



Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture¹

This standard is issued under the fixed designation E2476; 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.

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 appendices.

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

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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.

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 Assurance³

ICH Q8 (R2) Pharmaceutical Development⁴

ICH Q9 Quality Risk Management⁴

ICH Q10 Pharmaceutical Quality System⁴

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 Guide⁵

ISO 22000 Food Safety Management Systems—Requirements for any Organization in the Food Chain⁶

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 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 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 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,

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, P.O. Box 195, 1211 Geneva 20, Switzerland, <http://www.ich.org>.

⁵ Available from International Electrotechnical Commission (IEC), 3 rue de Varembe, 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>.

manufacturing, and scientific conditions and the availability of additional information 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 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, 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 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 CQAs are the primary measurements of product 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.) 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 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, 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).

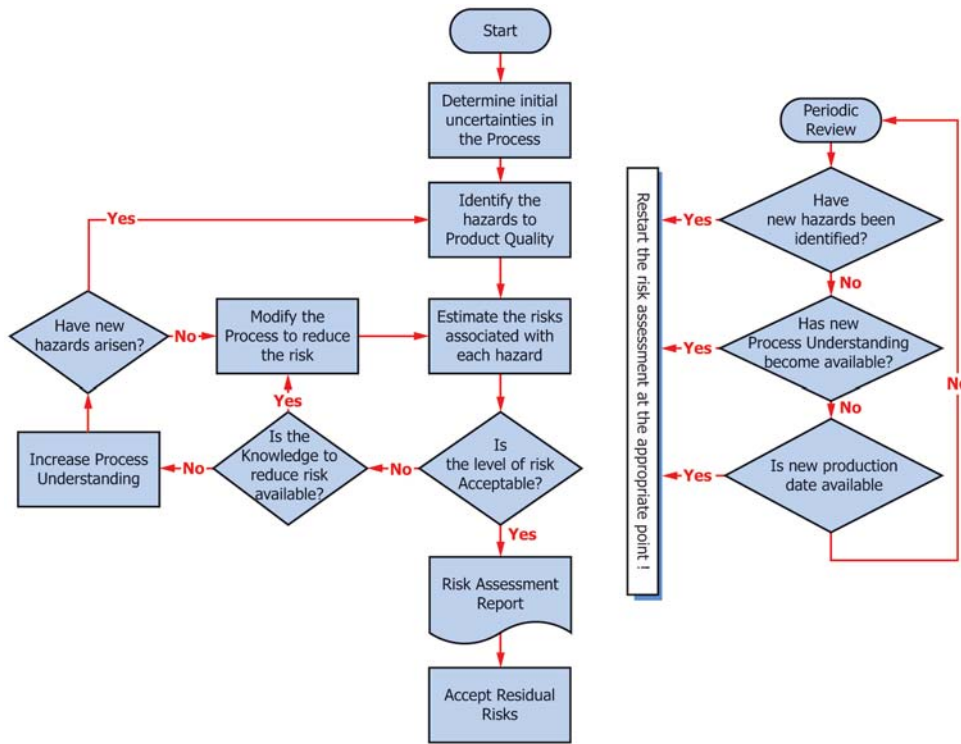


FIG. 1 Basic Application of Risk Assessment to PAT

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

(6) Manufacturer’s specifications and recommendations for use for all the above.

(7) Maintenance requirements.

(8) A process flow (as an equipment map).

(9) A list of required utilities.

(10) Information on prior failures of the process being considered, or, where this is not available, prior failures of closely related processes.

(11) Information on any accident or malfunction on the actual or an equivalent piece of equipment.

(12) Current process measurements and methodologies (including Standard Operating Procedures).

(13) IT infrastructure.

(14) Data handling.

(15) Purchasing policies and procedures in so far as they affect system uncertainty.

(16) QA policies and procedures in so far as they affect system uncertainty.

(17) Information regarding suppliers in so far as it affects system uncertainty.

