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GUIDE TO GOOD PRACTICES OF DRUG MANUFACTURE

ANNEXES

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ANNEX 20*

* This Addendum is voluntary.

QUALITY RISK MANAGEMENT

PREFACE AND SCOPE OF APPLICATION 1.

The new Annex 20 of the GMP corresponds to the ICH Q9 guideline on Quality Risk Management. Provides guidance on a systematic approach to quality risk management that facilitates compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools that can be used when applying a formal quality risk management approach.

2. To ensure consistency, GMP Part I, Chapter 1 on Quality Management has been revised to include aspects of quality risk management within the framework of the quality system. A similar revision is planned for Part II of the Guide. Other sections of the GMP Guide may be adjusted to include quality risk management aspects in future broader revisions of those sections.

3. With the revision of the chapters on quality management in GMP Parts I and II, quality risk management becomes an integral part of the manufacturer's quality system. However, Schedule 20 itself is not intended to create new regulatory expectations; provides an inventory of internationally recognized risk management methods and tools together with a list of potential applications at the discretion of manufacturers.

4. It is understood that the ICH Q9 guideline was developed primarily for quality risk management of medicinal products for human use. With the implementation in Annex 20, the benefits of the guideline, such as processes, methods and tools for quality risk management, are also available to the veterinary sector.

5. While the GMP guideline is primarily addressed to manufacturers, the ICH Q9 guideline has relevance to other quality guidelines and includes specific sections for regulatory agencies.

6. However, for consistency and completeness, the ICH Q9 guideline has been fully transferred to GMP Annex 20.

INTRODUCTION 7.

Risk management principles are used effectively in many areas of business and government, including finance, insurance, workplace safety, public health, pharmacovigilance, and by the agencies that regulate these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. Furthermore, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming apparent that quality risk management is a valuable component of an effective quality system.

8. It is commonly understood that *risk* is defined as the combination of the probability of *harm* occurring and the *severity* of that harm. However, it is difficult to achieve a shared understanding of the application of risk management among the various *stakeholders* since each stakeholder may perceive different potential damages, place a different probability on each damage that occurs and attribute different levels of severity of risk. each damage. In relation to pharmaceuticals, although there are a wide variety of interest groups, including patients and physicians, as well as government and industry, patient protection through quality risk management must be considered of paramount importance.
9. The manufacture and use of a pharmaceutical (medicinal) product, including its components, necessarily involves a certain degree of risk. The risk to its quality is only one component of the overall risk. It is important to understand that product *quality* must be maintained throughout the *product life cycle* in such a way that the attributes that are important to the quality of the pharmaceutical (medicinal) product remain consistent with those used in clinical studies. An effective quality risk management approach can further ensure the high quality of the pharmaceutical (medicinal) product to the patient by providing a proactive means of identifying and controlling potential quality issues during development and manufacturing. Also, the use of quality risk management can improve decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decision making; it can provide regulators with greater assurance of a company's ability to cope with potential risks and can beneficially affect the degree and level of direct regulatory supervision.

10. The purpose of this document is to provide a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, but supportive of, other ICH quality documents, and complements existing quality practices, requirements, standards and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some quality risk management tools that can enable more effective and consistent risk-based decisions, both by regulators and industry, regarding the quality of active ingredients and pharmaceutical products (medicinal) throughout the product's life cycle. It is not intended to create new expectations beyond current regulatory requirements.

11. It is not always appropriate or always necessary to use a formal risk management process (using tools and/or recognized internal procedures, eg standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) may also be considered acceptable.

12. Proper use of quality risk management can facilitate, but not obviate, industry's obligation to comply with regulatory requirements and is not a substitute for proper communications between industry and regulators.

SCOPE 13.

This guideline establishes the principles and examples of quality risk management tools that can be applied to different aspects of pharmaceutical quality. These aspects include the development, manufacturing, distribution and inspection and submission/review processes through the entire life cycle of active ingredients, pharmaceutical (medicinal) products, biological and biotechnological products (including the use of raw materials , solvents, excipients, packaging and labeling materials in pharmaceutical (medicinal), biological and biotechnological products).

