 4.0 operating model comprises the four elements Information Systems, Culture, Organization and Processes, and Resources and the two enablers Digital Maturity and Data Integrity by Design. Validation 4.0 is an application of the same operating model but applied to validation.

Digitalization allows the breakdown of processes and ultimately control strategies to the data level. Data is the foundational aspect of the characterization of products and the resulting decision-making associated with release to patients.

The power and potential of data connectivity, real-time transparency, running simulations, and broad and deep analytics to understand root cause and detect patterns, brings strong power and capability into quality management and validation, and enables process understanding.

4.3.2 Stepwise Approach

Supported by digitalization, visibility of more data is achieved any time when needed. And data is central to this operating environment.

There are four main aspects to Validation 4.0

- Quality by design
- Data integrity by design
- Integrated environments
- Records capture and information

Quality by Design: The basic premise is “by design,” which means this process needs to start early in order for the design to build in quality and achieve process understanding based on accurate data. Here, quality refers to both building the right product and ensuring the product is built right. For details on Quality by Design (QbD) refer to ICH Q8 [20]. This is a foundational aspect to validation because the basic premise of QbD is to iteratively develop pharmaceutical products through repeat cycles of characterizing product and process aspects via risk management.

Data Integrity by Design: Data is now the central point of control. The newer technologies and Pharma 4.0 itself are characterized by increased data flows and connecting data from many/all sources. See Chapter 2.

Integrated Environments: Data coming from many different sources is integrated: product-related, process-related, machine-related, and infrastructure-related (e.g., HVAC, media: water, steam, air).

Records Capture and Information: There are many controls that can be accommodated by the functionality of modern tools such as automatic attributability and the ability to perform verification in place of a second operator. The use of these technologies can also enable review by exception in many areas, leaving the experts who typically do these activities free to do higher-value activities.

4.3.3 Practical Steps

Starting with **process maps** (refer to Chapter 7) as early in the development process as possible provides a good foundation for documented QbD. In the early phases of new product development, the process flow can be a rudimentary view of the basic building blocks of any process.

This provides a great foundation to perform **risk assessments** at the data level. Here ICH Q9 [18] can be applied for each data type identified.

The iterative cycles of this process will provide more knowledge about what is important to control and what might not be as important for this particular product/process. The collective view of all the controls defined becomes the overall **risk control strategy** for this process/product.

As the control strategies are an output of iterative QbD and data integrity by design through QRM principles, the validation focus shifts toward a *documented demonstration* that the control strategy is in place and effective. This is the ultimate control.

As the maturity of this approach increases, organizations can start to *incorporate data and information from beyond the manufacturing process* to increase the robustness of process understanding. For example, raw material fluctuations that impact the process.

There also may be some *pharmacovigilance data* that can be correlated to particular process shifts that can be incorporated into the feedback loop.

4.4 Real Time Release Testing

With a focus change in pharmaceuticals toward more biotechnology, personalized medicines, and new treatments, which require new ways in how quality is monitored, managed, and assured, real-time analytical approaches are attracting new attention and interest.

Real Time Release Testing (RTRT) is a control-strategy approach relying on different technical and digital enablers. Since the QC process is no longer decoupled from the manufacturing steps, manufacturing and QC systems need to be fully interconnected. Furthermore, process analytical sensors, which are generating high amounts of release-relevant data, need to be fully integrated into IT/OT systems. Therefore, the overall automation architecture needs to reflect and support the use of new on-line analytical capabilities, which can be utilized in advanced process control and real time release approaches. Examples of RTRT applications are continuous manufacturing and process intensification for biologics.

Examples of such types of process analytical sensors are spectroscopic methods based on Near Infrared (NIR) or Raman instruments, which are routinely used in unit operations for the manufacturing of small or large molecules. In the case of RTRT these systems require a robust data flow. This starts with the collection of spectral raw data and continues with quality predictions executed by validated model and is completed by a compliant transfer of the release-relevant prediction values into GMP systems like MES and Laboratory Information System (LIMS). These systems will be responsible for issuing documents where the predicted quality attributes are reported, e.g., Electronic Batch Record (EBR) and a CoA, for a final release decision.

