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Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture[1]

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INTRODUCTION

This document provides guidance on the implementation of risk assessment and risk control for Process Analytical Technology (PAT) processes within the pharmaceutical industry. Wherever possible, other appropriate standards on risk assessment/management have been referenced and acknowledged. Where practical, further details of methods and additional references have been provided for information within the appendixes.

The application of risk assessment and risk control is pivotal to the creation of PAT systems, which are described as "science-based" and "risk-based." Such application starts at an early stage in the development of the process and continues throughout development and production. In the production phase, it is a crucial component of applying continuous improvement to the process.

RELATIONSHIP TO ICH Q9

The ICH Q9 Guideline for Quality Risk Management is intended for general application within the pharmaceutical industry. ICH Q9 describes the requirements for pharmaceutical quality risk management and considers the risk as "risk to the patient."

This document provides specific guidance on the risk assessment and risk control phases identified in ICH Q9 in a limited set of conditions. It is applicable where the manufacturing method is compliant with Process Analytical Technology (PAT) principles, and where the primary considerations are product quality and reduction of process and product variability. The only component of risk to patient considered here is risk to product quality. Other components fall outside the scope of the document. In addition, other areas identified in ICH Q9, such as general risk management and risk communication, are not considered here.

This document provides guidance which applies to the design, development, and operation of PAT systems. It should be considered as a specific extension, supporting the ICH Q9 guidance for these processes.

1. Scope

1.1 This document provides guidance on the assessment of risks to product quality within and related to PAT processes in the pharmaceutical industry. It addresses those risks to product quality arising from, associated with, identified by, or modified by the implementation of PAT in pharmaceutical development and manufacturing for primary, secondary, and biotech sectors of the industry. It does not replace those assessments of risk currently undertaken by pharmaceutical companies, but is, rather, an additional component focused specifically upon the evaluation and design of PAT processes. See Practice E2474, Guide E2500, and ICH Q8.

1.2 *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.* Note that safety in this context refers to operational and operator safety, not to patient safety.

[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.

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2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2474 Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology

E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

2.2 *Other Standards:*

FDA Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[3]

ICH Q8 (R2) Pharmaceutical Development[4]

ICH Q9 Quality Risk Management[4]

ICH Q10 Pharmaceutical Quality System[4]

IEC 60812 Analysis Techniques for System Reliability—Procedure for Failure Mode and Effects Analysis (FMEA)[5]

IEC 61025 Fault Tree Analysis (FTA)[5]

IEC 61882 Hazard and Operability Studies (HAZOP Studies)—Application Guide[5]

ISO 22000 Food Safety Management Systems—Requirements for any Organization in the Food Chain[6]

WHO Technical Report 908 WHO Expert Committee on Specifications for Pharmaceutical Preparations

3. Terminology

3.1 The terminology specific to this guide will be incorporated into Terminology E2363.

4. Significance and Use

4.1 This guide is intended to provide guidance regarding the use of risk ~~analysis~~management in the development, day-to-day running, and continuous improvement of pharmaceutical processes incorporating Process Analytical Technology (PAT). Since PAT is defined as being "risk-based" (see FDA Guidance for Industry), it is important that a consistent approach to the use of risk methodologies is adopted, to ensure rapid transfer of process understanding within the development and manufacturing teams, and to the regulators where that is appropriate.

4.2 This guidance only covers those aspects of risk assessment related to "risk to product quality." Other aspects (such as "risk to patient") should be covered in the conventional manner.

5. Principles of Risk Assessment and Risk Control

5.1 *Background*—Risk management has been widely used in manufacturing and service industries for many years. In some industries, risk management has become formalized into a highly structured approach which has become the subject of standardization. This standardization has a number of benefits including:

5.1.1 Widespread acceptance based on consensus among all interested parties, which makes regulatory approval easier,

5.1.2 Easy comparison of equivalent processes between sites, companies, and continents,

5.1.3 Ready transferability of skilled labor, and

5.1.4 Standardized training.

5.2 *High-Level Characteristics of Risk Assessment*—A risk assessment for a PAT process has, in addition to the principles outlined in ICH Q9, a number of key characteristics:

5.2.1 It is systematic and structured.

5.2.2 It is primarily evidence-based. Evidence may include direct experience, historical knowledge, professional judgment, etc.

5.2.3 It specifically focuses upon uncertainty ~~and/or variability~~ or variability, or both, in product quality and the causes of such uncertainty/variability.

