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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: 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.

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 the implementation of changes to existing systems, and their continuous improvement during operation.

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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E2474 Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

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 Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing

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

2.2 *Other Publications:*

FDA Guidance for Industry Process Validation: General Principles and Practices[3]

ICH Q8 Pharmaceutical Development [4]

ICH Q9 Quality Risk Management[4]

ICH Q10 Pharmaceutical Quality System[4]

ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)[4]

Pharmaceutical cGMPs for the 21st Century —A Risk-Based Approach[3]

3. Terminology

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

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

3.1.2 *design reviews*—planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the

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

[4] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.

3.1.3 *manufacturing systems*—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.

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

3.1.5 *verification*—a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.

4. Summary of Guide

4.1 This guide describes a risk-based 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.

4.2 This guide describes a systematic, efficient, and effective way of 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.

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

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

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, 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 may be used independently or in conjunction with other 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 Expert
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 focus on these aspects of manufacturing systems and should be documented. The verification process is defined in 7.4.

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.

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 Good Engineering Practice 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 Good Engineering Practices 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 should be achieved by suitable verification of execution, construction and installation activities.

6.7 *Subject Matter Experts:*

6.7.1 Subject matter experts 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 Subject matter experts should take the lead role in the verification of manufacturing systems as appropriate within their area of expertise and responsibility.

6.7.3 Subject matter expert responsibilities include 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 subject matter experts including the quality unit.

6.9 *Continuous 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.

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

7.1.1 Good Engineering Practice 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, and

7.2.2.4 Company quality requirements.

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, ICH Q11, and Guide E2475.

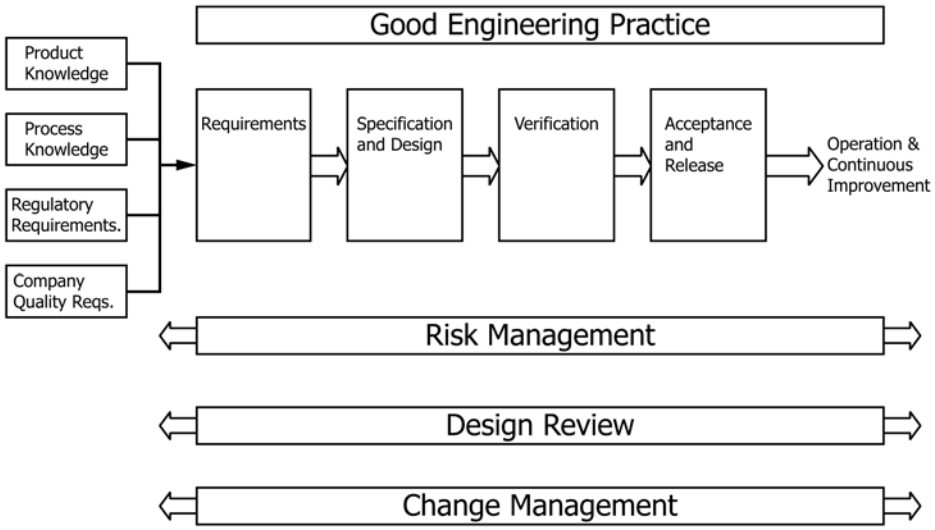

FIG. 1 The Specification, Design, and Verification Process

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 subject matter experts.

7.4 *Verification*—A systematic approach should be defined to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This verification approach should be defined and documented. The extent of verification and the level of detail of documentation should be based on risk, including those associated with product quality and patient safety, 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.

7.4.1 *Acceptance Criteria:*

7.4.1.1 Acceptance criteria are the criteria that a manufacturing system must satisfy in order to be fit for intended use and to be accepted by a user or other authorized entity.

7.4.1.2 Acceptance criteria should be defined by subject matter experts.

7.4.1.3 Acceptance criteria of critical aspects (that is, critical to product quality and patient safety) should be approved by the quality unit.