Predictive models are an essential element of a spectroscopic-release method. In the majority of use cases, vibrational spectroscopy is applied together with classical chemometric algorithms like PLS/PCA. Currently these chemometric modules are available as Commercial Off the Shelf (COTS) solutions, either from the instrument vendor or from companies providing these data analytical solutions. With the further development of new approaches in terms of AI, new algorithms and new open-source software platforms are attracting more attention particularly in R&D departments, which for final implementation in a GMP environment would pose new and different challenges.

4.5 Quality and Performance

4.5.1 *Current Isolated Quality Reporting*

Reporting is a central element of quality governance. Many quality system processes such as deviations and CAPA management or complaints and recalls handle their own reporting. Often, only statistics are reported, but not the progress in processes or projects. For this purpose, separate project progress reports are kept. Since a product is often the subject of several quality reports from diverse perspectives stored in separate systems at the same time, there is often no consolidated overview from the product point of view.

Additionally, activities to improve quality sometimes run in parallel in several departments and functions: in development, operations, QC, and their sub-functions and initiatives. In addition, improvements are often carried out simultaneously on raw materials, active ingredients, and formulations, which can have a reciprocal influence. Added to this are activities run in parallel reporting systems in engineering, IT, QC, as well as in projects and initiatives. Thus, it is often difficult to get an overall view of the quality situation of a product, a production unit, a plant, or a site.

Since the functional organization in most companies also creates “information silos,” it is difficult to get a cross-functional transparent picture of how a product or an entire factory is doing. This all leads to observations in GxP inspections that much of the potentially available data is not used systematically for decision-making.

Digital transformation can help eliminate information silos and improve data sharing and communication between departments, especially when the organization works toward a community and mission-oriented focus.

4.5.2 *Prerequisites for Pharma 4.0 Quality Reporting*

The digitalization of quality reporting needs the prerequisites derived from the Pharma 4.0 Operating Model (see Appendix 3):

- General
 - A rigid cross-functional data management process implemented
 - Data integrity regulations have been fully implemented and audited
 - Good track records for GxP inspections
- Organization and Processes
 - Technical processes defined
 - Organizational processes cross-functionally defined
 - Data contextualized
- Resources
 - Qualified and trained system owners available
 - Data science analysts available
 - Machines and equipment equipped with sensors/interfaces
- Information Systems
 - Data recovery and transmission is GxP compliant

- Data archiving and backup is GxP compliant
- Quality Culture
 - Quality policy addressing data and process orientation, silo breaking
 - Management commitment that can be measured
 - Open dialogue with all stakeholders including regulators practiced
 - TQM, continual improvement, total preventive maintenance anchored in the organization

4.5.3 Holistic View on Performance

Companies need to take a holistic perspective that considers global health authority expectations and considerations for their network of sites.

Before digitalization, organizations should move away from single dimension performance measurements. The drawback of measuring performance in only one dimension, or even a single KPI, is that every effort will lean toward it, neglecting other shortcomings or even have a deteriorating impact on other dimensions. What counts is the total optimum not the total of individual optima. Therefore, covering various dimensions of performance is an essential aspect of performance measurement systems. A KPI system should work as a net that spans a wide range of performance, leaving no blank areas.

Therefore, one should avoid silo suboptimization but rather look at the entire value chain.

4.5.4 From Lagging KPIs to Leading and Predictive Power

Performance measurement is nothing new. The Balanced Scorecard (BSC) article from Kaplan and Norton in the Harvard Business Review was published in 1992 [31]. Yet the questions of what to measure using what KPIs are still very dominant ones. KPIs are sought to be “leading” instead of “lagging,” which is instead of knowing what has happened, knowing what will happen by solely measuring a single KPI or compiling a KPI system with “leading” only metrics.

A KPI needs to be set into context, determining a specific goal toward which the KPI should “lead.” The reason is that “leading” in this sense means “predict,” and the more a specific goal is defined, the better a KPI can be developed to be leading or predictive. In fact, very often leading KPIs are rather “simple” metrics, such as absolute numbers or forecasted numbers of a particular entity, rather than complexly calculated ratios.

