

A HOLISTIC APPROACH TO PRODUCTION CONTROL FROM INDUSTRY 4.0 TO PHARMA 4.0

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This article presents the work of the newly formed ISPE Holistic Production Control Strategy Working Group, which has identified and summarized the need for a redefined control strategy implementation methodology.

PROBLEM STATEMENT

The current submission-based control strategy plays a key role in ensuring that critical quality attributes (CQAs) are met, and the quality target product profile (QTPP) is realized. It does not, however, consider GMP, facilities, utilities, equipment and other production-specific controls to mitigate risk and ensure an effective, reliable, and stable production process. In addition, the effect of unknown process parameters, raw material attributes, and impurities usually are not sufficiently addressed in the control strategy lifecycle management—it is often impossible to predict such variations for a production lifecycle already in development.

Transforming today’s development-based control strategy to commercial manufacturing by technology transfer and scale requires a best practice methodology that would change the current control strategy into a holistic production control strategy (HPCS).

This would create a flexible and robust production process with well-documented lifecycle management that could be applied to existing production operations as well as facilities of the future, from design concept to detailed design, and from implementation up to commissioning, qualification, and daily operations.

Speaking at the ISPE EU Annual Conference in Frankfurt in March 2016, Ian Thrussell, Expert Inspector at the World Health Organization, identified additional requirements: “The transformation in the design

and the execution of the control strategy has to follow a data integrity by design approach.”

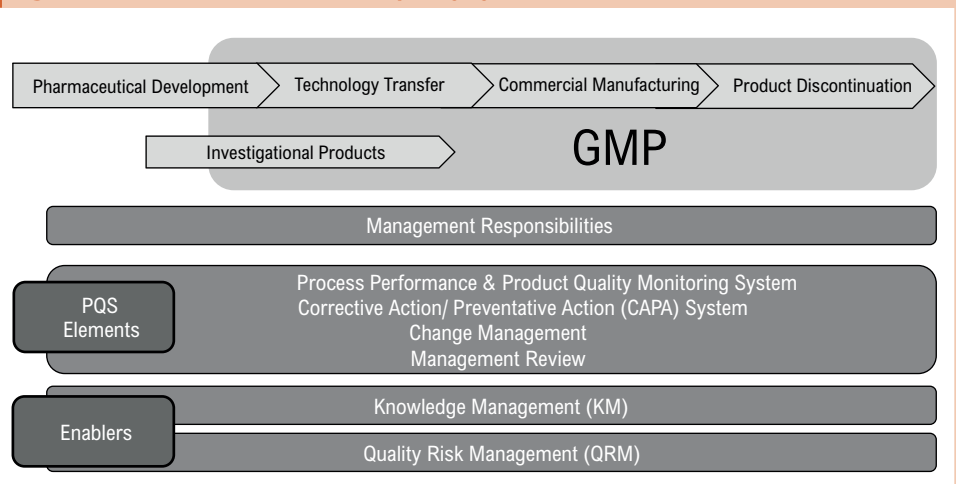
Data integrity by design is a structured risk-based approach that applies critical thinking to create process maps, process data maps, and data flows to design the production process in a flexible and robust manner. Professionals miss an opportunity for success when they don’t apply two key cross-functional factors: a process-oriented approach, and communication skills. Additionally, business process descriptions or process charts/maps and process data maps are not always developed and applied properly.

Critical thinking during the design, creation, and execution of the shop floor production process ensures repeatable, robust, and right-first-time execution of the commercial production process. The parameter space must be adapted throughout the product lifecycle, beyond the original design space and the submission-based control strategy.

ICH is currently drafting the Q12, “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management” Guideline, which will specify the post-approval change management of the product control strategy, and enable the application of new, robust, and flexible product and production-process monitoring plans and controls like continuous process verification (CPV).

All these concepts are currently isolated from each other, however. A new “holistic” production control strategy could be based on existing ICH-defined concepts, incorporate new elements and enablers that ad-

Figure 1: ICH Q10—Pharmaceutical quality system



dress challenges from digitalization and big data management, and include all activities throughout the value chain and the product lifecycle.

