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

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 Quality[5]

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

3.1.10 *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 significant sources of variability in process inputs are identified and explained,

(*2*) 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

(*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 product not meeting required specifications is below the maximum acceptable level of risk 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 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 of process understanding should be treated as an ongoing process. 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. 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 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 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 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 should be carried out using suitable experimental and investigative techniques. An understanding of these critical inputs (CPPs and critical raw material attributes), 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 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).

4.4.5 Note that for raw materials, 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
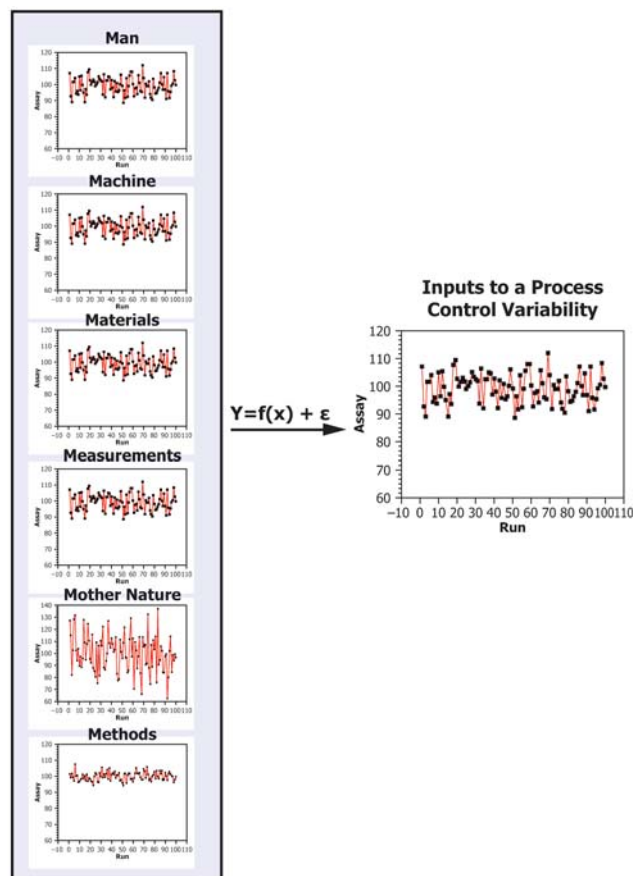
FIG. 1 Input, Process, and Output Diagram

product meeting the required specifications. Tools that may be applied during development and after commercialization include:

(1) Scientific theory,

(2) Prior knowledge,

(3) Design of experiments,

(4) Simulation of unit operations,

(5) Selection of a suitable technology platform,

(6) Mathematical models,

(7) Validated empirical/statistical models,

(8) Appropriate instrumentation, and

(9) 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.

4.5.3 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 "Pharmaceutical cGMPS for the 21st Century — A Risk-Based Approach"[6] 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) 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.

5.16 Coordinated application of both empirical and mechanistic models to a given process may be valuable for improving process understanding. This hybrid approach may be especially valuable when highly nonlinear microbial or biological phenomena are to be explained by first principle models.

5.17 *Descriptive Knowledge:*

5.17.1 Descriptive knowledge primarily focuses on *what* is occurring in the process, that is, action(s) and sequence(s) of events which are required to complete the process are listed, basically a process recipe, however limited or no additional information is provided.

5.17.2 *Definition of Descriptive Knowledge*—Knowledge derived solely from observation which reflects basic facts.

5.17.3 The focus is primarily on compliance with only a limited perspective on process understanding. Descriptive knowledge is based primarily on previous experience and supported by minimal development experimentation to establish the process parameter ranges and raw material quality attributes necessary to deliver a quality product.

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[6] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, available online, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM176374.pdf; available as of Sept. 1, 2016.

5.17.4 Descriptive knowledge is normally presented in the form of:

(1) High level process flowcharts, and

(2) Descriptive narrative text with limited specific process details.

5.17.5 Methods to enhance descriptive knowledge include:

(1) Product focused development,

(2) Information that helps to minimize variability (not just compliance),

(3) Establishing the quality attributes and process parameters that are critical, and

(4) Statistical process control.