(18) Information regarding the use of equipment, including training, agreed work practices, operating constraints, etc.

(19) Requirements for staff professional skills or training, or both.

7.2.4.2 This information should be updated as the process design changes or as new information becomes available.

7.2.4.3 All the tasks associated with a process should be clearly identified and any associated risks to product quality shall be evaluated. Such tasks may include, but not be limited to, the following:

(1) A detailed map of material flow including storage conditions and hold times.

(2) A detailed list of critical and non-critical equipment.

(3) Equipment power-up.

(4) Initialization.

(5) Testing.

(6) Process initiation.

(7) All modes of normal operation.

(8) Process close-down.

(9) All modes of special operation.

(10) Cleaning and housekeeping.

(11) Cleaning validation.

(12) Training.

(13) Routine maintenance.

(14) Fault-finding and repair.

(15) Current operating practices (including agreed work rules and practices).

(16) Quality control for all feeds into the process.

(17) Methods and procedures for ongoing auditing of CQAs.

(18) Recruitment and training procedures in so far as they affect the process.

7.2.5 Quantification of Hazards and Failure Mechanisms:

7.2.5.1 Risk evaluation, in turn, allows the user to make judgments on the acceptability of risk or on the urgency of finding means of mitigating the risk in a given process. It also provides a means by which the user can compare the risks associated with differing solutions to the problem. Risk evaluation should cover hazards and failure modes (situations and events) during all phases of the process lifecycle, and include external factors such as radio frequency interference, vibration, and so forth.

7.2.5.2 Where it is possible, a quantitative evaluation of risk is preferable and should be adopted at the earliest practical stage. In many cases, however, (and particularly where process understanding is limited) this is not possible. In these cases, the estimation of risk should be based upon the professional judgment of a team with skills covering all those areas pertinent to the particular case. This professional judgment should be justified (by references to theory, to experimental work, to case study, to external data, etc.) and well documented in as quantitative a manner as possible. The method and rationale shall be fully documented together with the identities of people who participated in the risk assessment. One possible framework for such quantitative assessment is FMEA (failure mode and effects analysis).

7.2.5.3 After all the significant sources of variability and uncertainty in the process have been identified and have, as far as is practical, been assessed, perform a structured estimation of the risks. This estimation will incorporate the following factors:

- (1) Severity of the consequences.
- (2) Likelihood of occurrence.
- (3) Likelihood of detection (of a problem or of a detection failure) once the problem/failure has occurred before harm has been incurred. This should include a recognition that detection may not be possible.

7.2.5.4 Care must be taken to adopt an appropriate weighting of the three factors to ensure the balance of the risk assessment.

7.2.5.5 The severity can be estimated by taking into account factors including:

- (1) Potential impact to the patient,
- (2) The variation in final product quality, and
- (3) The variation in the process,

Although they may have no impact upon product quality, some other issues may also affect the practicality of implementing a risk reduction such as:

- (1) The extent of material wasted, and
- (2) The business impact.

7.2.5.6 The probability of a problem occurring can be estimated by taking into account factors including:

- (1) The exposure of persons to the hazard, including sensitivity to exposure, potency, etc.,
- (2) The likelihood of occurrence (taken for instance from statistical data on machine reliability) of a hazard or failure mode,
- (3) The variability of materials,
- (4) The uncertainty of process parameters,
- (5) The uncertainty associated with predictive models of the process used for process control,
- (6) The measures already in place to reduce risks,
- (7) The speed with which a hazardous situation leads to harm,
- (8) The speed with which a failure mode leads to an undesirable outcome, and
- (9) The training of personnel.