5.2.4 It is an integral component of the decision-making process.

5.2.5 It guides risk control and mitigation; that is, it recognizes that the primary consideration is product quality and identifies those areas where risks must be reduced and provides a mechanism for assessing when the risk has been sufficiently reduced.

5.2.6 It is multi-layered. It can be applied at many levels, that is, lower-level, more detailed assessments feeding into higher-level, broader scope assessments. (For example, a higher-level risk assessment for the finished product will have lower-level risk assessments for each of the process stages which feed into it.) Breaking risk assessment into layers makes complex evaluations

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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), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

[4] Available from International ~~Conference on~~Council for 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.

[5] Available from International Electrotechnical Commission (IEC), 3 rue de Varembé, Case postale 131, CH-1211, Geneva 20, Switzerland, http://www.iec.ch.

[6] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

simpler to perform, simpler to understand, and simplifies the generation of a detailed response. It also assists in the process of identifying specific targets for reducing the risk.

5.2.6.1 In general, an initial high-level risk assessment will identify most of the high-risk areas. Subsequent lower-level risk assessments, and resulting mitigation actions, will focus initially upon these identified areas of high risk, moving to those areas of intermediate and lower risk at a later stage in the process. This later amelioration of the risk may be part of a continuous improvement process.

5.2.7 It is dynamic and iterative. It will remain active for the lifecycle of a product, responding to changing commercial, manufacturing, and scientific conditions and the availability of additional information ~~and/or process understanding.~~or process understanding, or both.

5.3 *High-Level Characteristics of Risk Control:*

5.3.1 Once risks have been clearly identified and prioritized, and the need for risk mitigation agreed, the process of risk control takes effect. Risk control has a number of key characteristics:

5.3.1.1 Risks which are identified during the ~~analysis~~assessment should receive a proportionate response. The response should be related to the probability of the event occurring, the severity of the results, and the detectability of the event.

5.3.1.2 Risk control actions for a new process occur in a specific order:

(1) Perform design changes to reduce the risk. (That is, enacting modifications to the basic process that deliver higher quality or more consistent product. This is a key reason for adopting PAT.)

(2) Add control features to reduce the process risk. (That is, putting extra features on the process the primary function of which is to reduce some facet of the risk, which is a key component of PAT.)

(3) Apply methods improving detectability (such as, standard operating procedures, guidelines, company practices, staff ~~training and/or~~training, staff selection, etc.) to reduce risk.

5.3.1.3 For an existing process, the sequence may be different.

5.3.1.4 These actions should ideally be applied in the order listed. When a risk is identified, the design team should first seek to remove the risk by changing the fundamental process design. If this is not possible, they should then seek to modify equipment design or process conditions to reduce the risk. Only if neither of these are practical should they use the third approach of imposing specific working practices. Some modification in this order may be necessary when an existing process is being considered and the costs associated with fundamental design change are prohibitive.

5.3.1.5 Once this process is complete, the remaining risks are known as residual risks. Residual risks are:

(1) Risks which remain higher than the acceptable risk level, but which cannot practicably be further reduced by redesign, risk control, or standard procedures/training/etc. When such risks occur, it will then be necessary to implement a post-process risk mitigation measures such as off-line testing.

5.3.1.6 Residual risks must be fully documented and should be subject to a formal acceptance procedure at least once before final process approval.

5.3.1.7 It is recognized that, in the application of risk control:

(1) Changes must be viable in technical, regulatory, and commercial contexts. Where changes do not meet these criteria, it must be explicitly so stated in the risk report.

(2) Reducing the risk on a process may still mean that the process carries high risk after a particular stage. Subsequent risk mitigation will be necessary.

(3) Changing a process to reduce one risk may aggravate another risk. The objective is to minimize the overall risk. This may result in a high risk remaining unaddressed at a particular stage, which then needs to be addressed by subsequent risk control actions.

(4) Changing a process to reduce one risk may introduce another risk. This risk, in turn, must be assessed and prioritized.

6. Preparation for Risk Assessment and Risk Control

6.1 Adequate preparation is a key component of an effective risk assessment and risk control strategy.

6.2 *Objectives of the Risk Assessment*—To achieve timely, effective results from a risk assessment and risk control process, the scope and objectives of the work shall be clearly defined at the earliest possible stage.

