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Commissioning and Qualification (Verification) in the Pharmaceutical Product Process Lifecycle

by David Dolgin

This article discusses the role of Commissioning and Qualification as "Stage 2a" of the Process Validation Lifecycle described in the US FDA's Guidance on Process Validation. It also explains how the concepts of Quality Risk Management and QbD are incorporated into facility and system verification efforts as detailed by two recently published ISPE Guides.

Background

In January 2011, the US FDA published an update on pharmaceutical process validation. Titled *Guidance for Industry – Process Validation: General Principles and Practices*, it represents the first update since 1987 to the agency's official guidance on the topic. Based on the principles of ICH Q8, Q9, and Q10 (*Pharmaceutical Development, Quality Risk Management,* and *Pharmaceutical Quality System,* respectively), this version of the process validation guidance aligns FDA's process validation expectations with the above ICH documents as well as with FDAs own 21st Century Risk-Based GMP initiative.

The FDA Process Validation Guidance (PVG) is structured on a lifecycle concept: The objective of "process validation" is a state of ongoing control of process variability. Process validation is not an event or task that can be completed, rather, it is a lifecycle of control across the entire product development and manufacturing product lifetime. One new aspect in this version of FDA guidance is the specific architecture that the agency applies to the lifecycle model described. It is a three-stage model that begins with process design and ends only with the discontinuation of manufacture. As shown in Figure 1, the stage traditionally containing the activities referred to as Commissioning and Qualification (C&Q) will be referred to as "Stage 2a" of the FDA Process Validation Lifecycle.

Figure 1 also depicts the inputs from the three ICH documents mentioned above and references a fourth industry standard: ASTM E2500-07, *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*.

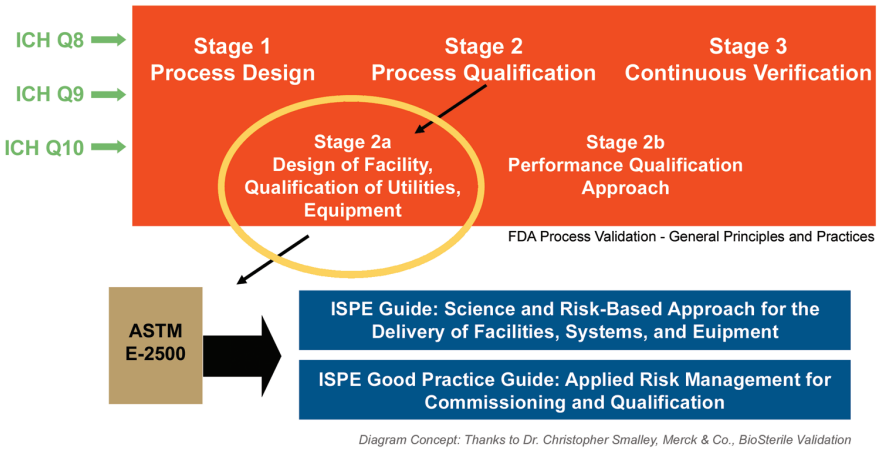

Figure 1. Where C&Q fits in the FDA process validation lifecycle.

As will be discussed, ASTM E2500-07 is cited by the FDA PVG as guidance for activities that verify that facilities, systems, and equipment are fit for their intended use (sometimes referred to as "Qualification"). Lastly, Figure 1 identifies two relatively recent ISPE Guides that facilitate implementation of the ASTM. There is more information on those guides to follow in this article.

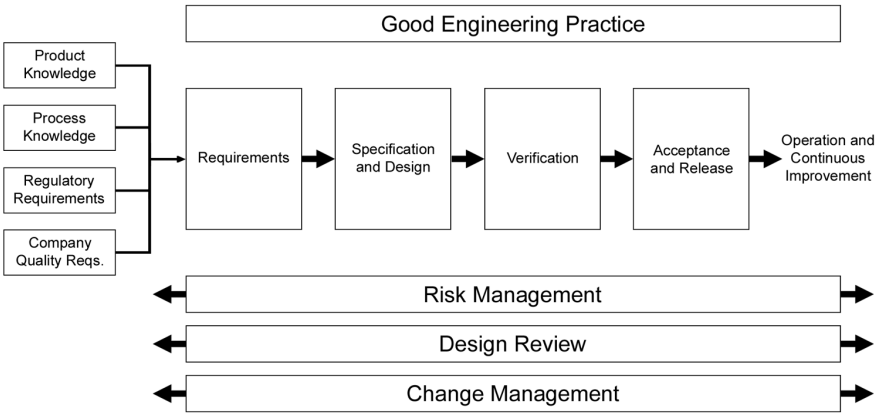

Figure 2. The specification, design, and verification process per ASTM E2500-07.

Quality by Design and Risk Assessment in the PVG Lifecycle

One of the fundamental principles of the PVG is that quality must be **designed** into a process from the beginning. It cannot be adequately ensured merely by inspection or sampling and testing. This truth applies equally to pharmaceutical manufacturing processes and to the equipment and facilities used to execute those processes. Facilities and systems must support the quality requirements of their associated processes in order to be deemed "suitable for intended use."

