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Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology[1]

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INTRODUCTION

Process design is the systematic conversion of information about needs for a product into knowledge about how to manufacture this product. Products and manufacturing processes should be designed using science- and risk-based design strategies to manage variation.

To attain this goal, integration of Process Analytical Technology (PAT) principles and tools during process design will enhance opportunities to build, maintain, and expand science- and risk-based process understanding throughout a product lifecycle. The product lifecycle includes the period in production as well as development.

Process understanding will be the foundation to establish manufacturing (process selection, methodology, implementation, and practice), process control (real-time control on the basis of measured critical quality attributes), effective risk mitigation, and product release concepts.

Process understanding will also enable regulatory strategies in that the level of regulatory scrutiny may reflect the demonstrated level of science- and risk-based process understanding.

1. Scope

1.1 This practice covers process design, which is integral to process development as well as post-development process optimization. It is focused on practical implementation and experimental development of process understanding.

1.2 The term *process design* as used in this practice can mean:

1.2.1 The activities to design a process (the process design), or

1.2.2 The outcome of this activity (the designed process), or both.

1.3 The principles in this practice are applicable to both drug substance and drug product processes. For drug products, formulation development and process development are interrelated and therefore the process design will incorporate knowledge from the formulation development.

1.4 The principles in this practice apply during development of a new process or the improvement or redesign of an existing one, or both.

1.5 *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:*[2]

E1325 Terminology Relating to Design of Experiments

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture

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

E2587 Practice for Use of Control Charts in Statistical Process Control

2.2 *FDA Standards:*[3]

FDA Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and

[1] This practice is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical Products and is the direct responsibility of Subcommittee E55.01 on PAT System Management, Implementation and Practice.

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[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), 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, http://www.fda.gov.

Quality Assurance, September 2004
FDA Guidance for Process Validation General Principles and Practices, January 2011
2.3 *ICH Guidance Standards:*[4]
ICH Q8 Pharmaceutical Development, Step 4 Document, August 2009
ICH Q9 Quality Risk Management, Step 4 Document, November 2005

3. PAT Process Design Practices

3.1 *Desired State*—In the desired state of a process, all sources of variation are defined and controlled, and end product variation is minimal. That implies that critical product attributes are controlled to target for all individual units of a product. As a result, processes are capable of consistently supplying, unit to unit and batch to batch, the desired quality.

PHILOSOPHY AND PRINCIPLES

3.2 *Practice #1: Risk Assessment and Mitigation*—Products and manufacturing processes should be designed to minimize variation. Therefore, process design is a means to mitigate the risk of having product units with varying quality. The process design requires the use of formal risk evaluation methodologies and mitigation assessments. See also Guide E2476, ICH Q9, and FDA Guidance for Industry for additional guidance.

3.3 *Practice #2: Continuous Improvement:*

3.3.1 Process design starts with the identification of first design options that reflect the desired process state and the desired product attributes. See also FDA Guidance for Process Validation and ICH Q8 for additional guidance.

3.3.2 Evaluation of the first and all following design options should follow an iterative process of design improvement.

3.3.3 Design improvement is continued post-launch (continuous improvement) to support management of process quality throughout the product lifecycle.

3.3.4 The iterative approach to continuous process design improvement includes:

3.3.4.1 Initiation of the design process based on information about product structure, composition, desired quality attributes, and so forth,

3.3.4.2 Definition of initial design concepts based on institutional knowledge, intuition, experience, first principles, and so forth,

3.3.4.3 Generation of design options,

3.3.4.4 Identification of feasible design options from development studies,

3.3.4.5 Detailed process development, and

3.3.4.6 Design review and learning from experience from development or implementation, or both, where quality risk management principles and methodology are applied on each step, and information and learning is fed-back and fed-forward between all steps.

3.4 *Practice #3: Process Fitness for Purpose:*

3.4.1 The evaluation of process design options uses risk assessment to establish a process that will consistently deliver the desired outputs. See also Guide E2476, ICH Q9, FDA Guidance for Industry, and FDA Guidance for Process Validation for additional guidance.