4.5.5 Where Digitalization can Help

Hence, to reap the benefits of a leading KPI, it should be reviewed regularly and have mechanisms in place to act upon them. Advanced analytics, such as ML models, provide more opportunities to detect predictive powers in KPIs. Since these ML models can better reflect complex reality and relations, they are superior to simple linear regression models and can reveal hidden patterns. In the future, such models will add real predictive power to KPIs. The question remains, how these findings and models will be integrated into a review system to translate insights into action.

The digitalization of data to be used in a reporting system allows for new kinds of analysis with multiple benefits. Higher data volumes can be reviewed in less time. Accessibility to data increases. Contextualized data adds explanatory power and facilitates drawing conclusions and taking decisions. By consolidating data, holistic views can be taken, for example:

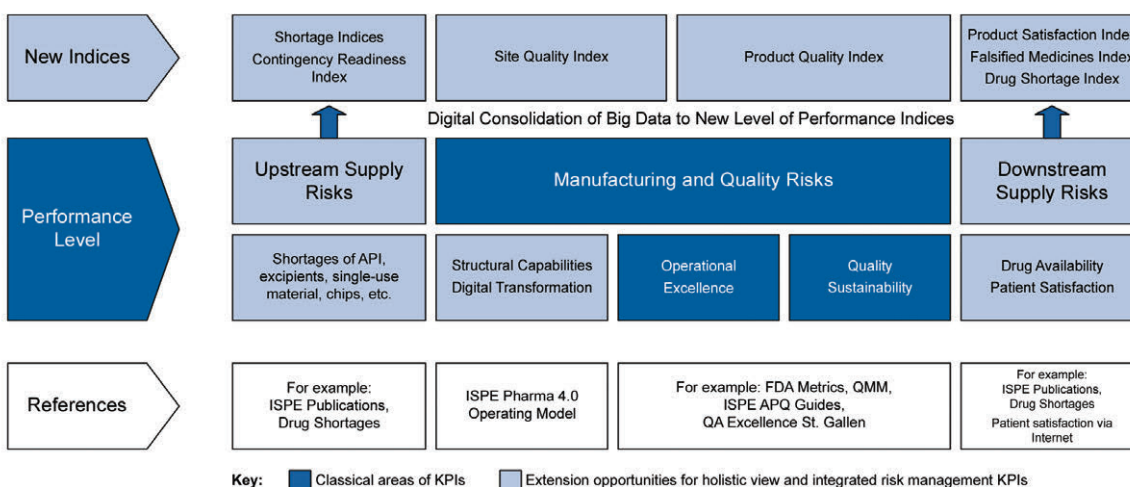
- The overall view of a **product**, its quality, its regulatory status in change management related to all target markets and related to the product lifecycle

- The overall view of all **GxP-related processes**, their performance, and their lifecycle
- The overall view of the **PQS and site/factory** with all controlled documents on infrastructure, environmental monitoring, preventive maintenance, etc.
- The overall view of **upstream supply chain performance/resiliency** with supply risks across all components and impending bottlenecks
- The overall view of **downstream supply chain performance/resiliency** with the overview of drug availability at the patient level and customer satisfaction
- The overall view of **pharmaceutical risk management** to ensure the supply of medicines, including the necessary measures for contingency and backup solutions
- The overall view of **structural capabilities for digital transformation readiness** as shown in the Pharma 4.0 Operating Model: resource, organization, processes, IT and new technologies, and culture.

This can and should be built based on the currently available concepts of performance measurement for manufacturing and quality, OPEX, quality metrics, QMM, advanced pharmaceutical quality, etc. (see Figure 4.3).

Figure 4.3: Digital Transformation applied to the Holistic Control Strategy

Digital Transformation applies the Holistic Control Strategy to a wider scope, including performance measurement of structural capabilities and supply risks.



From Reporting to Decision-Making

Data is the basis for decisions. Only in the context of its origin, definition (if necessary), and other data is its reliable information for decisions. It is therefore very important to be able to transparently trace the path from data to information as the basis for decisions. This is GxP-relevant in the true sense and thus the subject of audits and GxP inspections.

4.6 New Ways of Working in Digital Quality Management – Quality 4.0

4.6.1 Principles and Role of a Pharma 4.0 Quality System

Quality 4.0 involves implementing a **connected QMS**, that is, integration of advanced technologies, such as the IoT and AI, into pharmaceutical quality management processes and systems.