THE CHALLENGE: IMPLEMENTING ICH Q10 IN PRODUCTION

This information was presented at the 2016 Facilities of the Future Conference, 14–15 November 2016, Bethesda, Maryland, US

The proposed approach is based on the ICH Q10 view of the PQS product lifecycle and control strategy.

Figure 1 shows the original ICH Q10 visualization of the PQS. This concept is based on key principles (enablers) and control strategy design tools (elements) used throughout the pharmaceutical production lifecycle. ICH Q10 states that: “these elements should be applied appropriately and proportionally to each lifecycle stage recognizing opportunities to identify areas for continual improvement.”

Using this as a basis, the HPCS working group developed a concrete and practical corresponding picture to detail this approach in production.

Figure 2 shows enablers and elements, which are critical success factors for designing and executing a stable yet flexible and robust HPCS in commercial manufacturing.

The physical and operational design of the pharmaceutical equipment, facilities, logistics, and operational concepts (including work instructions, automation, and equipment) shall be based on business process descriptions, process maps, process data maps reflecting production experience, and best practices. Early collaboration from all pharmaceutical departments—quality assurance, quality control, process development, manufacturing operations, engineering, automation, and information technology (IT)—is required to design a robust, flexible, right-first-time facility that operates at the expected quality level to ensure that the CQAs are met and the QTPP is realized. A data integrity by design principle can also be implemented by applying a risk-based approach based on critical thinking.

While current ICH Q8 and Q10 definitions of control strategy remain valid, facilities of the future will have a high level of automation applying the newest technologies. Pharmaceutical production based on Industry 4.0* factory design will become “Pharma 4.0” when applied to GMP

Holistic Production Control Strategy

- Is a set of enablers and elements that provides a holistic view of production to ensure a flexible, agile, sustainable, and reliable pharmaceutical production that mitigates the risk to patients, products, processes, and the business.
- Covers products and materials designed for fully automated processes. It requires an educated workforce to manage integrated processes and data flows as well as modern platforms, machines, and facilities designed for digitalization and automation.
- Supports business processes with integrated GxP IT systems along the supply chain.
- Requires management to establish and foster an adequate framework and organizational culture for Pharma 4.0.

compliance, validation, and GAMP® requirements. HPCS encompasses best practice design methodology from the submission control strategy documentation to the master production control record, up to and including Pharma 4.0 documentation and requirements. This leverages the benefits from the new operational excellence opportunities of Pharma 4.0. A new “Workforce 4.0” will also be required to interact with the complex and intelligent equipment.

APPROACHING THE PROBLEM

Control strategy best practice methodology is outlined in the ISPE PQLI® Guides. HPCS implementation requires a cross-divisional approach and methodology that includes product and production data lifecycle management. This is not yet completely well established in all organizations.

HPCS enablers

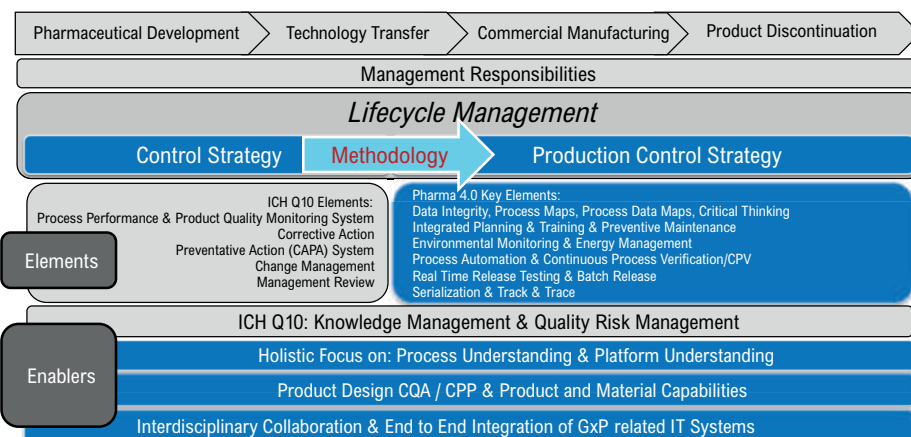
ICH Q10 identifies knowledge management and quality risk management as two major enablers throughout the pharmaceutical lifecycle and the bases for HPCS design and execution. Product design—including identifi-

cation of CQAs, critical process parameters (CPPs), and critical material attributes—is another key enabler for product and material capabilities.