7.2.5.7 The probability of a problem being detected can be estimated by taking into account factors including:

- (1) The visibility of failure or ability of failure to be inspected,
- (2) The number and effectiveness of automatic routes by which the problem would be detected; that is, the number and effectiveness of automated in-line tests which the problem would fail,
- (3) The difficulty of using this automatic method to detect the problem condition,
- (4) The dependence of automatic routes upon instrument condition (for example, calibration, sensitivity, etc.),
- (5) The mechanisms for informing the operators of such an automated test failure,
- (6) The number and effectiveness of non-automatic routes by which the problem would be detected (such as observation by the operator, off-line verification in labs),
- (7) The difficulty of using this non-automatic method to detect the problem condition,
- (8) The dependence of non-automatic routes upon external factors (including chance), and
- (9) The mechanisms for informing the operators of the result of such a non-automatic failure.

7.2.5.8 In any specific case, not all of these factors will apply and it is possible that factors not mentioned here are important. In addition, some factors may appear in more than one category. The assessment team has the responsibility to ensure that all the relevant, but only the relevant, factors are included in the assessment. They must also clearly document predetermined criteria for acceptance or thresholds of acceptance, although these may be determined at process or at company level.

7.2.6 *Identification of Actions and Residual Risks:*

7.2.6.1 The initial risk assessment of the manufacturing process will identify those risks requiring action (some low level risks may be accepted without action). The risk assessment and control team shall then be responsible for identifying and evaluating one or more potential methods of reducing each risk. Evaluation of the modified process shall be performed using exactly the same methods used for the initial evaluation. Multiple cycles through this procedure to evaluate different possible solutions or fine-tune a specific design change may be required. The end result will be one of two cases:

- (1) The changes have succeeded in reducing the risk to an acceptable level. These changes should then be incorporated into the process.
- (2) The changes have reduced the risk, but risk remains above the acceptable level. In this case the evaluation team must decide to either: (a) abandon the process, or (b) accept the risk as a significant residual risk and put in place all practical measures to minimize its effect on product quality.

7.2.6.2 The final outcome of the risk assessment and risk control shall be a report identifying all the changes made to the process and the impact upon the risk assessment, and clearly

listing all the residual risks and the procedures required to minimize them or ensure detection, or both.

8. Use of Risk Assessment to Determine Critical Quality Attributes and Critical Control Parameters for a PAT Process

8.1 Critical Control Parameters (CCPs) are that subset of Critical Process Parameters which can be changed under automated control to modify the trajectory of the process, and hence to modify the CQAs of the intermediate process product or the final drug product. CCPs are, therefore, the mechanism through which the control strategy is applied.

The extent to which it is possible to identify the CQAs and CCPs of a particular process or product is closely related to the level of process understanding. The starting point is likely to be comparatively simplistic and high level. For most drug products, the API content (as weight for example) is a CQA. However, as process understanding develops, so the understanding of the CQAs and CCPs will develop and the assessment will become multi-layered. The relationships between CQAs and CCPs will vary depending upon drug product and the processes used in manufacturing.

8.2 Basic Process for Identification of CQAs:

8.2.1 The basic process by which proposed CQAs and CCPs are assessed, either confirmed or rejected, is shown in Fig. 2.

8.2.2 It is typical of such processes that, once the overall product critical quality attributes have been determined by this method, an equivalent lower-level set of assessments is performed for each stage or unit process in the overall manufacturing processes. At this stage, it is possible that ‘stage’ CQAs will be identified which do not appear directly in the final product CQA list. They may, for example, be critical to an intermediate processing stage.

8.2.3 Such “stage” assessments follow the same general outline shown in Fig. 2. However, they will start with “Output Material Requirements” rather than “Target Product Profile.” This multi-layered approach allows complex processing systems to be broken down into a series of much simpler steps for evaluation and assessment, and reduces the probability of important issues being overlooked.