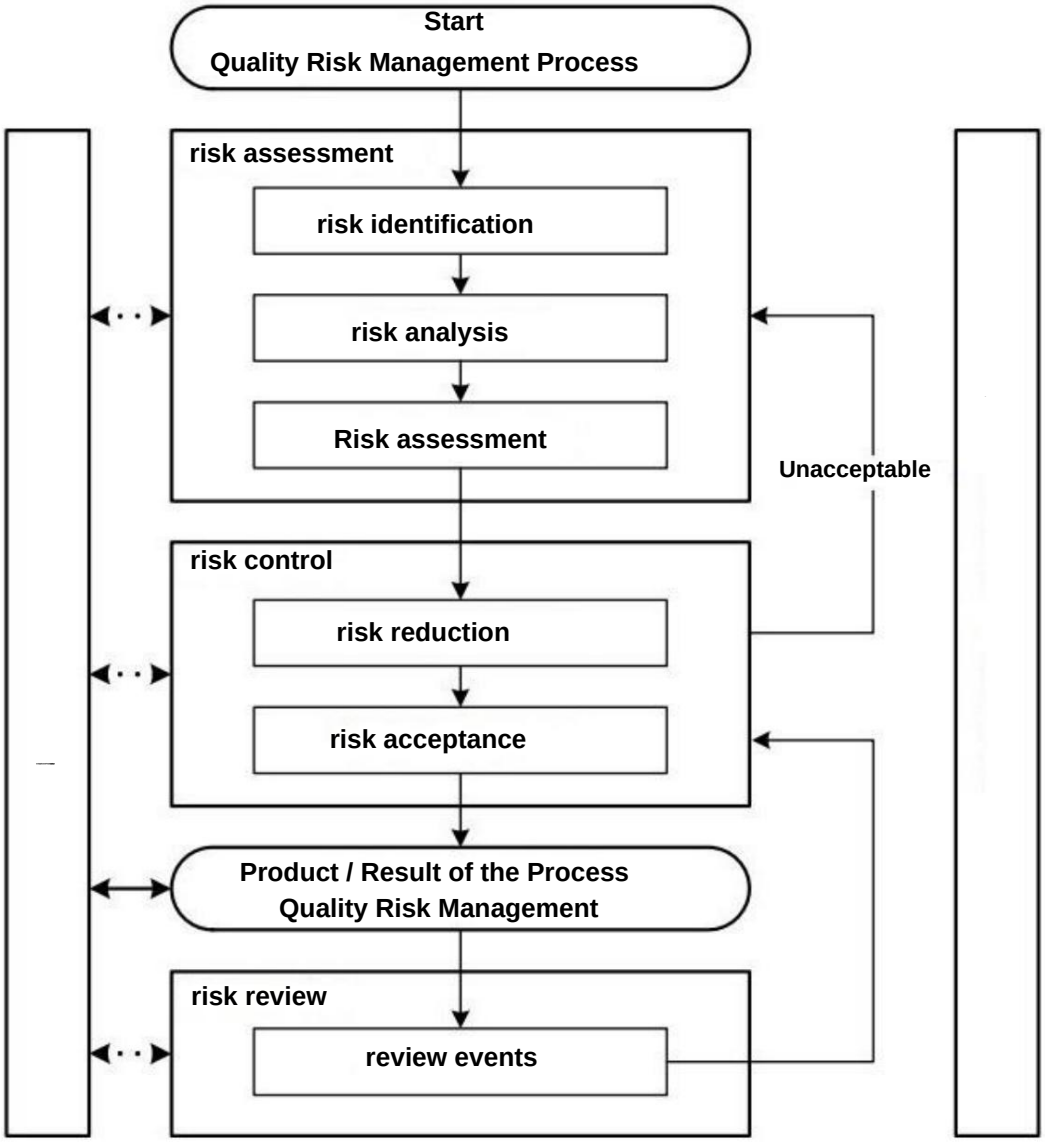
PRINCIPLES OF QUALITY RISK MANAGEMENT 14. Two fundamental

principles of quality risk management are: - Quality risk assessment should
be based on scientific knowledge and ultimately
instance, link to patient protection; and
- The level of effort, formality and documentation of the quality risk management process must be commensurate with the level of risk.

GENERAL PROCESS OF QUALITY RISK MANAGEMENT 15. Quality risk management

is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical (medicinal) product throughout the cycle of product life. A model for quality risk management is described in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework may differ from case to case, but a robust process will incorporate consideration of all elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



16. Decision nodes are not shown in the diagram above since decisions can occur at any point in the process. These decisions could be to go back to the previous stage and seek more information, to adjust risk models, or even to terminate the risk management process based on the information that supports such a decision. Note: “Unacceptable” in the flowchart refers not only to legal, legislative or regulatory requirements, but also to the need to return to the risk assessment process.

Responsibilities 17.
Quality risk management activities are usually, but not always, executed by interdisciplinary teams. When teams are formed, they should include experts from relevant areas (for example, the quality unit, business development, engineering, regulatory affairs, manufacturing operations, sales and marketing, legal, statistics, and clinicals), as well as to people who are familiar with the quality risk management process.

