A Comparison of the FDA’s Draft Process Validation Guidance and ASTM E2500

by Robert E. Chew, PE

Introduction

The pharmaceutical/biotechnology industry has shown great interest in the ASTM Standard E2500 for the Design, Specification, and Verification of facilities, equipment, and systems. Many companies are attempting to implement this standard. In quite a few instances, organizations responsible for compliance are concerned that this standard represents a significant change from how industry has practiced qualification in the past. There is a further concern regarding terminology (what certain documents need to be called) and the structure of documents with respect to EU regulatory expectations. The FDA’s new draft process validation guidance includes expectations for equipment qualification. How do the expectations in this new guidance compare with the approach defined by ASTM E2500, and how can the EU expectations be reconciled with these documents? This article provides an analysis of these provisions and a recommended approach to equipment qualification.

History

ICH Q9, Quality Risk Management, was finalized at Step 4 in November 2005 and has been adopted by the Japanese, EU, and US regulators as either guidance or incorporated into regulations. This document provides principles and examples of tools of quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, and the inspection and submission/review processes. One way (out of many) that risk management can be used is to focus the facility and equipment design and operation around risk to the patient. A qualification approach also can make use of quality risk management to focus on those aspects of the facility, equipment, and automation that provide control of risk to the patient, or otherwise help assure manufacture of a quality product.

The EU GMP’s Annex 15 on Qualification and Validation, published in 2001, states that “A risk assessment approach should be used to determine the scope and extent of validation.” The document then prescribes use of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) as being precursors to process validation. These terms are defined and general content is specified. These terms and provisions are echoed in the more recent ICH Q7A, GMPs for manufacture of active pharmaceutical ingredients, which has been adopted by the US, EU, and Japanese regulators as either regulation or official guidance.

In July 2007, ASTM E55 committee (which is developing standards related to pharmaceutical manufacturing) issued its Standard E2500 covering the design, specification, verification, and acceptance of facilities, equipment, and associated automation for use in pharmaceutical and biotechnology manufacturing. The purpose of this standard is to describe how to implement the ICH Q9 principles of quality risk management in a controlled and documented manner that meets regulations and demonstrates manufacturing systems are suitable for their intended use.

In November 2008, the FDA issued its draft update to the 1987 Process Validation Guidance. In January, the FDA delivered a webinar on this subject, hosted by ISPE. See related article on page 8 in this issue for a full discussion of the contents of this draft guidance. Industry has been provided with an opportunity to comment.
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on this draft guidance, and it remains to be seen the degree to which comments and changes will be incorporated into the final guidance.

ISPE has under development a new Baseline® Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment, which will provide details on how to implement a program based on ASTM E2500. ISPE also is developing a Good Practice Guide that will provide further options and approaches to qualification, including how to evolve practices based on the original Baseline® Guide Volume 5: Commissioning and Qualification, toward an ASTM E2500-based approach.

**Terminology**

For many years, a *Qualified system* meant that there existed a QA pre-approved, executed, and QA post-approved set of documents consisting of an IQ and OQ (and in many cases a PQ) protocol. For computer systems, and later most systems, this set of documents was expanded to include user requirements, functional requirements, traceability matrices, etc. The content of these protocols more often than not was dictated by local procedures. It did not matter whether the protocol content actually corresponded to critical aspects of the system or whether the qualification process actually yielded equipment that was fully functional and ready to manufacture quality product. What mattered was whether the local procedure was followed to develop, execute, and approve each protocol. Today, there are projects where money is being wasted and time is being lost as decisions are made to address procedural issues that are oblivious to good engineering and science and the impact on product quality.

This is changing. The most important change is what it means to *Qualify* a manufacturing system. This change began with ISPE’s Baseline® Guide Volume 5: Commissioning and Qualification. This Guide defined IQ, OQ, and PQ in terms of “aspects…that can affect product quality.” This is a more focused approach than the traditional approach of inspecting and testing against all engineering specifications (which can yield very thick protocols, a measure of success for some). ICH Q7A defines DQ as “verification that the proposed design…is suitable for the intended purpose.” ASTM E2500 defines verification as “a systematic approach to verify that manufacturing systems…are fit for intended use…” The FDA’s new Process Validation guidance states, “activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to as *Qualification*.” The draft guidance also states, “Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality.” In short, a *Qualified system* no longer means one with signed off protocols created and executed per a rigid procedure, but rather a system that has been shown to be *suitable for its intended use*.