8.2.4 Identification of Critical Quality Attributes:

8.2.4.1 The categories to be considered in developing a preliminary list of CQAs may include, but not be limited to:

- (1) API content
- (2) Delivery profile
- (3) Bioavailability/clinical performance/therapeutic effect
- (4) Contamination
- (5) Product physical integrity (physical stability)
- (6) Product degradation (chemical stability)
- (7) Biological stability

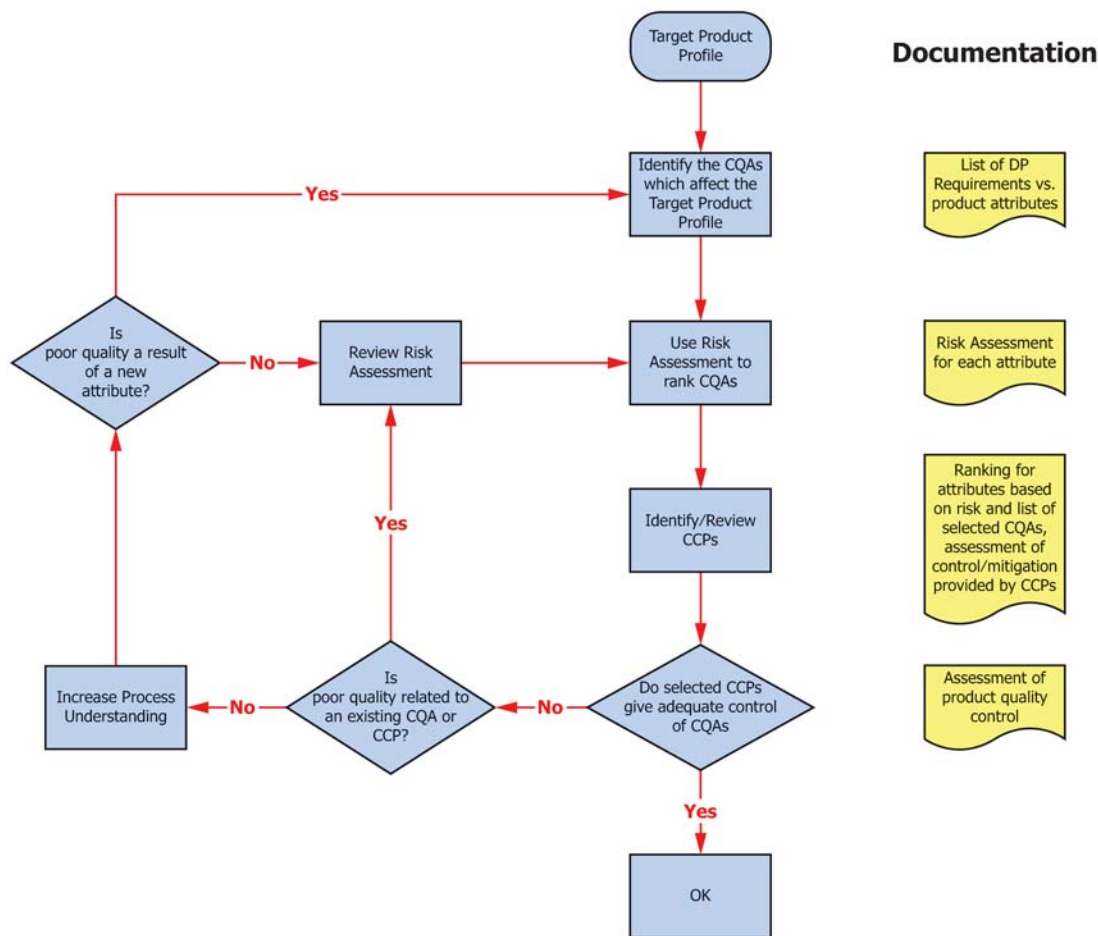


FIG. 2 Flowchart for Assessing CQAs and CCPs for Overall Process

- (8) Sterility
- (9) Impurities

8.2.4.2 Identification of Sources of Variability:

(1) Once the primary CQAs have been identified, identify those factors which give rise to variation in the CQAs. For example:

- API content may be affected in solid dose by blend uniformity and subsequent flow characteristics.
- API content may be affected in liquid dose by settling or solvent separation, or by operating temperature.
- API purity may be affected by particle size and speed of crystallization due to either inclusion or adsorption of impurities.