The connected QMS can enable real-time monitoring and analysis of data from multiple sources, such as manufacturing equipment, raw materials, and finished products. This can help to identify potential quality issues early on, allowing for rapid corrective action and continual improvement.

The connected QMS can also facilitate the automation of certain quality processes, such as testing and inspection, which can reduce the risk of human error and improve efficiency. Additionally, these systems can enable the use of predictive analytics and ML to identify trends and patterns in quality data, which can help prevent quality issues from occurring. In summary:

- Data-driven intelligent information management system providing the right information at the right time
- Connected systems and services, globally if necessary, toward seamless exchange with external partners, suppliers, market stakeholders
- Seamlessly integrated into operations, e.g., ERP, MES, QMS, LIMS, etc.
- From retrospective QC to proactive solution provider

4.6.2 Technical Features and Capabilities

An electronic QMS (eQMS) can enable a holistic control strategy by providing a framework for ensuring the safety, quality, and efficacy of products throughout the product lifecycle. These systems involve establishing clear processes and procedures for every stage of the product lifecycle, from raw material sourcing to distribution and use. Some specific ways in which an eQMS can support a holistic control strategy include:

- Establishing and documenting processes and procedures: eQMS can create, document, and manage the various processes and procedures involved in the product lifecycle.
- Tracking and monitoring quality data: eQMS can track and monitor quality data, such as test results, defects, and customer complaints, to identify trends and potential issues.
- Facilitating regulatory compliance: eQMS can manage and track regulatory submissions and other compliance-related activities, to ensure compliance with relevant health authorities, regulations, and standards. By building a bridge between Regulatory Affairs and Quality/Operations functions, real-time information flow can ensure that always current versions of manufacturing and quality documents are used.
- Supporting continual improvement: eQMS can identify and track opportunities for improvement and monitor the effectiveness of improvement efforts.

Overall, eQMS can provide a centralized platform for managing and tracking the various processes and activities involved in a holistic control strategy in the pharmaceutical industry. In summary:

- Automated executable workflows
- Process mapping toward the end-to-end automated process landscape
- Intelligent targeted content management
- Performance measurement
 - Connected data
 - Customizable dashboarding

- Real-time data oversight
- Computational power and intelligence
 - Big data, AI, analytics, simulations, insights
- UX, user-friendly and mobile applications
 - Augmented Reality (AR), Virtual Reality (VR), tablets, smart glasses, chatbot

4.6.3 Possible Applications

- Dashboarding (see Appendix 4)
 - Product and process performance
 - Quality system and site performance
 - Supply chain performance and risk management
 - Digital transformation readiness (Pharma 4.0 Operating Model)
- Deviation, root cause, CAPA management
- Complaints, recall management
- Audits and inspection management
- Standard Operating Procedure (SOP) management
- Learning management

4.6.3.1 Deviations, Root Cause, and CAPA Management

Deviations are part of daily production. The key is to quickly detect them, analyze them, and determine whether they are critical to the process or quality.

Deviation management is very often managed in a retrospective manner, where root cause analysis and review are conducted on a periodic basis. In Quality 4.0, this evolves by using real-time monitoring and data analytics and algorithms to identify potential deviations from established processes within the design space before they occur.

Consequently, CAPA can be implemented in a timely manner, based on data-driven insights and analysis. In addition, the use of predictive analytics and ML can help to identify potential deviations allowing for the implementation of preventive actions to avoid quality issues.

The following case studies in Appendix 1 are examples of Quality 4.0 root cause and CAPA management:

- Case Study 22: Using ML and Trending to Detect Data Integrity Issues (Section 11.2)
- Case Study 34: Predictive Production Yield, AI-based (Section 11.3)
- Case Study 236: Pharmacovigilance Improvement with Robotic Process Automation (Section 11.7)

4.6.3.2 Complaints and Recall Management

In complaints management, the use of advanced technologies enables the collection and analysis of customer feedback and complaints. For example, the integration of complaints intake systems (such as Customer Relationship Management (CRM) or other digital tools) with quality management processes enable the identification, tracking, and analyzing customer feedback and patient complaints. In addition, this integration can identify trends and patterns that may indicate potential quality issues in real-time. This allows for the implementation of preventive actions to continually improve product quality, regulatory compliance, and patient safety. This can help to proactively prevent quality issues, rather than reacting to them after they occur.

