



Standard Guide for Process Understanding Related to Pharmaceutical Manufacture and Control¹

This standard is issued under the fixed designation E2475; 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 The purpose of this guide is to establish a framework and context for process understanding for pharmaceutical manufacturing using quality by design (QbD) (Juran, 1992;² FDA/ICH Q8). The framework is applicable to both active pharmaceutical ingredient (API) and to drug product (DP) manufacturing. High (detailed) level process understanding can be used to facilitate production of product which consistently meets required specifications. It can also play a key role in continuous process improvement efforts.

1.2 Process Analytical Technology (PAT) is one element that can be used for achieving control over those inputs determined to be critical to a process. It is important for the reader to recognize that PAT is defined as:

“...a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in process materials and processes, with the goal of ensuring final product quality. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process...” (U.S. FDA PAT)

1.3 *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:³

E456 Terminology Relating to Quality and Statistics

E2281 Practice for Process Capability and Performance Measurement

E2474 Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology

E2617 Practice for Validation of Empirically Derived Multivariate Calibrations

2.2 *U.S. Government Publications:*⁴

FDA/ICH Q8 Pharmaceutical Development

FDA/ICH Q10 Pharmaceutical Quality Systems

U.S. FDA PAT Guidance Document, Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

3. Terminology

3.1 Definitions of Terms Specific to This Standard:

3.1.1 *critical inputs, n*—critical process parameters and critical raw material attributes for a given process.

American Society for Quality⁵

3.1.2 *empirical, adj*—any conclusion based on experimental data and past experience, rather than on theory.

3.1.3 *expert system, n*—an expert system is a computer program that simulates the judgment and behavior of a human or an organization that has expert knowledge and experience in a particular field.

3.1.3.1 *Discussion*—Typically, such a system contains a knowledge base containing accumulated experience and a set of rules for applying the knowledge base to each particular situation that is described to the program. Sophisticated expert systems can be enhanced with additions to the knowledge base or to the set of rules.

3.1.4 *first principles, n*—a calculation is said to be from first principles, or *ab initio*, if it starts directly at the level of established laws of physics and does not make assumptions such as model and fitting parameters.

3.1.5 *mechanistic, adj*—(*I*) of, or relating to, theories that explain phenomena in purely physical or deterministic terms: a mechanistic interpretation of nature.

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 Sept. 1, 2016. Published September 2016. Originally approved in 2010. Last previous edition approved in 2010 as E2475 – 10. DOI:10.1520/E2475-10R16.

² Juran, J., *Juran on Quality by Design: The New Steps for Planning Quality Into Goods and Services*, Free Press, New York, N.Y., 1992.

³ 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.

⁴ Available from U.S. Government Printing Office Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, <http://www.access.gpo.gov>.

⁵ Available from American Society for Quality (ASQ), 600 N. Plankinton Ave., Milwaukee, WI 53203, <http://www.asq.org>.