Designation: E2500 – 20

Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment[1]

This standard is issued under the fixed designation E2500; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is applicable to all elements of pharmaceutical and biopharmaceutical manufacturing systems including: good manufacturing practice (GMP) utility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems that have the potential to affect product quality and patient safety.

1.2 For brevity, these are referred to throughout the rest of this guide as *manufacturing systems*.

1.3 This guide may also be applied to laboratory, information, and medical device manufacturing systems.

1.4 This guide is applicable to both new and existing manufacturing systems. The approach may be used for implementation of changes to existing systems.

1.5 This guide is applicable throughout the life-cycle of the manufacturing system from concept to retirement.

1.6 *This standard does not address employee health and safety, environmental, or other non-GxP regulations. This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical Industry

E2474 Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology (Withdrawn 2020)[3]

E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture

E2537 Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing

E2629 Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems

E3051 Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing

2.2 *Other Publications:*

EU GMP Annex 15 Qualification and Validation[4]

FDA Guidance for Industry Process Validation: General Principles and Practices[4]

ICH Q8 Pharmaceutical Development [5]

ICH Q9 Quality Risk Management[5]

ICH Q10 Pharmaceutical Quality System[5]

ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)[5]

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.11 on Process Design.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] The last approved version of this historical standard is referenced on www.astm.org.

[4] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

[5] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, 9, chemin des Mines, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach[4]

3. Terminology

3.1 *Definitions*—For definitions of terms used in this guide, refer to Terminology E2363.

3.1.1 *acceptance criteria, n*—the criteria that a system or component must satisfy in order to be accepted by a user or other authorized entity.

3.1.2 *commissioning, n*—a planned, managed and documented approach to the setting to work, start-up, regulation and adjustment, and installation/ operation/ performance verification necessary to bring equipment, automation and systems to a fully operational state meeting safety and end-user requirements.

3.1.3 *design reviews, n*—planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.

3.1.4 *manufacturing systems, n*—elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems, that have the potential to affect product quality and patient safety.

3.1.5 *qualification, n*—a systematic approach to confirming that manufacturing systems, acting singly or in combination, are suitable (fit) for intended use with respect to patient safety and product quality. Qualification begins with defining suitability for use in a particular manufacturing context, typically based on process and quality risk control strategy, and ends with formal acceptance and release for manufacturing followed by life-cycle continuous improvement.

3.1.6 *subject matter experts (SMEs), n*—individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, engineering, automation, development, operations, and so forth).

3.1.7 *verification, n*—a broad umbrella term that includes specific actions to confirm, with a high degree of assurance, that a particular fabrication, configuration, installation, operation, or performance specification has been satisfied and is suitable for its intended purpose. Verification actions can be of a variety of types, including physical inspection, structural or functional test, document review, performance monitoring, etc. Commissioning and qualification activities are types of verification.

4. Summary of Guide

4.1 This guide describes a risk-based and science-based approach to the specification, design, verification and qualification of manufacturing systems and equipment that have the potential to affect product quality and patient safety.

4.2 This guide describes a systematic, efficient, and effective approach to ensuring that manufacturing systems and equipment are fit for intended use, and that risk to product quality, and consequently to patient safety, are effectively managed to the extent that these are affected by such systems and equipment. This approach provides an effective methodology for qualifying pharmaceutical and biopharmaceutical equipment, systems, facilities and associated automation.

4.3 The overall objective is to provide manufacturing capability to support defined and controlled processes that can consistently produce product meeting defined patient safety and quality requirements.

4.4 The approach described within this guide also supports continuous process capability improvements and enables innovation such as the implementation of process analytical technology (PAT) and single-use systems (SUSs). See Guides E2476 and E2629 for further guidance on risk assessment and verification of PAT systems. See Guide E3051 for guidance on SUSs.

4.5 The main elements of this guide are:

4.5.1 The underlying key concepts that should be applied,

4.5.2 A description of the specification, design, and verification process and their relationship to qualification, and

4.5.3 A description of the required supporting processes.

5. Significance and Use

5.1 Application of the approach described within this guide is intended to satisfy international regulatory expectations in ensuring that manufacturing systems and equipment are fit for intended use, for example, qualified, and to satisfy requirements for design, installation, operation, and performance.

5.2 The approach described in this guide applies concepts and principles introduced in the FDA initiative, *Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach*.

5.3 This guide supports, and is consistent with, the framework described in ICH Q8, ICH Q9, ICH Q10, and ICH Q11.

5.4 This guide is designed to conform with FDA, EU, and other international regulations regarding equipment and facility suitability for use and qualification.