This use of the term *Qualification* to mean a demonstration of suitability for use is equivalent to how ASTM E2500 uses the term *Verification*. The author believes that the term *Verification* has a more narrow and specific meaning in the medical device and other industries: *Verification* is the act of confirming, through objective evidence, that a particular feature or specification has been met. This definition fits with the use of the term verification in ICH Q7A, in that DQ, IQ, OQ, and PQ are defined in terms of “documented verification that…”

The third related term is *Commissioning*. The FDA draft guidance states, “It is essential that activities performed to assure proper facility design and commissioning precede PQ.” Commissioning is widely used in many industries, particularly the construction industry; therefore, it is a definition that is readily understood by many parties and is of benefit to project teams.

For purposes of this article, the following terminology will be invoked. For additional discussion of this choice of definitions, please see related article in the July/August 2008 issue of Pharmaceutical Engineering.

*Verification* – the act of confirming, through objective evidence, that a particular specification has been met.

*Commissioning* – a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

*Qualification* – a state, or determination, that the equipment has been found to be suitable for its intended use.

**Basis for Qualification**

What defines or what constitutes suitability for use? Neither the FDA guidance, nor EU GMPs, address this question in general terms, but instead merely provide examples of qualification activities. See Content and Execution below. ICH Q7A has the general requirement to comply with the approved design and to operate and perform as intended.

The ASTM E2500 standard provides a much clearer definition of what suitability for use is, and how it is assured. While both the FDA draft guidance and the ASTM standard discuss understanding the process science behind manufacturing, the standard goes further to define critical aspects as “functions, features, abilities, and performance characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety.” The standard requires the definition of product and process requirements, and the use of risk assessments to identify appropriate controls through design solutions and other means. Collectively, the process requirements and risk assessments can be used to derive the critical design and operating characteristics; these constitute “suitability for use.”

The ASTM E2500 standard prescribes a lifecycle approach: “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 approach applied throughout the system lifecycle.” The standard prescribes a series of steps necessary to design, specify, and verify the manufacturing systems. The FDA guidance includes a brief mention of the need to assure proper facility design and commissioning, but does not carry this idea to any greater detail.
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Defining Regulatory Expectations

The determination, via the ASTM process requirements and risk assessment process, of what constitutes suitability for use is a more robust and process-science driven approach than the FDA guidance “examples.” While one cannot argue with the general thrust of these examples, the potential is that industry will focus on these perceived requirements to the detriment of good science and good test engineering practices.

Planning for Qualification
Both the ASTM E2500 standard and the FDA draft guidance are remarkably similar with respect to planning, the only difference being use of Verification Plan (ASTM) vs. Qualification Plan (FDA). The EU GMPs also contain similar requirements. Table A illustrates the respective requirements for “plans.”

Content and Execution
The EU GMPs are the most prescriptive, defining DQ, IQ, OQ, and PQ. Neither the FDA draft guidance nor the ASTM standard defines how the design review and inspection and test programs should be structured; during ISPE’s webinar with FDA, the FDA presenter stated that there is no expectation for IQ/OQ/PQ per se. The EU GMPs prescribe content of IQ, OQ, and PQ with IQ having the most prescriptive detail. The FDA draft guidance states, “Qualification of utilities and equipment generally includes the following activities.” The examples are similar to the EU content examples and include:

- selection of materials of construction (note the words are selection, not verification!)
- operating principles and performance characteristics appropriate for their specific use
- built and installed per design specifications – and it clarifies this by stating “built as designed with proper materials, capacity, and functions, and properly connected and calibrated.”
- Operate in accordance with process requirements in all anticipated operating ranges. This is further amplified to include challenges under load, performance of interventions, start and stoppage as expected during routine operations, and ability to hold operating ranges as long as necessary during routine production operations.

