Designation: E2476 – 22

Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture[1]

This standard is issued under the fixed designation E2476; 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.

INTRODUCTION

This document provides guidance on the implementation of risk assessment and risk control for Process Analytical Technology (PAT) processes within the pharmaceutical industry. Wherever possible, other appropriate standards on risk assessment/management have been referenced and acknowledged. Where practical, further details of methods and additional references have been provided for information within the appendixes.

The application of risk assessment and risk control is pivotal to the creation of PAT systems, which are described as "science-based" and "risk-based." Such application starts at an early stage in the development of the process and continues throughout development and production. In the production phase, it is a crucial component of applying continuous improvement to the process.

RELATIONSHIP TO ICH Q9

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 Guideline for Quality Risk Management is intended for general application within the pharmaceutical industry. ICH Q9 describes the requirements for pharmaceutical quality risk management and considers the risk as "risk to the patient."

This document provides specific guidance on the risk assessment and risk control phases identified in ICH Q9 in a limited set of conditions. It is applicable where the manufacturing method is compliant with Process Analytical Technology (PAT) principles, and where the primary considerations are product quality and reduction of process and product variability. The only component of risk to patient considered here is risk to product quality. Other components fall outside the scope of the document. In addition, other areas identified in ICH Q9, such as general risk management and risk communication, are not considered here.

This document provides guidance which applies to the design, development, and operation of PAT systems. It should be considered as a specific extension, supporting the ICH Q9 guidance for these processes.

1. Scope

1.1 This document provides guidance on the assessment of risks to product quality within and related to PAT processes in the pharmaceutical industry. It addresses those risks to product quality arising from, associated with, identified by, or modified by the implementation of PAT in pharmaceutical development and manufacturing for primary, secondary, and biotech sectors of the industry. It does not replace those assessments of risk currently undertaken by pharmaceutical companies, but is, rather, an additional component focused specifically upon the evaluation and design of PAT processes. See Guide E2500 and ICH Q8.

1.2 *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] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.01 on Process Understanding and PAT System Management, Implementation and Practice.

Current edition approved Nov. 1, 2022. Published December 2022. Originally approved in 2009. Last previous edition approved in 2016 as E2476 – 16. DOI: 10.1520/E2476-22.

Note that safety in this context refers to operational and operator safety, not to patient safety.

1.3 *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 Process Analytical Technology in the Pharmaceutical Industry

E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

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

2.2 *Other Standards and Guidance Documents:*

FDA Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[3]

ICH Q8 (R2) Pharmaceutical Development[4]

ICH Q9 Quality Risk Management[4]

ICH Q10 Pharmaceutical Quality System[4]

IEC 60812 Analysis Techniques for System Reliability—Procedure for Failure Mode and Effects Analysis (FMEA)[5]

IEC 61025 Fault Tree Analysis (FTA)[5]

IEC 61882 Hazard and Operability Studies (HAZOP Studies)—Application Guide[5]

ISO 22000 Food Safety Management Systems—Requirements for any Organization in the Food Chain[6]

WHO Technical Report 908 WHO Expert Committee on Specifications for Pharmaceutical Preparations[7]

3. Terminology

3.1 The terminology specific to this guide will be incorporated into Terminology E2363.

4. Significance and Use

4.1 This guide is intended to provide guidance regarding the use of risk management in the development, day-to-day running, and continuous improvement of pharmaceutical processes incorporating Process Analytical Technology (PAT). A consistent approach to the use of risk methodologies should be adopted to ensure rapid transfer of process understanding within the development and manufacturing teams, and to the regulators where that is appropriate.

4.2 This guidance only covers those aspects of risk assessment related to "risk to product quality." Other aspects (such as "risk to patient") should be covered in the conventional manner.

5. Principles of Risk Assessment and Risk Control

5.1 *Background*—Risk management has been widely used in manufacturing and service industries for many years. In some industries, risk management has become formalized into a highly structured approach which has become the subject of standardization. This standardization has a number of benefits including:

5.1.1 Widespread acceptance based on consensus among all interested parties, which makes regulatory approval easier,

5.1.2 Easy comparison of equivalent processes between sites, companies, and continents,

5.1.3 Ready transferability of skilled labor, and

5.1.4 Standardized training.

5.2 *High-Level Characteristics of Risk Assessment*—A risk assessment for a PAT process has, in addition to the principles outlined in ICH Q9, a number of key characteristics:

5.2.1 It is systematic and structured.

5.2.2 It is primarily evidence-based. Evidence may include direct experience, historical knowledge, professional judgment, etc.

5.2.3 It specifically focuses upon uncertainty or variability, or both, in product quality and the causes of such uncertainty/variability.

5.2.4 It is an integral component of the decision-making process.

5.2.5 It guides risk control and mitigation; that is, it recognizes that the primary consideration is product quality and identifies those areas where risks must be reduced and provides a mechanism for assessing when the risk has been sufficiently reduced.

5.2.6 It is multi-layered. It can be applied at many levels, that is, lower-level, more detailed assessments feeding into higher-level, broader scope assessments. (For example, a higher-level risk assessment for the finished product will have lower-level risk assessments for each of the process stages which feed into it.) Breaking risk assessment into layers makes complex evaluations simpler to perform, simpler to understand, and simplifies the generation of a detailed response. It also assists in the process of identifying specific targets for reducing the risk.

5.2.6.1 In general, an initial high-level risk assessment will identify most of the high-risk areas. Subsequent lower-level risk assessments, and resulting mitigation actions, will focus initially upon these identified areas of high risk, moving to those areas of intermediate and lower risk at a later stage in the process. This later amelioration of the risk may be part of a continuous improvement process.

5.2.7 It is dynamic and iterative. It will remain active for the lifecycle of a product, responding to changing commercial,

[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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

[5] Available from International Electrotechnical Commission (IEC), 3 rue de Varembé, Case postale 131, CH-1211, Geneva 20, Switzerland, http://www.iec.ch.

[6] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[7] Available from World Health Organization (WHO), https://www.who.int.