5.5 This guide may be used independently or in conjunction with other Committee E55 standards published by ASTM International.

6. Key Concepts

6.1 This guide applies the following key concepts:

Risk-Based Approach
Science-Based Approach
Critical Aspects of Manufacturing Systems
Quality by Design
Good Engineering Practice
Subject Matter Experts
Use of Vendor Documentation
Continuous Process Improvement

6.2 *Risk-Based Approach:*

6.2.1 Risk management should underpin the specification, design, and verification process, and be applied appropriately at each stage.

6.2.2 Two primary principles of quality risk management are identified in ICH Q9:

6.2.2.1 The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

6.2.2.2 The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

6.2.3 These principles should be applied to specification, design, and verification of manufacturing systems.

6.2.4 The scope and extent of quality risk management for specification, design, and verification activities and documentation should be based on the risk to product quality and patient safety.

6.3 *Science-Based Approach:*

6.3.1 Product and process information, as it relates to product quality and patient safety, should be used as the basis for making science- and risk-based decisions that ensure that the manufacturing systems are designed and verified to be fit for their intended use.

6.3.2 Examples of product and process information to consider include: critical quality attributes (CQAs), critical process parameters (CPPs), process control strategy information, and prior production experience.

6.4 *Critical Aspects of Manufacturing Systems:*

6.4.1 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.

6.4.2 For brevity, these are referred to throughout the rest of this guide as *critical aspects*.

6.4.3 Verification activities should specifically include (though not be limited to) these critical aspects of manufacturing systems and should be documented. The verification process is defined in 7.4. Commissioning is comprised of all verification activities. Qualification includes those verification activities that center on items determined to be critical aspects

6.5 *Quality by Design:*

6.5.1 Quality by design concepts should be applied to ensure that critical aspects are designed into systems during the specification and design process. The critical aspects of the design and associated acceptance criteria should be documented. This will typically require that a risk assessment be performed in conjunction with the development of specifications to identify risks to be mitigated as well as CQA to be achieved.

6.5.2 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.

6.6 *Good Engineering Practice:*

6.6.1 Good engineering practice (GEP) should underpin and support the specification, design, and verification activities.

6.6.2 GEP is defined as those established engineering methods and standards that are applied throughout the life cycle to deliver appropriate and effective solutions.

6.6.3 Examples of GEPs include:

6.6.3.1 Specification, design, and installation activities should take full account of all applicable requirements, including GxP, safety, health, environmental, ergonomic, operational, maintenance, recognized industry standards, and other statutory requirements.

6.6.3.2 Adequate provisions related to quality should be included in specification, design, procurement, and other contractual documents.

6.6.3.3 Life-cycle documentation covering planning, specification, design, verification, installation, acceptance, and maintenance should be produced.

6.6.3.4 An appropriate degree of oversight and control of the construction, installation, and verification of equipment, systems, and facilities should be achieved.

6.7 *Subject Matter Experts:*

6.7.1 SMEs are defined as those individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, engineering, automation, development, operations, and so forth).

6.7.2 SMEs should take the lead role in the verification of manufacturing systems as appropriate within their area of expertise and responsibility.

6.7.3 SME responsibilities include participation in risk management activities, planning and defining verification strategies, defining acceptance criteria, selection of appropriate test methods, execution of verification tests, and reviewing results.

6.8 *Use of Vendor Documentation:*

6.8.1 Vendor documentation, including test documents may be used as part of the verification documentation, providing the regulated company has assessed the vendor, and has evidence of:

6.8.1.1 An acceptable vendor quality system,

6.8.1.2 Vendor technical capability, and

6.8.1.3 Vendor application of GEP such that information obtained from the vendor will be accurate and suitable to meet the purpose of verification.

6.8.2 If inadequacies are found in the vendor quality system, technical capability, or application of GEP, then the regulated company may choose to mitigate potential risks by applying specific, targeted, additional verification checks or other controls rather than repeating vendor activities and replicating vendor documentation.

6.8.3 The decision and justification to use vendor documentation, to support the verification of critical aspects of the manufacturing element, should be based on the intended use of the manufacturing system, and should be documented and approved by SMEs including the quality unit.

6.9 *Continuous Process Improvement:*

6.9.1 As experience is gained in commercial production, opportunities for improvements should be sought based on periodic review and evaluation, operational and performance data, and root-cause analysis of failures. Additionally, as product knowledge and understanding is gained, critical attributes may change as new risks or process needs arise.