The author feels the above attempts by regulators to engage in the practice of defining the approach and scope of inspections and testing are overly prescriptive. For example, the last sentence regarding the ability to hold operating ranges as long as would be necessary during routine production could lead a team to conclude they have to show the ability to control bioreactor temperature, pH, dissolved oxygen, etc., over a time period equal to a normal cell culture batch, which could be days or weeks. A test engineer would not assess this as being necessary, but would instead understand the science of the process and test those control loops under expected worst case challenge conditions for heat transfer or oxygen uptake, etc. Eventually, of course, such control is by default demonstrated during development batches or process validation lots. However, teams may interpret the guidance regarding qualification of equipment preceding PQ lots as being a hard requirement and endeavor to execute such tests in a non-optimal manner.

The ASTM standard prescribes that specific methods, performance, and documentation of inspection and testing activities are to be determined by subject matter experts. The verification activities should be conducted using a systematic approach and documented, the extent of which is scaled based on risk to patient, risk to product quality, and the complexity and novelty of the equipment. This is a science and risk-based engineering approach. The use of subject matter experts, as defined by the standard, is in complete agreement with 21 CFR 211.25, Personnel Qualifications.

<table>
<thead>
<tr>
<th>Plan Element</th>
<th>ASTM</th>
<th>FDA</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy/studies or tests to use/timing or sequence/scheduling</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Define acceptable documentation of detailed activities</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QA approval (for systems with critical aspects)</td>
<td>X</td>
<td>X</td>
<td>Note 1</td>
</tr>
<tr>
<td>Acceptance criteria</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Developed and approved by subject matter experts</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Responsibilities/organizational structure</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Incorporate risk management to prioritize activities and adjust level of effort in both performance and documentation thereof</td>
<td>X</td>
<td>X</td>
<td>Note 2</td>
</tr>
<tr>
<td>Choice to use system-based planning or one overall project plan</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Managing change during the project</td>
<td>Note 3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Validation policy, and reference to existing documents</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Note 1: Common expectation is that the validation master plan be approved by QA.
Note 2: The Principle (preamble) states “A risk assessment approach should be used to determine the scope and extent of validation.” It is presumed that the scope and extent are discussed in the validation plan.
Note 3: ASTM positions Change Management as a required supporting process to the project, but does not mention it in the context of the verification plan. It is likely teams would choose to include such a subject in their verification plans.

Table A. Comparison of ASTM, FDA, and EU expectations for contents of a “Qualification Plan (FDA/EU)” or “Verification Plan (ASTM E2500).”
Defining Regulatory Expectations

Review, Approval, and Release

ASTM E2500, the EU GMPs, and the FDA draft guidance document all require a summary report following the field inspections and testing. This report is to summarize the findings, highlight any deviations, and describe any changes to the plan/protocol that may have occurred. The ASTM standard describes a two-step process, Verification Review, which is performed by an independent (second check) subject matter expert, followed by an Acceptance and Release, which includes the quality unit for systems with critical aspects. In other words, technical experts review the technical results and make a determination as to suitability for use, while the quality unit provides a final approval of this determination and official release for manufacturing, at which point the system is placed under QA pre-approved change control (vs. change management during the project).

It should be noted that NONE of the three documents describe the typical onerous and formal deviation resolution process present in most projects today. Only the EU GMPs and the ASTM standard mention deviations, and both discuss them in terms of documentation via the final summary report. While the FDA draft guidance does not specifically mention deviations, the subject can be inferred under the contents of the qualification plan: “the criteria appropriate to assess outcomes [should include how to deal with deviations].”

Summary and Recommendations

Table B summarizes the similarities and differences between the US FDA, EU GMPs, and ASTM E2500 with respect to demonstrating manufacturing systems are suitable for their intended use.