Product recalls are no different. Recalls can be costly to all involved parties, pharmaceutical companies, regulatory agencies, and most importantly, patients. Using digital adopting, proactive, data-driven tools and systems can track and manage the recall process, including communication with patients, regulatory agencies, and other stakeholders about the recall. In particular, a connected quality system with a connected supply chain management system can accelerate the organization of recalled products.

4.6.3.3 Audit Management

For the internal quality audits as well as for inspections from outside agencies or customers, a fully digitalized quality system can help:

- Prepare documents for the auditors/inspectors
- Transmit documents in advance to the auditors/inspectors
- Prepare training for auditees on relevant documents, including how to find and identify documents
- Organize contact with experts during inspections, also personnel not on-site
- Quickly identify and find information requested during inspection
- Provide historical data, e.g., from former batches or inspections or correspondence with auditors or inspectors
- Support closing discussion and follow-up via a connected CAPA system
- Facilitate communications throughout the organization and site network for global network assessments and continual improvement

4.6.3.4 SOP Management

Frequently, SOPs are very extensive, bear many signatures, and are often not updated in a timely manner. In addition, their content may not be available to consultants or experts. Even frequent training brings only weak improvements. The digitization of SOPs offers a range of new opportunities for a new concept of providing timely, up-to-date and, above all, current information. Such a concept may have the following parts:

- SOP 4.0 is set up according to the meaning of Standard Operating Procedure: a precise and easy-to-understand step-by-step process flow, integrated end-to-end into the digital enterprise process landscape, and as automated (or at least guided) workflows directly executable in operations (MES). Forms and templates are structured data fields allowing direct entry or automated filling of measured data (via sensors).
- Quality requirements are defined as modular content units managed by object-based attributes assigned to the right process step, roles, products, countries, etc.

- The output format of those SOPs could be chosen by the user in a customizable manner, for example, text, voice, pictures, video, etc., according to the best fit for operational need or individual preference.
- The respective SOP management system is a state-of-the-art workflow and content management system and works like an intelligent information management system, providing the right information at the right time to the right place/person, either directly integrated into the operation or through mobile access from anywhere.

It can be managed in the following manner:

- The lifecycle management of SOP 4.0 as process flows and/or modular content units follows the same requirements as for the classical documentation from change request, creation, review, approval, effective setting, and archiving.
- Modular content units, whether they are text elements, processes, videos, or graphical elements, etc., have a unique identifier, maintained under a review and approval process, in a lifecycle with a defined review due date.
- The respective workflow and content management system need to be validated to the same level of quality standards as for a documentation management system.

Digital technical features supporting this concept are:

- Automated workflows with notification at any time for all impacted stakeholders, plus the option of a forced implementation of dedicated processes and/or modular content units, managing the entire SOP lifecycle from change requests through implementation on the shopfloor/area efficiently and effectively.
- Integration of user-friendly devices like smart glasses, AR/VR, chatbots, and videos enhances the user-experience, and therefore reduces deviations.
- Business Intelligence (BI) based on real-time data allows an ongoing and user-friendly Quality oversight through customized reporting and dashboarding
- Process mining to measure real-time performance execution of the entire SOP lifecycle and individual processes drives continual improvement.
- Natural Language Processing (NLP) is a very powerful application to analyze and transform unstructured data of typical text-based documents into structured data = object-based content:
 - NLP feature Similarity Analyzing can monitor regulatory changes of external regulations, check impact to internal processes, and later track compliance of implementation. It can be used to analyze complexity, especially redundancies of the SOP library.
 - NLP feature Entity Recognition can be used for clustering and auto-tagging of SOP content elements, e.g., roles and responsibilities, definitions.
 - NLP feature Summary Extraction can extract meaningful content from long text passages or across multiple documents.
- Business Process Management (BPM) simulations enhanced by what-if scenarios to analyze the impact of change on process flows and respective resource assignment, plus propose an optimum stage to avoid bottle necks and process-related deviations.