6.3 *Selection of the Risk Assessment/Control Group:*

6.3.1 The group assessing these risks shall include experienced practitioners with all of the relevant key skills to identify and evaluate the key factors in the process under consideration. The group should therefore include, or have direct access to, subject matter experts with expertise or extensive experience in appropriate areas such as:

6.3.1.1 Drug(s), intermediates, and excipients in the form appropriate to the industry sector,

6.3.1.2 Design and function of the drug product,

6.3.1.3 Scientific ~~and/or technical issues~~ or technical issues, or both, of process design,

6.3.1.4 Design and function of the process equipment,

6.3.1.5 Measurement systems,

6.3.1.6 Development of process and control models,

6.3.1.7 Design and function of process controls,
6.3.1.8 Existing production,
6.3.1.9 Current operating practices (including agreed work rules and practices),
6.3.1.10 Known problems with the product, either in manufacturing or subsequent use,
6.3.1.11 Company quality records and procedures,
6.3.1.12 Company laboratory capabilities and practices,
6.3.1.13 Recruitment and training policies in so far as they impact the process,
6.3.1.14 Company maintenance records and procedures, and
6.3.1.15 Company validation practices and procedures or continuous quality verification.

6.3.2 Individuals may fulfill one or more of these roles. It is not necessary for everyone to be present throughout the assessment, but a core group that is involved throughout should be clearly identified.

6.3.3 At least one member of the group should be fully trained to perform risk assessments.

6.4 *Collection and Preparation of Information*—As far as is possible, all relevant information necessary for the risk assessment should be collected or prepared before the start of the process. This helps to ensure that the assessment process does not become fragmented.

6.5 *Consistency of Approach:*

6.5.1 The estimation of risk will usually be quasi-quantitative, and, therefore, on an arbitrary scale. However it is important that measures are put in place to ensure that:

6.5.1.1 The estimation of risk is consistent from one project to another,

6.5.1.2 The estimation of risk is consistent from one assessment team to another, and

6.5.1.3 The estimation of risk is sufficiently transparent that it can be readily understood by a third party assessor (such as a representative of a regulatory agency).

7. Application of Risk Assessment and Risk Control to PAT

7.1 *Objectives:*

7.1.1 The advent of PAT has created a requirement for a view of risk assessment which has a number of specific objectives.

7.1.1.1 The focus is upon risk to product quality (that is, the quality of the end-product of the process).

7.1.1.2 The intent is to identify risks to product quality within the process and adopt measures to mitigate those risks until an acceptable quality is ensured. This means that all identified risks must be minimized to an acceptable degree, and residual risks must be explicitly identified and acknowledged.

7.1.1.3 The risk management occurs as an integral part of the design, development, and operational phases of the process, and it drives technical or methodological change where risk is assessed as unacceptable.

7.1.2 The objectives of the risk assessment process for PAT are to provide information to drive the following processes:

7.1.2.1 Identification of the Critical Quality Attributes (hereafter referred to as CQAs) both for the final drug product and the intermediate process products and the limits within which they may acceptably ~~vary. (The~~vary (the CQAs are the primary measurements of product ~~quality.),~~quality),

7.1.2.2 Identification of those factors which can be adjusted to control the variation in these CQAs, and hence those factors which are important to the specification and design of the process (see Practice E2474 and Guide E2500),

7.1.2.3 Identification of those factors which may result in the final drug product or the intermediate process product not being imbued with desired CQAs during the process, including the sources of variability in the CQAs, and,

7.1.2.4 Definition of a control strategy (see ICH Q10) to ensure that the intermediate process products and the final drug product CQAs are held within the pre-defined limits during the manufacture and lifecycle of the drug product.

7.1.3 It is important that the risk assessment process is clearly focused upon the intermediate process product and final drug product CQAs to ensure that the effort required to undertake the risk assessment does not become excessive. Nevertheless, there are two distinct categories in this list: the determination of the CQAs, and the determination of how to measure and control the CQAs. These two topics are dealt with independently in Sections 8 and 9.

7.2 *Basic Concepts of Risk Assessment When Applied to PAT:*

7.2.1 Risk assessment, as applied to PAT, is a systematic approach to identifying the variability of a process and any associated hazard or failure mode, and it focuses and supports the development process understanding. (Note that process understanding includes product ~~understanding.).~~understanding.) It comprises a number of principle steps as shown in outline form below.

7.2.2 It should be noted that, to maintain simplicity, the process in Fig. 1 is shown as a single flow. In practice, risk assessment will be ongoing throughout the full lifecycle of the drug product. Documents such as the Risk Assessment report will therefore undergo continual revision, both during development and as part of change control during the production phase.