5.18 *Correlative Knowledge:*

5.18.1 Correlative knowledge is primarily about "which output(s) (*Y*s) are correlated to which input(s) (*X*s)" but with some understanding of the scientific rationale for *why* this has occurred. Correlations can be temporal (auto-correlations) or cross-correlations.

5.18.2 *Definition of Correlative Knowledge*—Knowledge based on the identification of the interrelationship between variables identified in the "process description or process recipe." Where prior knowledge indicates that factors do not influence each other, the relationship can be viewed as univariate; otherwise, a more thorough statistical investigation for correlations and interactions should be used.

5.18.3 Correlative knowledge is normally presented in the combination of:

(1) More detailed process flowcharts including control limits for inputs and in-process test limits; and

(2) Correlations between inputs and outputs are noted; however, experimental work has usually been limited to only one dimension/variable at a time and may not have addressed interactions between variables.

5.18.4 The experimental work to establish which of the input variables are the critical variables that affect the critical quality attributes may be incomplete.

5.18.5 This analysis is schematically represented in an Ishikawa or fishbone diagram (Fig. 2).

5.18.6 Once these qualitative correlations have been established, experimental work taking one dimension/variable at a time can be used to develop data driven correlations. The impact of each correlation should be described in terms of the strength and the direction of its influence.

5.18.7 Methods to enhance correlative knowledge include the application of risk based approaches, such as:

(1) Data and root cause analysis (if quantitative data is available), and

(2) Risk analysis (for example, failure modes and effects analysis).

5.19 *Causal Knowledge:*

5.19.1 Causal knowledge is achieved when the underlying reason for the correlation is known. By this stage, significant scientific knowledge has been established.

5.19.2 *Definition of Causal Knowledge*—Knowledge based on what causes the interrelationships identified in the "correlation." This kind of knowledge is also associated with an awareness about interactions among variables and which variables are critical and which variables are not. With this level of knowledge, processes may be robust and more focused optimization can begin.

5.19.3 Causal knowledge is normally presented and characterized by:

(1) Identification and measurement of "critical" variables, and

(2) Measurements designed to monitor or control, or both, the underlying process.

5.19.4 Causal knowledge will be characterized by an improved understanding of how process controls and variables affect outcomes of the process (for example, product quality, yield).

5.19.5 Methods to enhance causal knowledge include:

(1) Design of experiments (DOE);

(2) New measurements (for example, online or atline process measurements as described in the U.S. FDA PAT guidance) are added to monitor or control, or both, the underlying process;
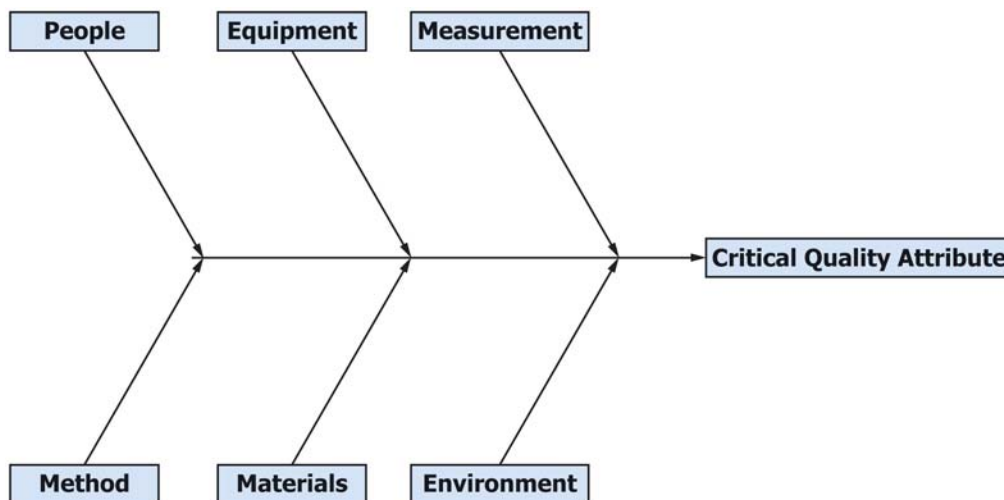

FIG. 2 Data Driven Correlative Model of Factors Affecting Desired Product Quality

(3) Measures of predictability;

(4) Expert systems;

(5) Using multivariate data analysis (MVDA);

(6) Using multivariate statistical process control (MSPC);

(7) Evolutionary operations (EVOPs); and

(8) Robust engineering.