6.9.2 Change management should provide a dependable mechanism for prompt implementation of technically sound

improvements following the approach to specification, design, and verification described in this guide.

7. Process

7.1 *Overview*—The process of specification, design, and verification of manufacturing systems should include the following activities:

Requirements Definition
Specification and Design
Verification
Acceptance and Release

When this process is followed, the systems and equipment will achieve a qualified state to begin manufacturing operations.

7.1.1 GEP should be applied throughout the process.

7.1.2 Risk management should be performed as appropriate to evaluate the risks to product quality and patient safety related to the manufacturing system and corresponding design solution. Risk management is a supporting process and is defined in 8.2.

7.1.3 Design reviews should be performed as appropriate throughout the life-cycle of the manufacturing system. The design review process is a supporting process and is defined in 8.3.

7.1.4 Change management should be applied throughout the process. The change management process is a supporting process and is defined in 8.4.

7.2 *Requirements Definition:*

7.2.1 Specific requirements should be identified and should provide the basis of further specification, design, and verification of the manufacturing system.

7.2.2 These specific requirements relative to product quality and patient safety should be based upon:

7.2.2.1 Product knowledge and understanding,

7.2.2.2 Process knowledge and understanding,

7.2.2.3 Regulatory requirements,

7.2.2.4 Company quality requirements, and

7.2.2.5 Known risks to patient safety or product quality such as microbial or particulate contamination.

7.2.3 Product and process knowledge and understanding, including knowledge of sources of variability in the product and process, the identification of critical quality attributes, and process control strategy information, should be based on scientific data gathered during experimental and development work and manufacturing experience. Product and process knowledge forms the basis of scientific understanding as described in ICH Q8 and ICH Q11.

7.2.4 The quality unit should be involved providing input to both the regulatory and company quality requirements, including requirements from existing product submissions/licenses if appropriate. Additionally, the quality representative should be closely involved in reviewing risks to the product as well as mitigations.

7.3 *Specification and Design:*

7.3.1 Firms should develop appropriate mechanisms to communicate requirement inputs, including product quality considerations, to those responsible for design, so that the manufacturing system may be properly designed based upon relevant knowledge of product, process, and other requirements. Practices for process design where process analytical technology is employed may be found in Practice E2474.

7.3.2 Specification and design activities should include a focus on those aspects that have been identified as being critical to product quality and patient safety. These critical aspects of the manufacturing system should be identified and documented by SMEs.

7.4 *Verification:*

7.4.1 The verification activities should be defined and documented. The extent of verification and the level of detail of documentation should be based on risk and the complexity and novelty of the manufacturing system. Information on verification can be found in Guides E2537 and E2629 and FDA Guidance for Industry Process Validation: General Principles and Practices.

7.4.2 Commissioning should include verification actions to confirm that the equipment and systems have been properly installed and are operating correctly. Commissioning should

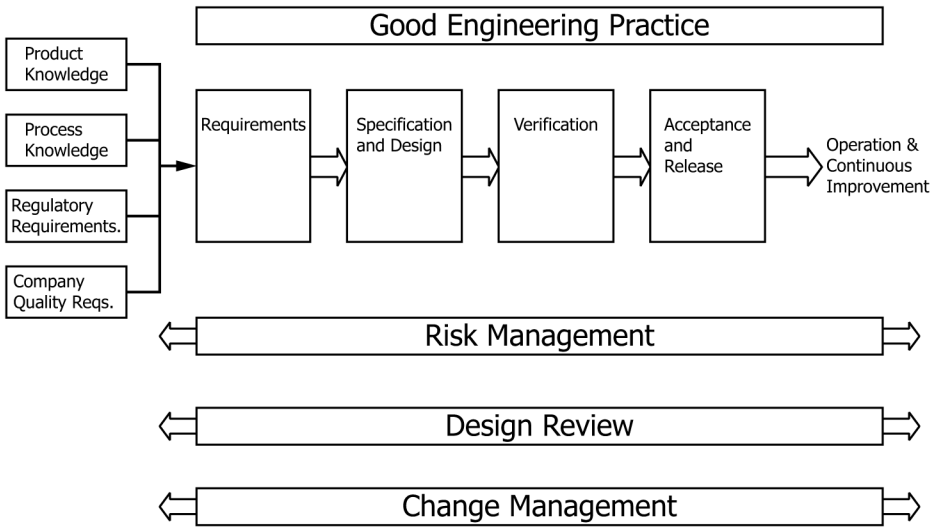

FIG. 1 The Specification, Design, and Verification Process