Holistic process and platform understanding needs cross-organizational interdisciplinary collaboration from all departments and stakeholders combined with integration of all GxP-related IT systems to enable data

* Often called the fourth industrial revolution, Industry 4.0 is the digitization of manufacturing, including “big data,” connectivity, analytics, the Industrial Internet of Things, and digital-to-physical transfer.

Figure 2: From ICH Q10 to Pharma 4.0—holistic production control



integrity. Enhanced data science approaches in production must become the foundation for decision-making to operate in automated environments, implement process analytical technology (PAT) in its holistic definition, and allow modern advanced technologies like continuous manufacturing.

HPCS elements

By applying a design process based on process maps and underlying process data maps, Pharma 4.0 will ensure data integrity by design.

Data integrity is much more than ensuring a good audit trail: It is about quality of data, the right content, and respecting the ALCOA+ principles.¹ Auxiliary materials and excipients, for example, could have the same name and quality-specific reference number across the global network of a company to avoid mix-ups and misunderstandings. Critical thinking is needed to design a robust, repeatable, but still flexible production process. This includes thorough data science approaches and architectures. When establishing a quality risk map using ICH Q 9, for example, one of the most important steps is risk identification, which requires experience, a balanced

view on risk, and the ability to imagine what can go wrong. Hence, prior knowledge should be available in a structured form.

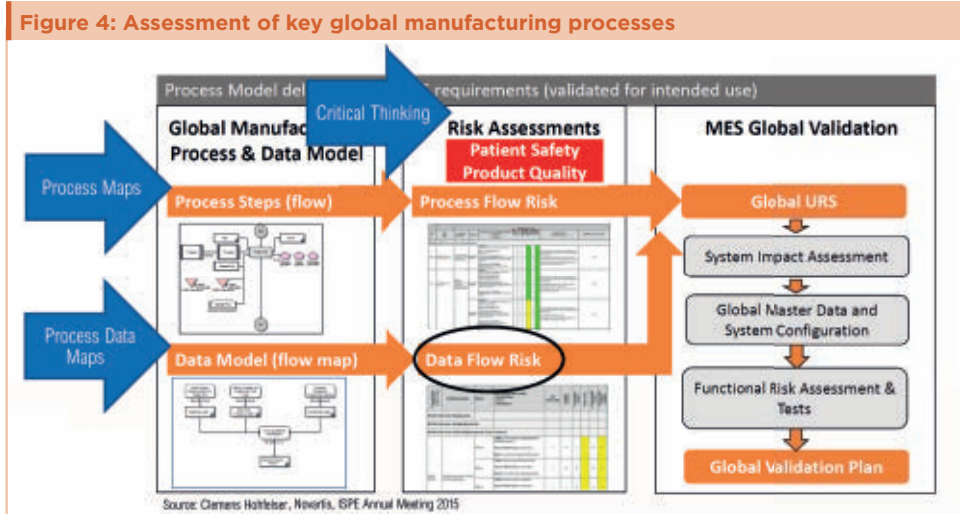
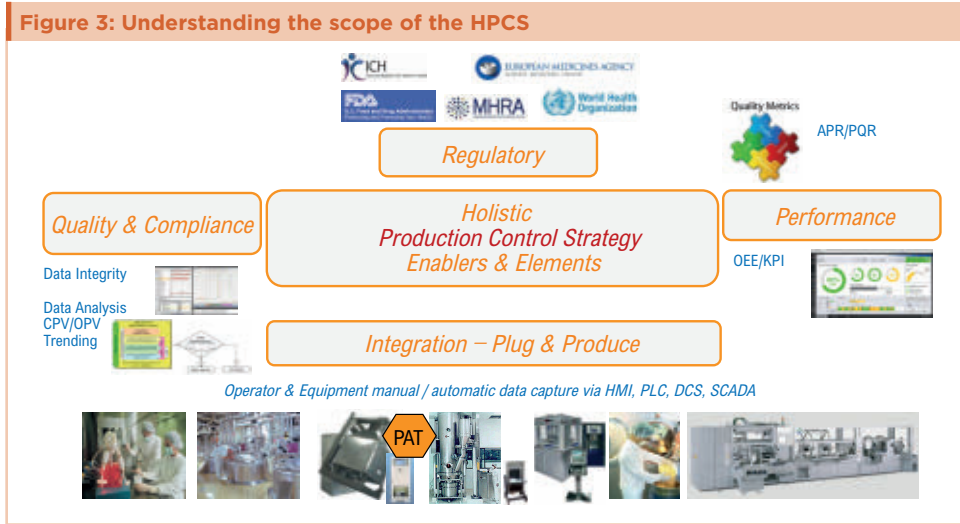
Integration of all supporting computerized systems is key, both vertically and horizontally across systems, as well as throughout the product lifecycle and the value chain. This includes physical data interfaces, process automation to support CPV (by applying modern technologies like PAT), and predictive process controls to establish real time release testing (RTRT). Big pharma companies that recognize this need have started to establish a one-source “data lake” for system integration, plus fast real-time and ad hoc reporting for management decisions.