18. Decision *makers* should: - take responsibility
for coordinating quality risk management through
various functions and departments in your organization; and
- ensure that a quality risk management process is defined, implemented and reviewed and that adequate resources are available.

Initiating a quality risk management process 19. Quality
risk management should include systematic processes designed to coordinate, facilitate, and enhance science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process may be as follows: - Define the problem and/or risk question,
including any relevant assumptions that
to identify potential risk
- Assemble the background information and/or data on the hazard, damage or potential impact on human health relevant to the risk assessment
- Identify a leader and necessary resources
- Specify a timeline, deliverable results, and the appropriate level of decision-making.
decisions for the risk management process

Risk assessment 20.
Risk assessment consists of the identification of hazards and the analysis and evaluation of the risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined description of the risk problem or question. When the risk in question is well defined, the appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more easily identified. To help clearly define the risk(s) for risk assessment purposes, three fundamental questions are often helpful: 1. What could go wrong?

2. What is the probability (chance) that it will go wrong?
3. What are the consequences (severity)?

21. ***Risk identification*** is a systematic use of information to identify hazards that refer to the risk question or problem description. Information may include historical data, theoretical analysis, informed opinions, and stakeholder concerns. Risk identification refers to the question “What could go wrong?”, including the identification of possible consequences. This provides the basis for further stages in the quality risk management process.

22. ***Risk analysis*** is the estimation of the risks associated with the identified hazards.
It is the qualitative or quantitative process of linking the probability of occurrence and severity of the damages. In some risk management tools, the ability to detect damage (detectability) also influences the risk estimate.
23. ***Risk assessment*** compares the identified and analyzed risk against the given risk criteria. Risk assessments consider the strength of the evidence for the three fundamental questions.

24. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the product. Revealing assumptions and reasonable sources of uncertainty will increase confidence in this product and/or help identify its limitations.
Uncertainty is due to the combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge, gaps in pharmaceutical science and process understanding, sources of harm (eg, failure modes of a process, sources of variability), and the probability of detection of problems.

25. The result of a risk assessment is either a quantitative estimate of risk or a qualitative ***description*** of a series of risks. When the risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as 'high', 'medium' or 'low', which should be defined in as much detail as possible. Sometimes a “risk score” is used to further define descriptors in the risk classification. In quantitative risk assessments, a risk estimate provides the probability of a specified consequence, given a set of circumstances that generates the risk. Therefore, quantitative risk estimation is useful for a particular consequence at a time. On the other hand, some of the risk management tools use a measure of relative risk to combine various levels of severity and probability into an overall estimate of relative risk. Intermediate steps within a rating process may sometimes employ quantitative risk estimation.

Risk control 26.
Risk control includes making decisions to reduce and/or accept risks. The purpose of risk control is ***to reduce*** risk to an acceptable level. The amount of effort used for risk control should be proportional to the importance of the risk. Decision makers can use different processes, including cost benefit analysis, to understand the optimal level of risk control.

27. Risk control could focus on the following questions: - Is the risk
above an acceptable level?
- What can be done to reduce or eliminate the risks?
- What is the right balance between benefits, risks and resources?
- Are new risks introduced as a consequence of the identified risks that are being
controlling?

28. ***Risk reduction*** focuses on quality risk mitigation or prevention processes when it exceeds a certain (acceptable) level (see Fig. 1). Risk reduction could include measures taken to mitigate the severity and likelihood of harm. Processes that improve the detectability of quality hazards and risks can also be used as part of a risk control strategy. The application of risk reduction measures can introduce new risks into the system or increase the importance of other existing risks. Therefore, it may be appropriate to return to the risk assessment to identify and assess any possible changes in risk after the implementation of a risk reduction process.

29. ***Risk acceptance*** is the decision to accept risk. Risk acceptance may be a formal decision to accept residual risk or it may be a passive decision in which residual risks are not specified. For some types of damage, even quality risk management best practices may not eliminate the risk entirely. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and must be decided on an individual basis.

Risk Communication 30.

Risk communication is the sharing of information about risk and risk management among decision makers and others. Parties can communicate at any stage of the risk management process (see Figure 1: dashed arrows.). The product/result of the quality risk management process must be adequately communicated and documented (see Fig. 1: solid arrows). Communications could include those between interested parties; for example, regulators and industry, industry and patient, within a company, industry or regulatory authority, etc. The information included could relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detection or other aspects of quality risks. Communication does not have to take place for each and every risk acceptance. Between industry and regulatory authorities, communication regarding quality risk management decisions can take place through existing channels as specified in regulations and guides.

Risk Review 31.

Risk management should be an active part of the quality management process. A mechanism must be in place to review or monitor events.

