Designation: E2475 – 23

Standard Guide for Process Understanding Related to Pharmaceutical Manufacture and Control[1]

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 the principles of quality by design (QbD) (Juran, 1992;[2] ICH Q8). The framework is applicable to both drug substance (DS) and 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 continual 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..." (USFDA 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, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.4 *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:*[3]

E456 Terminology Relating to Quality and Statistics

E2281 Practice for Process Capability and Performance Measurement

E2617 Practice for Validation of Empirically Derived Multivariate Calibrations

2.2 *U.S. Government Publications:*[4]

ICH Quality Implementation Working Group Points To Consider (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

ICH Q8 Pharmaceutical Development

ICH Q9 Quality Risk Management

ICH Q10 Pharmaceutical Quality Systems

ICH Q11 Development and Manufacture of Drug Substances

ISO 14971 Medical devices—Application of risk management to medical devices

USFDA 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.

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

[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.

Current edition approved Nov. 15, 2023. Published December 2023. Originally approved in 2010. Last previous edition approved in 2016 as E2475 – 10 (2016). DOI:10.1520/E2475-23.

[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.

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

3.1.6 *process capability, n*—statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control. **E2281**

3.1.7 *process inputs, n*—the combination of all process parameters and raw material attributes for a given process.

3.1.8 *process understanding, v*—to recall and comprehend process knowledge such that product quality can be explained logically or scientifically, or both, as a function of process inputs and respond accordingly.

3.1.9 *quality attribute, n*—a physical, chemical, biological, or microbiological property or characteristic of a product.

3.1.10 *residual error, n*—the difference between the observed result and the predicted value (estimated treatment response); Observed Result minus Predicted Value. **E456**

3.1.11 *uncertainty, n*—an indication of the variability associated with a measured value that takes into account two major components of error: (*1*) bias, and (*2*) the random error attributed to the imprecision of the measurement process. **E456**

4. Process Understanding

4.1 From physical, chemical, biological, and microbiological perspectives, a process is considered to be well understood when:

(1) All critical sources of variability are identified and explained,

(2) variability is managed by the process, and

(3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

4.2 Well-controlled processes result in the probability of product not meeting required specifications at a level that is below the maximum acceptable limit as predetermined by the user. Accordingly, process understanding requires the comprehension and recall of process knowledge sufficient for the logical, statistical, or scientific understanding, or combination thereof, of how significant process parameters and attributes of raw and in-process materials relate to, or impact the quality attributes of, the product being produced. Sufficient process understanding should be achieved to reduce risk to an acceptable level for the patient, manufacturer, or any other stakeholder.

4.3 *A Lifecycle Commitment (Development and Commercial Manufacture):*

4.3.1 Process understanding is fundamental to QbD. It is important to realize that due to commercial realities (for example, finite resources, time, and money), a process will typically be commissioned as soon as the degree of process understanding is sufficient to permit operation of the process with an acceptably low, user specified, level of risk of producing out of specification product. While it may be appropriate to commission a process once this minimum degree of process understanding is achieved, the risk that the process may transition out of control steadily increases over time (for example, process drift), and could exceed the maximum acceptable risk without warning, unless an ongoing program to enhance process understanding is in place.

4.3.2 Accordingly, the improvement of process understanding should be treated as an ongoing exercise. Learning should continue throughout the product and process life cycle to improve the level of process understanding to include process parameters and other factors (for example, environmental, changes of scale, changes in raw materials, changes in personnel) which may have changed from the initial design of the chemical or biological DS or DP through manufacturing of the unit dose to final packaging. Work to enhance process understanding continuously throughout the life cycle of the product and process can provide assurance that the process will continue to have an acceptably low risk of producing out of specification results.

4.3.3 Manufacturers should have an ongoing program for monitoring and improving upon their operations to enhance product quality.

4.4 *Process Understanding for the Whole Process:*

4.4.1 For each product, process understanding covers the process from the initial design of the chemical or biological DS through manufacturing of the unit dose or device to final packaging. In addition, the critical quality attributes of the raw materials will in turn become inputs to the DP manufacturing process, as will process parameters.

4.4.2 Fig. 1 schematically illustrates that the performance of any process output (*Y*) is a function of the inputs (*X*), which can be classified into one of six categories (that is, operator, equipment, measurements, methods, materials, and environmental conditions).

4.4.3 Comprehensive understanding of the relationships of the process inputs and operating parameters to quality attributes of the resulting product is fundamental to developing a successful risk mitigation or control strategy, or both. Identification of critical process parameters (CPPs) and critical raw material attributes (CMAs) should be carried out using suitable experimental and investigative techniques. An understanding of these critical inputs (CPPs and CMAs), and their monitoring and control, is essential when designing a process that is able to consistently and reliably deliver product of the desired quality.

