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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] ~~FDA/ICH Q8).~~ICH Q8). The framework is applicable to both ~~active pharmaceutical ingredient (API) and to~~ 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 ~~continuous~~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…" (U.S. FDA PAT)~~
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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~~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

[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.

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[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.

E2281 Practice for Process Capability and Performance Measurement
~~E2474 Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology (Withdrawn 2020)[4]~~
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
~~FDA/ICH Q8~~ICH Q8 Pharmaceutical Development
ICH Q9 Quality Risk Management
~~FDA/ICH Q10~~ICH Q10 Pharmaceutical Quality Systems
ICH Q11 Development and Manufacture of Drug Substances
ISO 14971 Medical devices—Application of risk management to medical devices
~~U.S. FDA PAT~~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.
~~American Society for Quality[6]~~

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*—(*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] 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.

4. Process Understanding

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

(1) All ~~significant~~critical sources of variability ~~in process inputs~~ are identified and explained,

(2) variability is managed by the process, and

(3) ~~The effect of these sources of variability on~~ product quality attributes can be accurately and reliably ~~estimated based on the inputs to the process, and~~predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

~~*(3)* Significant process parameters are continuously managed and controlled to ensure that the process must produce product which is continuously within required specifications to the user specified required degree or confidence.~~

4.2 ~~A well-controlled process is a process where the risk of producing~~ Well-controlled processes result in the probability of product not meeting required specifications at a level that is below the maximum acceptable ~~level of risk~~ 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 ~~raw material attributes~~ 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 ~~development~~improvement of process understanding should be treated as an ongoing ~~process.~~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 ~~or which may have newly emerged since the time the process was first commissioned.~~ 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 ~~are encouraged to continuously monitor and improve~~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 ~~drug substance~~ 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 ~~drug product~~ 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 ~~critical raw material attributes),~~ 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.