5.19.6 Commercial tools, such as expert systems, can also assist in the acquisition of causal knowledge.

5.19.7 Understanding these causal relationships is important for developing, manufacturing, and improving the quality of the product.

5.20 *Mechanistic Knowledge:*

5.20.1 Mechanistic knowledge is primarily concerned with the dominant physical, chemical, microbial, or biological mechanisms underlying the ways in which the causal variables interact (that is, *how* things occur).

5.20.2 *Definition of Mechanistic Knowledge*—Knowledge based on the explanation of how "causal" relationships occur. Mechanistic knowledge is based on the development of models from basic physical, chemical, microbial, or biological mechanisms of observed phenomena.

"A mechanistic approach is justified (*a*) whenever a basic understanding of the system is essential to progress or (*b*) when the state of the art is sufficiently advanced to make a useful mechanistic model easily available."[7]

5.20.3 This level of knowledge can provide scale-up and technology transfer with a solid foundation. With this level of knowledge, processes are more likely to be robust and the deeper knowledge facilitates further optimization.

5.20.4 When to use a mechanistic model is a matter of scientific judgment.

"A study to discover the appropriate mechanistic model may be difficult and time consuming and might be improvident if the understanding does not translate to meaningful benefit to the product, process or customer/patient."[7]

5.20.5 Methods to enhance mechanistic knowledge include:

(1) Methods identified to enhance causal knowledge,

(2) Providing a capability to look for patterns of behavior across the product's lifecycle,

(3) Connecting investigations from throughout the lifecycle of a product and process to development reports, and

(4) Investigating the nature of empirical models which may suggest possible theoretical or mechanistic mechanisms, and thus better scientific understanding.[8]

5.21 *First Principles Understanding:*

5.21.1 First principle knowledge is primarily about application of theoretical knowledge to the actual manufacturing process.

5.21.2 It expands mechanistic knowledge as described above and as a result explains the fundamental reasons (that is, *why* an event takes place).

5.21.3 *Definition of First Principles Understanding*—Understanding based on a theoretical understanding of prevailing mechanisms and why they occur. Therefore, first principles knowledge may allow for prediction of behavior over a significantly wider range of situations. With this level of knowledge, the existing process robustness may be further optimized, and potentially generalized to other similar unit operations, processes and products. As with any model, confirmation of acceptability of the product and process should be obtained before extrapolating beyond previously established acceptable operating ranges.

5.21.4 Characteristics of first principles understanding include:

(1) Methods identified to enhance mechanistic knowledge,

(2) High degree of predictability,

(3) Ability to design-in performance and process innovation, and

(4) Ability to design better experiments earlier due to prior knowledge about a more appropriate design space.

5.21.5 Methods to enhance first principle knowledge include:

(1) Extension and refinement of empirical and mechanistic models at a fundamental level.

6. Risk and Uncertainty in the Context of Process Understanding, Predictability, Control, and Product Quality Requirements

6.1 In an ideal state, process knowledge and process understanding address the "how" and "why" aspects of a product's performance, respectively. As previously mentioned, there will be a blend of states of understanding at any point in time. The development of a predictive model is a demonstration of the optimal understanding of product quality.

6.2 Continuous improvement should occur throughout the lifecycle of a product ensuring that the overall risk profile of the product is maintained (FDA/ICH Q10). Some goals are to improve the overall product and process knowledge and understanding and to build in the controls necessary to ensure product quality and reduce risk. This is (partially) accomplished by reducing the residual error or uncertainty in a product or process by understanding the impact of inputs to a process (people, equipment, measurements, methods, materials, environmental conditions) with greater confidence.

7. Keywords

7.1 control; pharmaceutical manufacture; process understanding

[7] Box, G., Hunter, W., and Hunter, J., *Statistics for Experimenters*, John Wiley & Sons, New York, N.Y., 1978, p. 153.

[8] Box, G., and Draper, N., *Empirical Model Building and Response Surfaces*, John Wiley & Sons, New York, N.Y., 1987, p. 406.