Preventive maintenance to enhance performance and minimize downtimes could be integrated into a process planning procedure that optimizes the collaboration of all production-related equipment, operators, and their training, as well as environmental monitoring, including energy consumption. A “ready-to-run” visual shows all conditions required to start production:

Is the employee qualified? Has he/she undergone updated SOP training? Has the machine, room, and equipment clearance been done? Are all maintenance cycles in compliance with internal SOPs? Has the product dossier been updated with the latest corrective/preventive actions and change management?

Environmental monitoring and energy management are similar to preventive maintenance, and should be integral parts of a release to start production. Integrated energy management will ensure that all processes have sufficient electricity and backup. Even seconds of downtime can destroy a batch. All other infrastructure system malfunctions could be defined as relevant for quality and compliance, and integrated into the supervision process.

Automation and CPV usually apply only to their bespoke products. Products more than 10 years old are often not suitable for automated processes, as they depend largely on unwritten operator knowledge of both the process and the interaction between equipment and environmental conditions. The strategic target of a development project, therefore, could



Source: Clemens Hofhelsler, “Data Integrity in Manufacturing Execution ... A Process Oriented Approach.” Presented at the ISPE 2015 Annual Meeting, 8–11 November 2015, Philadelphia, Pennsylvania, US. Reprinted with permission.

¹ See Special Report on Data Integrity, *Pharmaceutical Engineering* 36, no. 2 (March–April 2016): 39–67.

be pharmaceutical processes with automated PAT-related controls when CPV is applied.

Real-time and batch releases in a Pharma 4.0 world would be harmonized so that batch and document release are synchronized; this would prevent holding the real-time release of a process until all documents had been reviewed.

Other commercial and regulatory requirements like mass serialization and track and trace against counterfeit products are also key elements of HPCS. As the product code and security number are now considered compliance relevant they must be an integral part of the whole supply chain; this also prevents false positives. Even a high-quality product can hold up the supply chain if its serialization numbers are not correct.

These are all generic key elements of Industry 4.0 applied specifically as Pharma 4.0. In general, all GxP-related IT systems such as enterprise resource planning, enterprise content/documents management, and enterprise quality management could be integrated in one enterprise manufacturing intelligence system.

PHARMA 4.0: HPCS

The holistic view of the production control strategy consists of four key areas where enablers and elements are applied. Regulatory requirements and guidelines provide overall governance (Figure 3):

1. Manufacturing process work instructions

The master production control record is still the key regulatory element for the description of the manufacturing process. Processes that follow the paradigm of a flexible execution need a flexible control strategy. In addition, the elements of preventive maintenance and optimized process planning influence the production process flow.

2. Quality and Compliance

ICH and FDA process validation guidelines help establish flexible production processes, including the CPV and ongoing process verification; these enable close monitoring and control of CQAs and CPPs. Combining data integrity and data lifecycle management approaches with practical knowledge management processes is still a challenge in the industry.