4.4.4 One common method for achieving the desired state is through multivariate analysis and control. The acceptable operating envelope of the critical inputs defines the relationship between input ranges and product quality.

4.4.5 Note that for raw materials, in addition to inherent variability, an additional source of variability derives from the potential for adulteration. This requires that manufacturers understand their incoming supply chain and suppliers quality

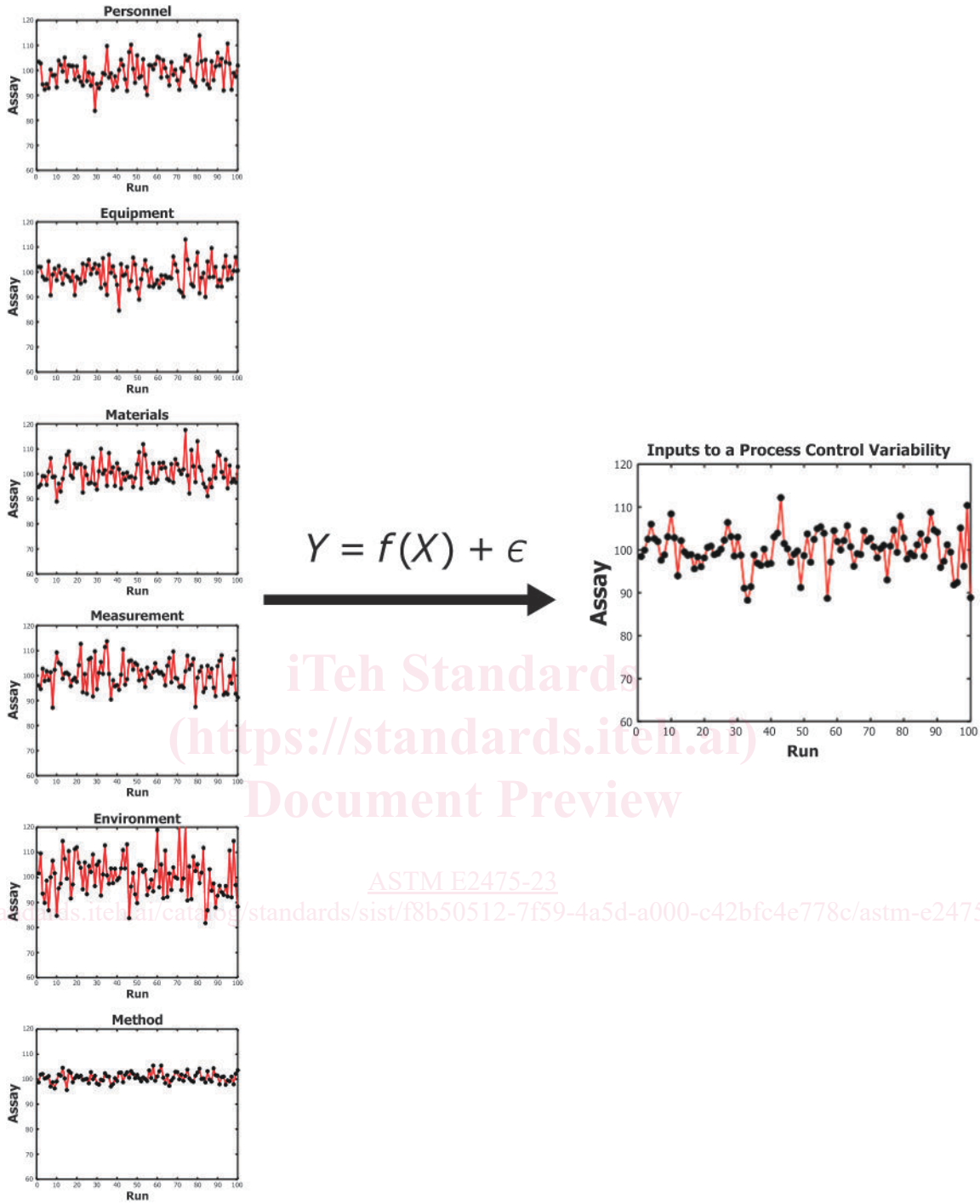

FIG. 1 Input, Process, and Output Diagram

systems, and include methods to detect adulteration of materials in addition to confirming identity as necessary, bearing in mind that adulteration may be difficult to detect by standard methods. It also requires that manufacturers use suppliers that are aware of these concerns and are prepared to implement their own precautionary measures, and to permit transparency into their respective supply sources.

4.5 *Tools of Process Understanding:*

4.5.1 Process understanding begins with process design and usually a structured, small scale development program which focuses on efficiently delivering a product that meets the required specifications. Tools that may be applied during development and after commercialization include:

(1) Scientific theory,

(2) Prior knowledge,

(3) Risk analysis,