Designation: E2500 – 13

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

[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 E55.03 on General Pharmaceutical Standards.

Current edition approved Nov. 1, 2013. Published November 2013. Originally approved in 2007. Last previous edition approved in 2012 as E2500 – 07 (2012). DOI: 10.1520/E2500-13.

[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