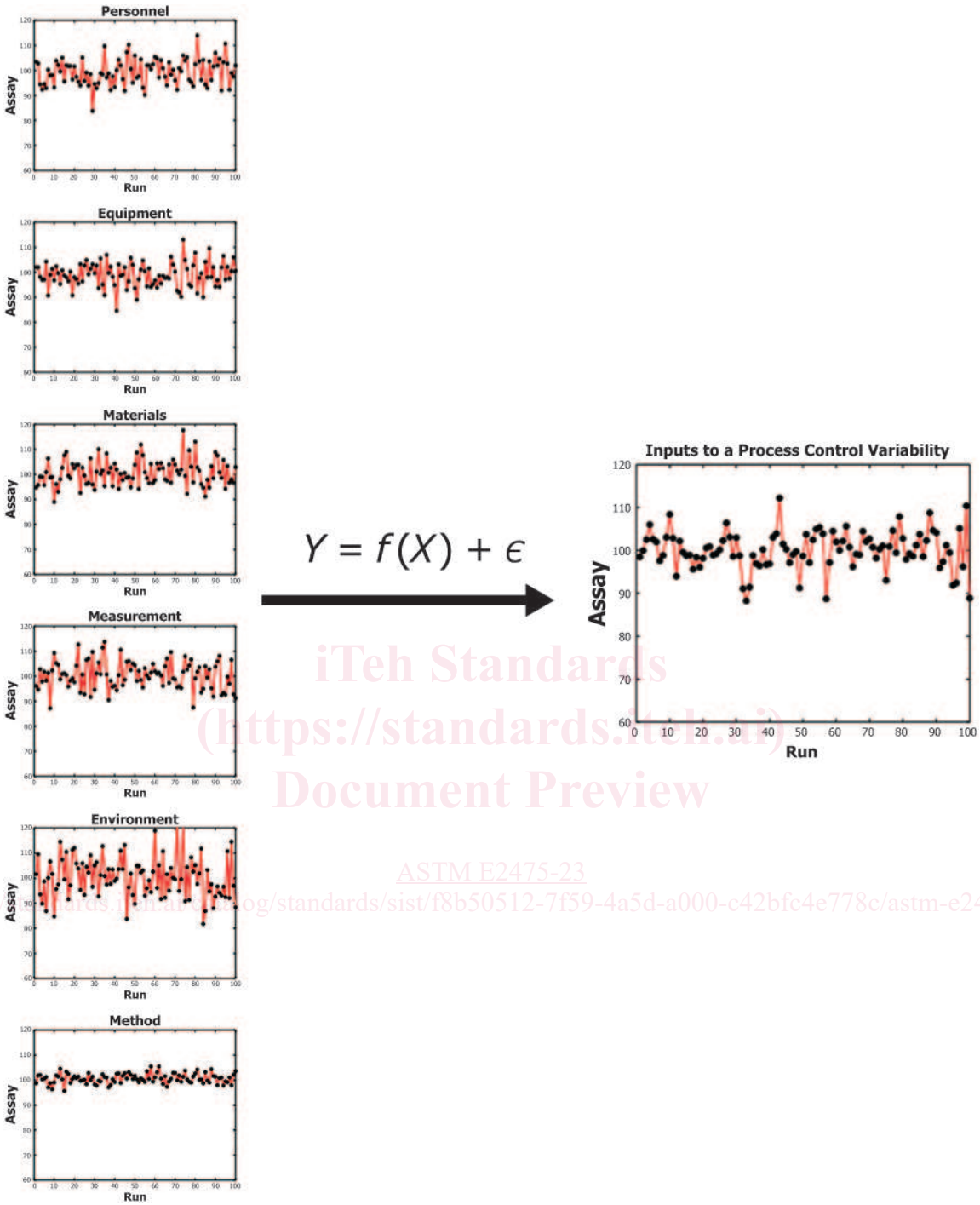

FIG. 1 Input, Process, and Output Diagram

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 ~~the design space, control strategy and operating range(s).~~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 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 ~~(Practice E2474)~~ and usually a structured, small scale development program which focuses on efficiently delivering a product ~~meeting~~ 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,
(4) Design of experiments,
(5) Simulation of unit operations,
(6) Selection of a suitable technology platform,
(7) Mathematical models,
(8) Validated empirical/statistical models,
(9) Appropriate instrumentation, and
(10) Appropriate analytical methods.

~~4.5.2 The measurement technologies include but are not limited to spectroscopic, acoustic, or other rapid sensor technologies. The development of these and other advanced techniques will continue to enable or enhance predictive control for commercial pharmaceutical processes.~~

4.5.2 The measurement technologies encompass offline, atline, online, and inline technologies. Online and inline measurement technologies can include but are not limited to spectroscopic, acoustic, or other rapid sensor technologies. The development of these and other advanced techniques will continue to enable or enhance predictive control for commercial pharmaceutical processes.

The ability to measure process parameters and quality attributes inline, online, or atline in real time can contribute to process understanding and the ability to control the process. These technologies offer the development scientist, commercial production engineer and manufacturing personnel the opportunity for additional insight. This is achieved through the increased measurement frequency and availability of more comprehensive data.

5. Process Knowledge

5.1 Process knowledge is the cornerstone of process understanding. There are various levels of process knowledge, and these are listed from lowest to highest state of understanding:

(1) Descriptive knowledge (what is occurring?),
(2) Correlative knowledge (what correlations are empirically observed?),
(3) Causal knowledge (empirical, what causes what?),
(4) Mechanistic knowledge (explanations for observed causality), and
(5) First principles knowledge (underlying physical, chemical, and biological phenomena of the mechanistic explanations).

5.2 Process knowledge is the accumulated facts about the process. This accumulated knowledge is generally embodied in a model of the process. Accordingly, *process model* is often used synonymously with *process knowledge*.

5.3 Process understanding is demonstrated by the extent to which process knowledge can be used to predict and control the process outcomes; a well understood process will combine knowledge from various sources to ensure a well controlled process and consistent product quality.