The key to defining facility and equipment quality requirements is based on the process knowledge gained during Stage 1 – Process Design. The PVG states, "This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes." Specifically, the PVG clarifies that the FDA expects manufacturers to:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

ASTM E2500-07

ISPE, beginning in 2005, with the encouragement of the FDA, began to act as a "change agent" by developing and championing a standard for a new and non-traditional approach to verify that equipment, facilities, and utilities were fit for their intended use. By 2007, ISPE had developed and submitted a draft to ASTM's Committee E55 on Manufacture of Pharmaceutical Products. The Committee approved ASTM E2500-07 in November of that year.

ASTM E2500-07 is the first guidance on system and facility verification with the status of a "consensus standard." Peer-reviewed and revision-controlled, the ASTM describes a risk- and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety. With its status as a "consensus standard," ASTM E2500-07 provides the FDA an approach to facility and system verification that the agency could officially recognize as an acceptable methodology.

Based on the framework of ICH Q8 and Q9, and expanding on principles and concepts introduced in the FDA initiative, *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach*, ASTM E2500-07 is intended to satisfy international regulatory expectations in ensuring that manufacturing systems and equipment are fit for intended use and to satisfy requirements for design, installation, operation, and performance. It describes a lifecycle approach of its own, beginning with the definition of requirements, followed by specification and design, verification (containing the elements of traditional C&Q), acceptance and release, and continuous improvement.

The FDA Process Validation Guidance references ASTM E2500-07 as "useful" in meeting the requirements under 21 CFR Part 211, Subpart C, of the cGMP regulations on *Buildings and Facilities*, and states, "It is essential that activities performed to assure proper facility design and commissioning precede Process Performance Qualification (PPQ-legacy process validation)."

Controlling variation in pharmaceutical manufacturing processes requires strategies that depend on specific aspects of facility and system design and function. These aspects, re-

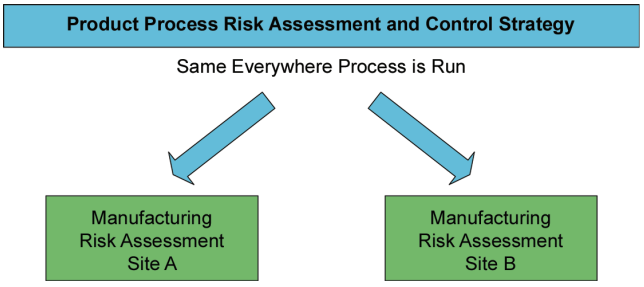

Figure 3. Levels of risk assessment.

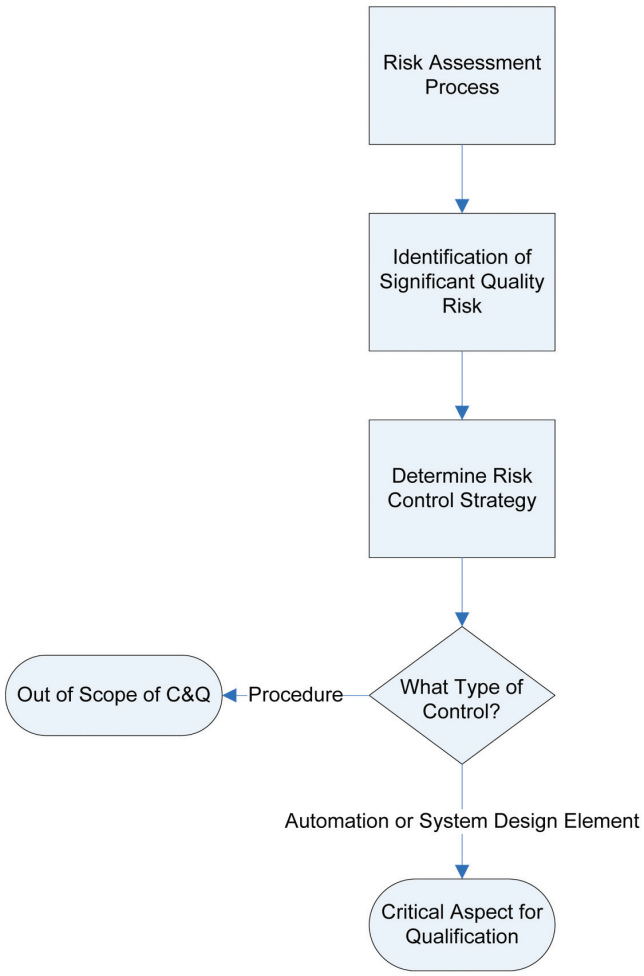

Figure 4. Identification of critical aspects through risk assessment.

ferred to as "critical aspects" by ASTM E2500-07, are the focus of risk-based verification activities described by the ASTM and elaborated on below. The identification of critical aspects of facilities and systems is accomplished primarily through multiple risk assessments as shown in Figures 3 and 4.