7.4.2 *Verification Strategy:*

7.4.2.1 The acceptance criteria and verification strategy should be documented in appropriate verification plans.

7.4.2.2 The verification plan should define what constitutes acceptable documentation of subsequent verification activities.

7.4.2.3 The verification plan should be developed and approved by subject matter experts. Verification plans for systems containing critical aspects should be approved by the quality unit.

7.4.3 *Verification Activities:*

7.4.3.1 Subject matter experts should perform or oversee verification activities, and document verification results, as defined in the verification plans.

7.4.3.2 Vendor verification documentation may be used, as described in 6.8.

7.4.3.3 The completion of verification activities should be documented.

7.4.4 *Verification Review:*

7.4.4.1 All completed verification documentation should be reviewed by suitably qualified and independent subject matter expert(s), who did not execute the verification test.

7.4.4.2 The reviewers should ensure that all tests have been completed and appropriately documented.

7.4.4.3 Departures and deviations from verification plans should be addressed and resolved by the reviewer and/or other appropriate subject matter expert(s).

7.5 *Acceptance and Release:*

7.5.1 Subject matter experts should confirm that the manufacturing system is fit for intended use. This confirmation should be documented.

7.5.2 Such documentation should include a review or overview of the results, and a review of any non-conformance with stated acceptance criteria of critical aspects.

7.5.3 The documentation should contain a clear statement as to whether or not the manufacturing system is fit for intended use, based on this review. The persons involved in making this determination should be identified and documented.

7.5.4 Such documentation should be prepared and approved by subject matter experts. Such documentation for systems with critical aspects should be approved by the quality unit.

7.5.5 Following these approvals, the manufacturing system may be released for operational use.

8. Supporting Processes

8.1 The specification, design, and verification process described should be supported by risk management, design review, and change management, as described in the following subsections.

8.2 *Quality Risk Management:*

8.2.1 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug and the safety of the patient.

8.2.2 Risk assessments should be performed at appropriate stages to evaluate the risks to product quality and patient safety related to the manufacturing systems and corresponding design solutions.

8.2.3 The risks pertaining to delivery including vendor or construction risk, and risks due to technological novelty or complexity should be considered relative to their ultimate impact on product quality and patient safety.

8.2.4 Risk assessments should be performed by appropriate subject matter experts.

8.2.5 Based on risk assessments, appropriate controls and verification techniques should be selected to manage risk to an acceptable level, focusing on those relating to the critical aspects of the manufacturing system.

8.2.6 The level of control and verification should be commensurate with the level of risk to product quality and patient safety.

8.2.7 Where risks cannot be eliminated by design, other appropriate risk control mechanisms should be applied.

8.2.8 More details on risk management can be found in ICH Q9 and Guide E2476.

8.3 *Design Review:*

8.3.1 Design reviews are planned and systematic reviews of specifications, design, design development, and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system.

8.3.2 Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.

8.3.3 Design reviews should be employed to ensure that:

8.3.3.1 Product and process requirements are satisfied by the design.

8.3.3.2 Critical aspects of manufacturing systems are appropriately addressed.

8.3.3.3 Risks to product quality and patient safety have been identified.

8.3.3.4 Unacceptable risks are mitigated by design or by other means.

8.3.4 Design review should be performed by appropriate subject matter experts.

8.3.5 Design reviews should be documented. The individuals performing the review should be identified.

8.3.6 Design review documentation should include a statement that the item in question is acceptable, provided the proposed corrective actions are completed.

8.4 *Change Management:*

8.4.1 Change management processes should be established and be applied throughout the life-cycle.

8.4.2 Before acceptance, change management should be applied. This process should be managed by, and changes approved by, subject matter experts. Changes affecting critical aspects of manufacturing systems should be communicated to the quality unit.

8.4.3 After acceptance, prior to manufacturing for commercial use, operational change management should be applied. Under operational change management, all changes related to specific requirements relative to product quality and patient safety require prior approval by the quality unit, unless predefined arrangements are established covering specific types of changes or circumstances.