It is this author’s opinion that if a project team follows the requirements of the ASTM E2500 standard, it will have met the expectations of both US FDA and EU regulators for demonstrating manufacturing system suitability for use. While project teams may choose to be sensitive as to what labels are attached to what documents and to a few particulars of the regulations, overall the ASTM standard provides the most robust, science- and risk-based methodology of any of the documents discussed.

For those who feel more comfortable having documents labeled “DQ, IQ, OQ, and PQ,” the following is suggested with respect to documents typically produced during an ASTM E2500-based project.

- The final risk assessment and identification of critical aspects/acceptance criteria and confirmation that the design includes all process requirements could be labeled the DQ.
- A checklist of these critical aspects and their acceptance criteria could be used to review the verification/commissioning work to confirm all critical aspects have been checked.

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Defining Regulatory Expectations

<table>
<thead>
<tr>
<th>Qualification Expectation</th>
<th>ASTM</th>
<th>FDA</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus on science-based process understanding and meeting process requirements</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Equipment and facilities suitable for intended use</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>QA approves [qualification] [verification] plan</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>QA approves [qualification] [verification] report</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>QA approves protocols</td>
<td>Note 1</td>
<td>Note 1</td>
<td>Note 2</td>
</tr>
<tr>
<td>Risk assessment to “scale” effort, documentation</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Flexibility on how effort is structured</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Specific aspects to check are spelled out</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Critical aspects derived from risk assessments and process requirements</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of project change management</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Use of subject matter experts: how to verify, adjudicate departures from specification</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of vendor documents</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design and testing of facility, process, equipment based on process understanding</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Final report to summarize findings and deviations</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Note 1: The QA unit is to approve the acceptance criteria and other high level aspects of the qualification planning effort as discussed under Planning for Qualification.

Note 2: QA approval is inferred. EU Annex 15 requires approval of protocols, but does not state by whom.

Table B. Summary comparison of key expectations of ASTM E2500 program, FDA process validation guidance, and EU GMP Annex 15.

These checklists could be labeled “IQ/OQ” protocols. These checklists could actually be created or copied from the final risk assessment and list of critical aspects, eliminating a separate protocol pre-approval step – the approval of the DQ also could serve as the approval of these checklists.

- A similar approach could be taken for PQ work or a more traditional PQ protocol could be used that includes the specific test cases and instructions for execution.
- These checklists that are labeled IQ/OQ protocols also could be used as the final verification report and the approval thereof would constitute the acceptance and release phase of ASTM standard.

As a cautionary note, it is the author’s experience that teams attempting to implement ASTM E2500 with respect to risk assessments and contents of protocols spend significant effort trying to understand and spell out the detailed mechanics of documentation format, structures, what goes where, etc. It also is the author’s experience that teams tend to view risk assessments solely through the lens of focusing on the inspection and testing (verification/qualification) effort. That is not the intent of ICH Q9, Quality Risk Management. Instead, it is the author’s recommendation that teams approach risk assessments with a holistic view – conduct risk assessments with the idea of identifying, assessing, and controlling risk to the patient through a variety of means (engineering and other quality system-related means). The risk assessments should commence at a high level starting with conceptual design, continuing through more detail as the design develops. It will then become apparent to teams as to how to use these results – to improve the design, to improve procedures, to improve training, to improve other aspects of the quality system, not to mention providing a focus on the critical design and operating aspects of the manufacturing systems.

References

2. See the FDA/International Conference on Harmonisation (ICH) guidance for industry:
   a. Q8 Pharmaceutical Development
   b. Q9 Quality Risk Management
   c. Q10 Pharmaceutical Quality Systems

About the Author

Robert E. Chew, PE is President and CEO of Commissioning Agents, Inc. and has 20 years of experience in the pharmaceutical industry. He was a member of the Author Task Team which produced the recent ASTM E2500-07 International Standard. Chew also is a member of the team currently writing the ISPE Baseline Guide Volume 12: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment. He is a former member of ISPE’s International Board of Directors, and has been a frequent speaker for ISPE globally. He graduated in 1981 with a BS in chemical engineering from Case Western Reserve University. He can be reached by telephone: +1-317-710-1530 or by email: Robert.Chew@Cagents.com.

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