(2) Identification of CQAs associated with drug product characteristics should be retained for future reference and extension as the process understanding becomes more sophisticated.

(3) The factors giving rise to variation in the high-level (that is, final product) CQAs, on analysis, may give rise to lower-level CQAs (that is, CQAs for the output of a single

process or stage) or CCPs, or both. Bringing the individual process step or stage under control and reducing the output variability will result in a reduction in the variability of the final product CQAs.

9. Use of Risk Assessment to Evaluate Control in PAT Processes

9.1 The same approach shall be used to evaluate the overall control of both the processes as a whole, and each individual process step. See Fig. 3.

9.2 The identification of CCPs falls into two stages:

9.2.1 The identification of those CCPs which already exist within the process.

9.2.2 Once the first set of CCPs have been used, and shown to be insufficient for purpose, the second stage is the identification of those CCPs and control strategies still required to bring the risk down to an acceptable level.

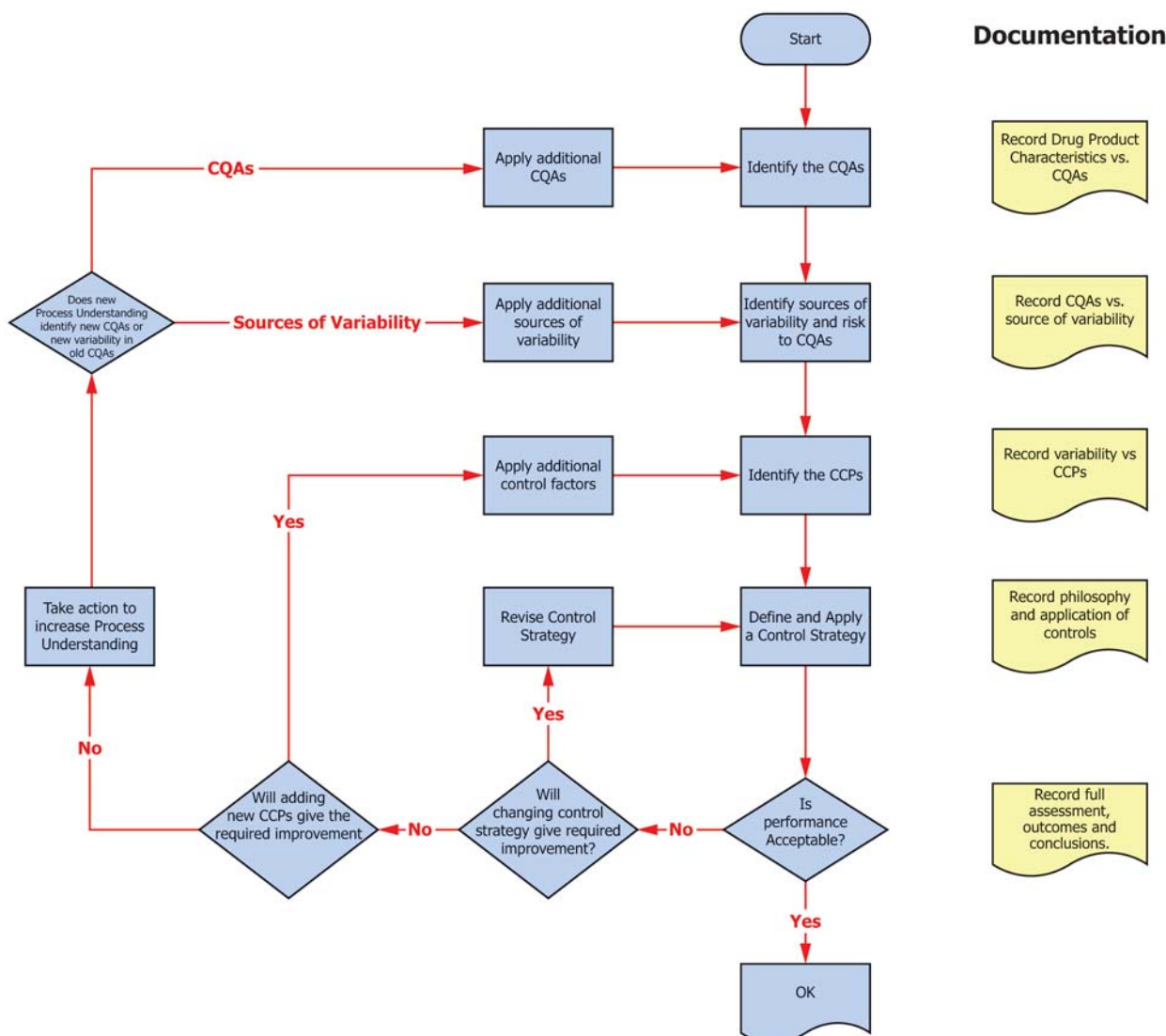


FIG. 3 Flowchart for Overall Control of Process

9.3 In this case, the key item being assessed is not the CQA, but rather it is the strategy used to ensure control over the CQA.

10. Keywords

10.1 critical quality attribute (CQA); manufacturing; Process Analytical Technology (PAT); process understanding; risk management

APPENDIX

(Nonmandatory Information)

X1. INFORMATIVE GUIDE TO METHODOLOGIES SUPPORTING RISK ASSESSMENT

X1.1 This appendix provides some limited information on techniques and methodologies that may be used as part of the risk assessment and risk control process. The list is not definitive, nor does it imply that users must adopt all of the techniques and methodologies discussed.

X1.2 The user is free to choose which of techniques and methodologies are applied to a particular process, based upon evaluating which are most appropriate and sensitive.

X1.3 The techniques and methodologies have been broadly divided into groups below, however this is not a rigid distinction.

X1.4 Identification of Risk Factors