3.4.2 Process fitness should be established regarding:

3.4.2.1 Product characteristics, product quality definition.

3.4.2.2 Process characteristics, for example, unit operation quality.

3.4.2.3 Process systems (for example, control system, measurement system).

3.4.2.4 System components (for example, design elements, modules, interfaces).

3.4.2.5 Commercial fitness for purpose.

3.5 *Practice #4: Intrinsic Performance Assessment:*

3.5.1 Processes should be designed with intrinsic process assessments and control systems that are integral components of the manufacturing operations. This approach is fundamentally different from conventional design approaches that rely on separation of process from process output assessment, for example, by sampling, averaging, and off-line testing.

3.5.2 This has the following implications for process design:

3.5.2.1 Process steps (unit operations) are evaluated as connected operations, because outputs are inputs for subsequent steps.

3.5.2.2 Measurements are focused on assessment(s) of critical quality attributes or factors, or both, associated with process condition rather than on documenting compliance.

3.5.2.3 Measurements are discriminating (to account for the multivariate process nature), rather than averaging (because information is lost through averaging of data).

3.5.2.4 Process performance-based optimization reduces total variability (that is, input material, process, and analytical variability).

3.5.2.5 Process measurements and controls are designed in.

3.6 *Practice #5: Manufacturing Strategy:*

3.6.1 There is a mutual relationship between the development of the manufacturing process and the risk mitigation strategy for a given product, as the process is designed to deliver the product with desired attributes. See also Guide E2476, ICH Q9, FDA Guidance for Industry, and FDA Guidance for Process Validation for additional guidance.

3.6.2 The design of the manufacturing process should form part of the risk mitigation strategy for a product. For example, the risks to the patient for a low dose/high potency drug will be different from a high dose drug, and therefore the manufacturing process designed in each case will reflect those differences.

3.6.3 This has the following implications:

3.6.3.1 To achieve unit-to-unit consistent quality, all material transitions (that is, chemical, physical, or mechanical transformations) have to be the same for all units of the product.

3.6.3.2 Since process scale is a risk factor, process design should incorporate strategies to mitigate that risk through scaleable or scale-independent manufacturing operations. For example, continuous processing technology is an approach to achieve scale-independency. Where a process is scaled-up,

[4] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

product quality and process robustness can be assured by measuring the in-process material attributes and critical quality attributes, rather than the machine parameters and using these to ensure end product quality.

3.7 *Practice #6: Data Collection and Formal Experimental Design*—Experimental design tools (such as Design of Experiments (DoE)) are used to ensure that data is collected throughout the design space in a manner that minimizes the necessary experimental load and maximizes the information extracted about the process. Several cycles of such experimental work, each focusing more closely on the likely operating area, may be required to establish initial production process conditions. See also Terminology E1325, Practice E2587, and FDA Guidance for Process Validation for additional guidance.

METHODOLOGY

3.8 *Practice #7: Multivariate Tools*—Multivariate tools are used to generate predicted values for the critical quality attributes, to generate values for factors directly or indirectly linked to process condition, or to generate qualitative information about material. Multivariate tools can be used to understand and control process and product variability.

3.9 *Practice #8: Process Analyzers*—In-, on-, at-line process analytical tools are used for rapid measurements which can be used to evaluate material attributes and process performance and enable process control.

3.10 *Practice #9: Process Control:*

3.10.1 The combination of univariate and multivariate data derived in real-time from the process is used to evaluate effects on process critical quality attributes. These in turn are used to evaluate the necessary process parametric settings to ensure both the desired process trajectory and end product quality or desired state. This feedback loop, and any associated feed-forward and feed-back of data from stage-to-stage, comprises the process control. See also Practice E2587 and Guides E2475 and E2629 for additional guidance.

3.10.2 Process endpoints are based on achieving desired critical quality attributes.

4. Keywords

4.1 design space; desired state; manufacturing; PAT; pharmaceutical process design; process analytical technology; process understanding; quality risk management