7.2.3 There are three primary components of risk assessment:

7.2.3.1 An understanding of the uncertainties of the process (which includes materials, processing, equipment, detection systems, feedback control, systems and instrument accuracy, and repeatability),

7.2.3.2 An identification of the hazards and failure mechanisms, and

7.2.3.3 An estimation of the risks associated with each hazard and failure.

7.2.4 *Determination of Uncertainty in the Process and Possible Failure Mechanisms:*

7.2.4.1 Determination of the uncertainty in the manufacturing process requires a detailed and thorough understanding of the components used within the manufacturing process, and of each of the various stages of that process. Since one of the objectives of PAT is to foster an increasingly accurate and detailed understanding of the mechanical, physical, chemical, and biological aspects of the manufacturing process, it is likely that the sophistication of the risk ~~analysis~~assessment performed upon a process will directly reflect the level of process understanding.

Pharmaceutical manufacturing processes are, typically, complex, multi-stage operations which involve many different materials and items of equipment. To effectively analyze the risks associated with such a manufacturing operation, it is necessary to break it down into simple stages (although care must also be taken to ensure that inter-dependencies and interactions are also considered). These stages may be based upon individual ~~processes and/or equipment and/or components.~~ processes, equipment, or components, or a combination thereof. Risk assessment should therefore start with as many of the relevant items from the following list as is possible:

(1) A detailed map of the process flow (as a chemical/physical/biological process).

(2) An evaluation of the thermodynamics, physical/chemical/biological behavior, mass balance, etc. of any critical process stage.

(3) An evaluation of the physical/chemical/biological risks of any potentially harmful product (main, by-, or waste-) of the process.

(4) Known physical, chemical, and biological variability of all raw and process materials used (including variability in physical, chemical, or biological stability).

(5) A detailed list of equipment used (including equipment for measuring, processing, moving, containment, etc.).

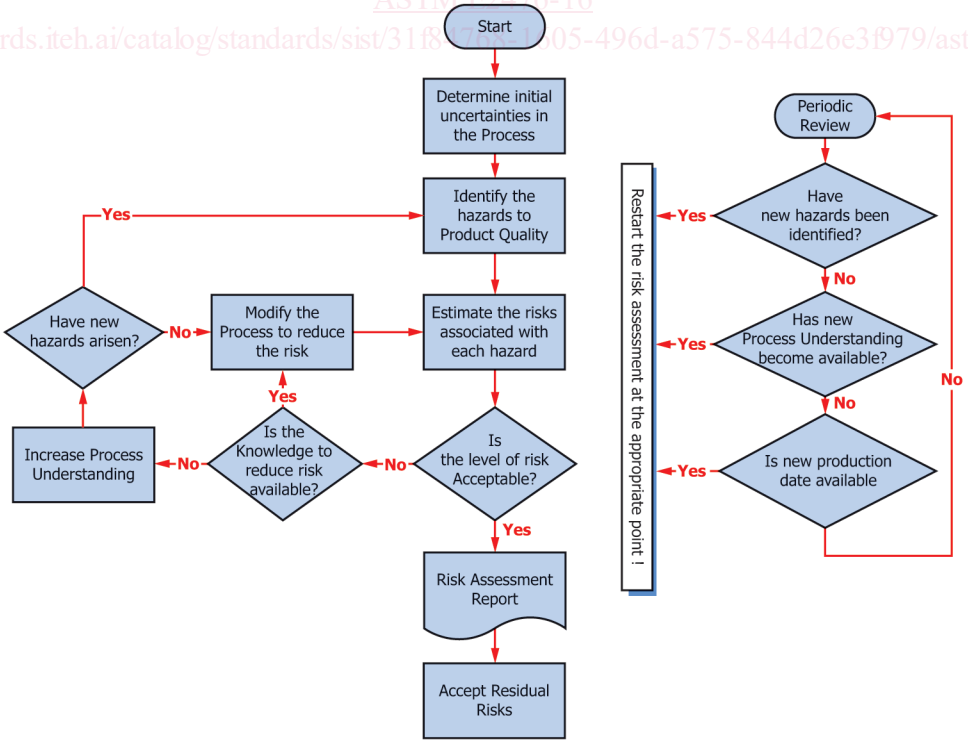

FIG. 1 Basic Application of Risk Assessment to PAT