X1.4.1 *Brainstorming*—Brainstorming is a mechanism for identifying all possible events which could lead to a reduction in product quality. To be effective, the initial stages of brainstorming should allow ideas to be recorded with little or no critical appraisal. Once the group is satisfied that all potential mechanisms for reducing product quality have been identified, then critical analysis is applied to determine the level of risk.

X1.4.2 *Fishbone (Ishikawa) Diagrams*—Fishbone diagrams are a more structured method of approaching risk identification. They work backwards up the process, seeking to identify all possible sources of risk at a particular process stage. This gives the method its characteristic structure, each potential risk being broken down by potential causes as far as possible.

X1.4.3 *Failure Modes and Effects Analysis*—FMEA has been used extensively in other industries as a structured method of identifying and recording risk to product quality. It combines the assessment of severity of the consequences, probability of occurrence and probability of detection. The product of these three factors is usually expressed as a Risk Priority Number (RPN). Typically the factors are scaled 1 to 5 for severity (from 1 for low severity to 5 for high severity), 1 to 5 for probability of occurrence (from 1 for low probability to 5 for high probability), and 1 to 5 for probability of detection (from 1 for high detectability to 5 for low or zero detectability). Typically the three numbers are multiplied together to give the RPN. This RPN may be used to rank risks. Historically, it has

been used primarily to focus on the impact of system or component failure, and to classify it by severity. While it can be used to feed directly into the risk control process, it is more commonly used as the front-end of FMECA (Failure Modes and Effects Criticality Analysis) (see X1.5.1) where the criticality of the failure is also considered. See IEC 60812.

X1.5 *Evaluation of Single Risk Factors*—The techniques below are primarily used to evaluate risks in isolation from each other.

X1.5.1 FMECA:

X1.5.1.1 Failure modes, effects, and criticality analysis is an extension of FMEA, which adds criticality analysis. While it is possible to perform FMECA fully quantitatively, it is far more common to perform it quasi-quantitatively using numerical classes for the factors.