In a Pharma 4.0 world, however, the concept of quality assurance must be adapted to cross-functional business processes and must redefine the tasks and responsibilities of systems, cross-functional process owners, and content owners in the various business functions.

3. Performance

To ensure a cost-efficient production process, data must be evaluated, analyzed, and used to optimize the process. Quality metrics will be applied to measure the efficiency of the overall production process. Enabling flexible processes can also shorten production lead time.

In a Pharma 4.0 world, operational excellence goals should be redefined. If targets continue to be “solo-ed” the total optimum will never be reached. This management challenge is supported by knowledge from senior experts and knowledge management tools.

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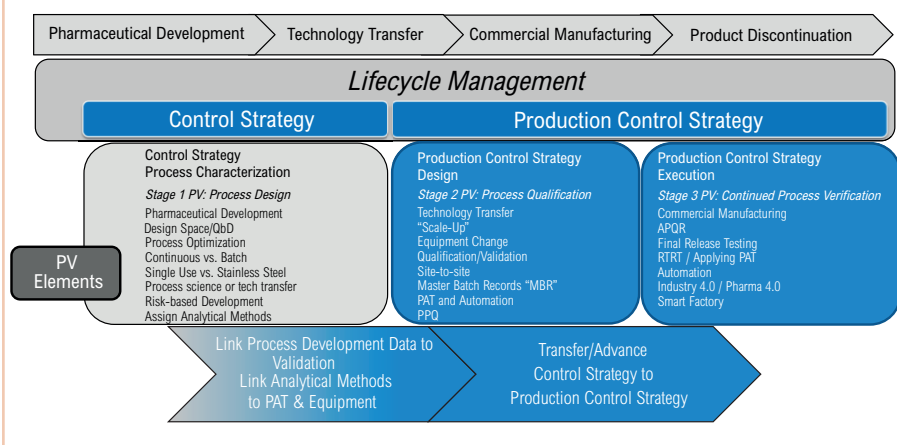
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Figure 5: Three-stage Pharma 4.0 process validation



Source: ISPE Biotech Special Interest Group

Figure 6: Interdisciplinary collaboration

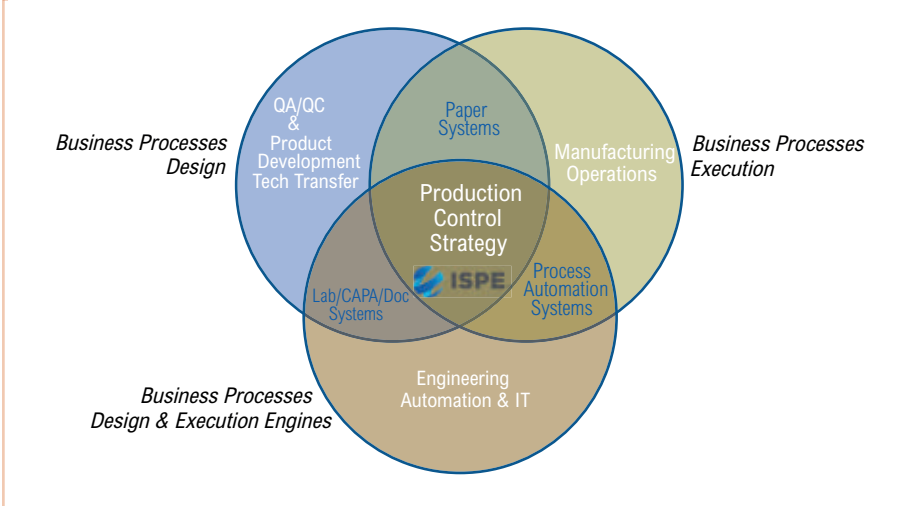
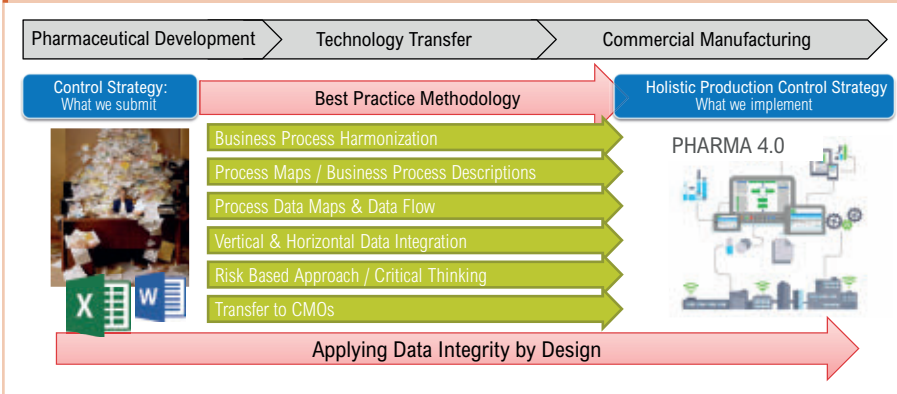