The Product Process Risk Assessments shown in Figure 3 are an output of Stage 1 – Process Design, and apply to a given manufacturing process based on the chemistry and process-science specific to that process. Manufacturing risk assessments are site-specific, building on the Process Risk Assessments and taking into account sources of potential variability induced by local factors such as environment, available equipment, personnel, site experience, facility layout, etc.

Critical Aspects – Design-Based Control Strategies

ASTM E2500-07 contains the following definition of Critical Aspects: "Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding."

Manufacturing process risk assessments help inform the detailed designs of systems and facilities and can be used to identify Critical Aspects as a focus for design, testing, and verification documentation. Note that not all risk control strategies are matters of engineering design subject to verification (Qualification). The term "Critical Aspects" is used by the ASTM to indicate risk control design features and functions, not procedural controls or testing.

As indicated by Figure 4, Critical Aspects can be an output of a risk assessment. The specific type of assessment methodology is not as important as the identification of risks and their associated control strategies. Failure Modes, Effects, and Criticality Analysis (FMECA) is an example of a type of risk assessment method that does an excellent job of identifying specific risks/control, making it well suited for Critical Aspect identification. However, it is not the only option, and teams should select the best method based on each situation.

Applying ASTM E2500-07 to Stage 2a

Some of the key concepts that ASTM E2500-07 applies to facilities, equipment, and systems are analogous to process guidance in the PVG. For example:

- "Quality by design concepts should be applied to ensure that critical aspects are designed into systems during the specification and design process." (ASTM E2500-07, section 6.5.1)
- "Assurance that manufacturing systems are fit for intended use should not rely solely upon verification after installation but be achieved by a planned and structured verification approach applied throughout the system life cycle." (ASTM E2500-07, section 6.5.2)

To effectively apply QbD and Quality Risk Management to the design and delivery of manufacturing facilities, equipment, and systems, a foundational level of process knowledge regarding the intended use of said assets must be available. From their knowledge of the intended use of a given item, Subject Matter Experts (SMEs) in that application can define the appropriate quality requirements. According to ASTM E2500-07, specific requirements affecting product quality and patient safety should be based on:

- Product knowledge
- Process knowledge
- Regulatory requirements
- Company quality requirements

Product and process knowledge comes from Stage 1 – Process Design development along with relevant manufacturing

experience and history with the same or similar processes, thereby linking product and process requirements to the engineering designs of the facilities and systems that support those requirements.

ISPE Implementation Guidance

While ASTM E2500-07 provides the necessary high-level strategy for science- and risk-based verification that facilities and systems are fit for use, many companies are highly invested in C&Q methodologies and systems that significantly predate ICH Q9 and the ASTM. The mechanisms of IQ and OQ, along with associated rules for their use, are embedded in quality systems across the pharmaceutical industry, and these systems may not be easily adaptable to the ASTM approach. To meet the practical needs of firms wishing to update their C&Q systems to align with risk-based practices and to achieve the efficiencies of cost and time they can provide, ISPE published two new guidance documents in 2011 that provide options for the implementation of science- and risk-based verification:

Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment (FSE Guide) (published in June 2011)	Applied Risk Management for Commissioning and Qualification (ARM Guide) (published in October 2011)
• A pure ASTM E2500-07 approach • Direct implementation of ASTM • Verification terminology only • ASTM E2500 roles/ responsibilities in place for adopting organization	• A bridge document – how to transition from traditional approaches to a risk-based approach based on ASTM E2500-07 • Hybrid approaches, elements of both traditional and risk-based • Traditional C&Q terminology • Organizational transition based on maturity

Which Guide for My Company?

Although the topics are similar, they have different uses as summarized below:

FSE Guide for Organizations	ARM Guide for Organizations
• With new or flexible quality systems • Without significant legacy terminology and quality qystem mechanisms • Organizationally capable of Good Engineering Practices (GEPs) and risk assessments	• With established quality systems • With embedded terminology • Non-risk based cultures • Organizational maturity needs development

Summary

The FDA Process Validation Guidance establishes a three-stage lifecycle, where Stage 2 is bifurcated into two sub-stages, 2a and 2b, and where stage 2a is equivalent to the Commissioning and Qualification of equipment, systems, facilities, etc. The FDA guidance references ASTM E2500-07 as one of the sources for information on executing stage 2a.

ISPE has provided the community with two updated best practice guides facilitating the implementation of ASTM E2500-07 and/or risk-based approaches. Both were published in 2011. *Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment* describes a direct implementation of the ASTM and its terminology, and *Applied Risk Management for Commissioning and Qualification* provides transitional and hybrid approaches for adoption by established organizations and quality systems.

Both of these guides follow the concepts of ICH Q9 *Quality Risk Management* in its application by the ASTM, and support state-of-the-art verification approaches to assure that systems are fit for their intended use – the objective of Stage 2a of the FDA Process Validation Guidance.

References

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3. ASTM E2500-07, *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,* ASTM International, www.astm.org.
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About the Author

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