X1.5.1.2 Results are typically recorded in a matrix which can then be sorted to identify the key risks to product quality and assist in determining the maximum acceptable risk. See IEC 60812.

X1.5.2 *Fault Tree Analysis*—Fault Tree Analysis (FTA) uses a logical diagram to show the relationship between an undesirable event and causes of that event. The technique works backwards from the known result and uses deductive logic. By breaking down the risk-generating mechanism into simple steps, it is possible to assign either quantitative or quasi-quantitative values to each step, and hence to evaluate the resulting risk. See IEC 61025.

X1.5.3 *Event Tree Analysis*—Event Tree Analysis (ETA) is the mirror image of FTA. The starting point is an “initiator” condition, and ETA allows deductive evaluation of the results of this condition by identifying all the possible consequences of the initiator and the resulting outcomes.

One difficulty with ETA is that is the initiator condition occurs many steps before the fault condition, then the “event tree” can become exceedingly large and difficult to manipulate and evaluate.

X1.5.4 Cause-Consequence Analysis:

X1.5.4.1 Cause-consequence analysis (CCA) is a combination of fault tree and event tree analysis. This technique

combines cause analysis (the primary focus of fault tree analysis) and consequence analysis (the primary focus of event tree analysis).

X1.5.4.2 The purpose of CCA is to identify sequences or chains of events that can result in undesirable consequences. Since numerical probabilities or estimates are assigned to each of the events, the probabilities of each of the various consequences can be calculated, thus establishing the initial information required to calculate a risk level.

X1.5.5 *Hazard and Operability Studies*—Hazard and Operability Studies (HAZOP) has been widely used in the assessment of process safety, but the same principles can readily be applied to assessment of product quality. The technique is usually performed using a series of guidewords at each stage to define the required attributes (NOT, MORE OR LESS THAN, AS WELL AS, OTHER THAN, etc.). These can readily be used to create a set of process limits beyond which product quality is not acceptable. See IEC 61882.

X1.5.6 *Hazards Analysis and Critical Control Points*—Hazards Analysis and Critical Control Points (HACCP) was developed primarily for the food and drink industry, and is a technique which uses an analysis of the hazards to focus upon the control mechanisms. While it can be used to identify and assess risk control on the process, it is also a very effective way of evaluating the impact of standard operating procedures, guidelines, training, etc. See ISO 22000 and WHO Technical Report 908.

X1.6 *Evaluation of Multiple Risk Factors*—At times it may be necessary to evaluate the risk arising to product quality from

multiple, dependent sources. In these circumstances, the techniques above are not entirely satisfactory and the user should consider a more sophisticated methodology.

X1.6.1 *Quality Function Deployment (House of Quality)*—Quality Function Deployment (QFD) is widely used in Japan as a tool for process and product improvement. It employs a matrix structure to allow the interactions between multiple factors to be considered, appropriately weighted, and evaluated. Although most QFDs are two-dimensional, it is possible to apply the method in multiple dimensions to ensure that all the appropriate interactions have been considered.

This method has the additional advantage that it is possible to “fold” into the matrix the assessment of different risk mitigation options, thus providing a detailed record of the assessment of both risk and mitigation.

X1.6.2 *Fault Graph Analysis/Digraph Matrix Analysis*—This methodology uses mathematics and graph theory to create a map of the process. This map can then be interrogated to identify not only single faults, but also linked multiple faults. The mathematical nature of the process ensures that the results are quantitative, however the work involved in establishing the initial map is sufficiently great to discourage application unless there is a demonstrated need for such an approach.

X1.6.3 *Mathematical Methods*—There are also a variety of mathematical methods which can be applied to assess the risk to product quality. These include Markov methods and Monte Carlo simulations. These may be applicable where complex processes with interdependent variable cause high concern about the level of risk to product quality.

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