5.4 At any point in time for any manufacturing process, the level of understanding will likely be a combination of various levels of understanding. As more knowledge is obtained throughout the lifecycle of a product, the relative contribution to understanding of the various levels is likely to change.

5.5 Prior knowledge is any knowledge that may be available through previous experience. Prior knowledge may come from a number of sources including scientific literature, company experience from research and development, and existing commercial products as a result of lab and manufacturing investigations. All knowledge that is available should be considered and placed in context in order to optimize the overall level of understanding.

5.6 Within most organizations in the early stages of QbD implementation, process understanding tends to be based mainly on *descriptive* and *correlative* and scientific knowledge. The framework outlined in the ~~FDA's~~USFDA's "Pharmaceutical cGMPS for the 21st Century — A Risk-Based Approach"[5] should encourage the pharmaceutical industry to enhance understanding by adding process knowledge at the *causal, mechanistic*, and *first principles* levels.

5.7 Mechanistic and first principles process models can offer advantages over process models which are a combination of only descriptive, correlative, and causative process knowledge. Proper evaluation of risk may be more challenging in the absence of mechanistic or first principles process knowledge. The user is responsible for determining the level of process knowledge which is appropriate for each specific circumstance.

5.8 The subsequent subsections provide greater detail and discussion for each state of knowledge.

5.9 This guide does not differentiate between programs to develop understanding for products and processes for new molecular entities or existing products and processes. The tool sets for each circumstance may be different considering the available sources of data that can be used, such as existing experimental data, historical databases or practical or logistical constraints.

5.10 The level of understanding that is chosen for each product or process should be based on a sound science and risk-based approach. The desired level of understanding will depend on a number of factors including quality, criticality, time and cost. Maintenance of comprehensive, contemporaneous documentation of the science, risk and knowledge is important.

5.11 Mechanistic and first principles models may provide an enhanced ability to indicate alternative process operating parameters which will also produce acceptable product. When process models of any kind are being used, appropriate independent validation of the model should be conducted before applying any model outside of the region of the process operating space for which the model has already been validated. As always, it is the user's responsibility to determine, using a risk-based approach, the appropriate level and frequency of model validation.

5.12 Periodic evaluation and re-validation (Practice E2617~~)~~, ICH Quality Implementation Working Group Points To Consider (R2)) of models should be conducted throughout a product's lifecycle. This is true from research and development phases and throughout commercialization of a product, where additional data (for example, non-conformances, investigations) from multiple manufacturing lots and a large patient base can lead to further understanding and improved control. ~~Models should be periodically re-evaluated, revised, or re-validated as appropriate.~~

5.13 *Empirical models* are built by applying appropriate numerical methods to representative datasets. The numerical methods rely on the correlations between the measured data and the process parameters. Empirical models depend on the availability of sufficient quantities of representative data. Empirical models require that there are stable, reliable correlations of variance in the data to product quality attributes, but these models do not require explicit process knowledge.

5.14 *Mechanistic models* are built on a fundamental knowledge of the underlying interactions in the process. In addition, experiments may be conducted to reveal or test, or both, those interactions. Generally, mechanistic models comprise some combination of physiochemical, biochemical, or energy and mass balance terms, or combination thereof. Mechanistic models often require less data than empirical models but a deeper understanding of the physics, chemistry, or biology of the process. Mechanistic models must also be qualified for deployment by appropriate, user determined validation. On a risk management basis, mechanistic models generally require much less ongoing validation than empirical models.

5.15 Accurate mechanistic models may provide more reliable estimations of the process behavior and offer more opportunities for process insights. Accurate mechanistic models are frequently used to inform and guide the design of processes whereas properly validated empirical models are frequently used as the basis for process control.

[5] Available from U.S. Food and Drug Administration ~~(FDA),~~(USFDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, available online, ~~http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticesGMPforDrugs/UCM176374.pdf;~~https://www.fda.gov/media/77391/download; available as of ~~Sept. 1, 2016.~~Oct. 23, 2021.