Prerequisites for SOP 4.0:

- Technical infrastructure

- IT system: State-of-the-art object-based BPM validated according to standards for documentation management
- End-to-end integrated and connected IT systems and API interfaces with process and data landscape and cloud infrastructure
- Digital features and user-friendly applications like tablets, smart glasses, AR/VR, videos, etc., in use and integrated
- Organizational
 - Process and data management capabilities
 - Multiskilled know-how in digital, quality, project management
 - Open minded, silo-breaking mentality, thinking holistically, end-to-end
 - Management to foster empowerment and decision-making toward the operational team, process ownership instead of functional hierarchies

4.6.3.5 Learning Management

Today's generation draws more and more of its knowledge from Internet networks. Training methods and training offers must be oriented to this in order to be effective. Digital formats (e-learning) can be linked with other knowledge sources from the unit, for example, Operations, so that an always up-to-date learning offer is available. Learning success and performance monitoring can also be integrated in this way.

Principles of an e-learning system may be employer-centric, competency-based, activity-driven learning units in an engaging format and timing to ensure competency and compliance prior to performing operations: just-in-time instruction and guidance.

- **Content:** The learning curriculum will be defined based on the fit gap analysis of the needed competency/capabilities level (e.g., beginner, advanced, expert) per activity-role and the existing competency level of the employee per role. The job-role of each employee is composed of multiple modular activity-roles, such as function, responsibility in operations, product, machine, country, etc.
- **Timing:** The right timing and appropriate learning phase will be defined based on whether an employee is onboarding or immediately prior to operation; therefore, the curriculum of each employee will be modular and, where needed, contain gated learning phases, ensuring a didactical flow and appropriate competency effectiveness demonstration before starting the respective operation.
- **Format:** Learning units will be defined and created based on professional adult learning methods with utilization of innovative and engaging technologies, blended e-learning for foundational onboarding or domain knowledge, crisp information sharing, learning nuggets for refreshers, and just-in-time instruction via smart glasses and or chatbots during operations. Operational training in critical working practices (e.g., in aseptic filling) could be carried out in a VR environment (similar to a flight simulator) until competency is achieved.

This structural learning can be enriched by an engaging, intuitive, collaborative knowledge management environment (communities) and infrastructure that fosters a culture of intrinsic self-development and collaborative knowledge sharing, such as a Wiki-library, or Google-like search engines, matching: finding an expert, learning pools, apps for social media-like information sharing, etc. Subscription to specific topics of interest and/or cookies could constantly increase the horizon of knowledge (see Chapter 5).

4.7 Quality Culture in a Digitalized Environment

Working in a digital environment changes the roles and responsibilities of everyone involved. Reference is made to *ISPE Cultural Excellence Report* [32]:

- Understanding and willingness of management to invest in a high performing QMS platform and digital technologies, plus new QMS organization and skills
- Understanding and willingness of classical Quality experts to understand and appreciate this new way of learning management, and knowledge and collaboration with Learning and Knowledge, and digital experts. Plus accepting modular standardization, workflow, and content management.
- New roles and organizational investment into Learning and Knowledge Manager and digital experts
- User: from burden to pleasure. Human beings like learning and bringing Quality learning to an engaging environment that makes it fun will enhance compliance and Quality engagement.
- Quality leader: from complexity and “compliance risk” orientation to oversight at any time, higher compliance, and higher Quality engagement.
- Business leader: Quality learning and general enterprise knowledge management are integrated and therefore there are more synergies, agility for changes, and an attractive workplace

Quality culture messages as in classical structures:

- Quality is everybody’s responsibility
- All work is process (Crosby 1964 [23])
- It is about mindset and behavior, Quality in all that we do, etc.
- Customer focus means to critically reflect, focus only on tasks and projects, invest in what helps the customer, and remove what is not necessary (removing waste = OPEX)
- Focus on continual improvement, which can help to identify and address any issues or challenges that may arise in the product lifecycle.

Quality culture messages specific to digitalized environments:

- Openness to innovation, new technologies, and business opportunities
- Openness to visibility and transparency enabled by digitalization and connectivity
- Holistic view, end-to-end value network in focus
- Promote collaboration and teamwork to foster a sense of shared purpose and collective ownership of the holistic control strategy
- Intrinsic strive for self-learning
- Customer’s needs are achieved better using digital tools