Figure 7: HPCS best practice implementation



4. Integration: Plug and produce

The HPCS-enabled smart factory will be integrated horizontally and vertically by standard interfaces, which will ease integration of prequalified equipment. This is already established in the semiconductor and other industries. Integration for plug-in compatibility should also comply with data integrity requirements (such as audit trail); data security; seamless integration of on-line, inline, and at-line PAT instrumentation process control; and RTRT or packaging serialization and track and trace. Future integration concepts should follow this plug-and-produce concept to reduce costs and enable flexible production solutions and provide a cost-efficient lifecycle management interface.

In Pharma 4.0 the industry needs globally defined technical standards such as GAMP or ISO as well as standards for product quality profiles and technical suitability for automated processes. Some materials should be removed from developer material lists as unsuitable for technical processes (e.g., for high physicochemical variability).

Products made for small batches and personalized medicine need other standards than a mass product for large populations.

HPCS IN PROCESS VALIDATION

The ISPE Process Science Working Group, part of the Biotech Special Interest Group (SIG), enhanced the ICH PQS lifecycle picture and applied it to the three stages of process validation (Figure 5). This shows the evolution of the control strategy to the HPCS across the three process validation stages.

WORKFORCE 4.0

An HPCS needs interdisciplinary collaboration of all organizational business units responsible for the production process, technology, and quality. Per ICH Q10, this also includes management, since they are responsible for quality and HPCS compliance. We call this Workforce 4.0.

HPCS in a Nutshell

Potential cost savings are enormous. Regulatory guidelines are in place to leverage this potential, but examples to put them into practice are still missing. At the same time, regulatory authorities and inspectors increasingly apply requirements for quality risk management and safe production for pharmaceutical products. The trend to megadigitization—the Industrial Internet of Things or Industry 4.0—offers the opportunity to realize these potentials. This is more than just the next wave of hot topics; it will lead to one of history's biggest paradigm changes for pharmaceutical manufacturing.

To create a successful cross-functional approach to these new concepts, the pharmaceutical industry must align with its main stakeholders: regulators, investors, manufacturing leaders, and key suppliers. An ISPE SIG is studying how best to transition commercial manufacturing from current control strategies to an HPCS using a Pharma 4.0 framework.

Three main areas need attention:

Leadership: Senior management understanding, ownership, and responsibility for cross-functional stakeholder management.

Capabilities: Cross-divisional knowledge, understanding, and collaboration.

Toolbox: Identify, implement, and train methods and best practices to implement an advanced HPCS.

SUMMARY

There is a huge potential in applying Industry 4.0 technologies along the end-to-end supply chain. Regulatory prerequisites for this approach are already in place. While the industry may still be hesitant to implement these technologies and change well-established, qualified, and validated production processes, development of the ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" Guideline will enhance the regulatory basis for this approach.

The goal of the Pharma 4.0 SIG and its Holistic Production Control Strategy and Plug and Produce Subgroups is to provide best practice implementation methodologies, approaches, and practical examples on how to apply the technologies and integration approaches and to improve quality by well-understood and -controlled processes. With these in place, data integrity, quality, compliance, and predictive production processes will be the reward. ◊

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