32. The product/output of the risk management process should be revised to take into account new knowledge and experience. Once the quality risk management process has been started, the process should continue to be used for events that may affect the original quality risk management decision, if these events are planned (for example, the results of the product reviews, inspections, audits, change control) or are not planned (for example, root cause failure investigations, recalls). The frequency of any review should be based on the level of risk. Risk review could include reconsideration of risk acceptance decisions (section 4.4).

RISK MANAGEMENT METHODOLOGY 33. Quality risk

management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods for performing quality risk management process steps based on current knowledge of risk assessment of probability, severity, and sometimes detectability.

34. Traditionally, quality risks have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, collection of observations, trends and other information. Such approaches still provide useful information that could support topics such as complaint handling, quality defects, deviations, and resource allocation.

35. In addition, the pharmaceutical industry and regulators can assess and manage risk using recognized internal risk management tools and/or procedures (eg standard operating procedures). Below is a non-exhaustive list of some of these tools (more details in Annex 1 and Chapter 8):

- Basic risk management facilitation methods (flow charts, check sheets, etc.)
- Analysis of Effects and Failure Mode (AMEF)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard and Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Classification and Filtering of Risks
- Statistical tools support

36. It may be appropriate to adapt these tools for use in specific areas related to the quality of active ingredients and pharmaceutical (medicinal) products. Quality risk management methods and supporting statistical tools can be used in combination (eg Probabilistic Risk Assessment). Mixed use provides flexibility that can facilitate the application of quality risk management principles.

37. The degree of rigor and formality of quality risk management must reflect the available knowledge and be proportional to the complexity and/or criticality of the topic to be dealt with.

INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS 38. Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). . As noted in the introduction, the appropriate use of quality risk management does not obviate the industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and could affect the extent and level of regulatory oversight. direct.

In addition, quality risk management can facilitate better use of resources by all parties.

39. Training of industry and regulatory personnel in quality risk management processes provides a greater understanding of decision-making processes and reinforces confidence in quality risk management results.

40. Quality risk management should be integrated into existing operations and properly documented. Annex II provides examples of situations where use of the quality risk management process can provide information that could be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create new expectations beyond the requirements established in current regulations.

41. Examples of industry and regulatory operations (see Annex II): - Quality management 42.

Examples of industry operations and activities (see Annex II): - Development - Installation,

equipment and critical services - Management of Materials - Production

- Stability

tests and laboratory control - Packaging and labeling 43. Examples of regulatory operations (see Annex II): - Valuation and inspection activities 44. Although regulatory decisions will continue to be taken at the regional level, the Common understanding and application of quality risk management principles could facilitate mutual trust and promote more consistent decisions among regulators based on the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

DEFINITIONS Risk

acceptance - The decision to accept risk (ISO Guide 73).
Risk analysis - Estimation of the risks associated with the identified hazards.
Quality - Degree to which a set of properties inherent to a product, system or process meets the requirements (see ICH definition Q6a specifically for "quality" of active ingredients and pharmaceutical (medicinal) products).
Product Life Cycle - All phases of the product's life from initial development through commercialization to product discontinuation.
Risk communication - Exchange of information about risk and risk management between the decision maker and other interested parties.
Risk control - Actions that apply risk management decisions (ISO Guide 73).
Damage - Impairment to health, including damage that may occur from loss of quality or availability of the product.
Detectability - The ability to discover or determine the existence, presence, or fact of a hazard.

Decision Maker(s) - Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.
Risk Assessment - Systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of the risks associated with exposure to those hazards.

Risk assessment - Comparison of estimated risk to given risk criteria using a quantitative or qualitative scale to determine risk significance.

Quality risk management - Systematic process for the assessment, control, communication and review of risks to the quality of pharmaceutical (medicinal) products throughout the product life cycle.

Risk management - Systematic application of quality management policies, procedures and practices to the tasks of risk assessment, control, communication and review.
Severity - A measure of the possible consequences of a hazard.
Risk identification - Systematic use of information to identify potential sources of harm (hazards) in reference to the risk question or problem description.
Stakeholder - Any individual, group, or organization that can affect, be affected, or perceive itself to be affected by a risk. Decision makers could also be interested. For the purposes of this guideline, the main stakeholders are the patient, the health professional, the regulatory authority and the industry.

Danger - Potential source of harm (ISO/IEC Guide 51).
Risk reduction - Measures taken to reduce the probability of harm occurring and the severity of that harm.
Requirements - Explicit or implicit needs or expectations of patients or their surrogates (eg healthcare professionals, regulators and legislators). In this document, “requirements” refers not only to legal, legislative or regulatory requirements, but also to those needs and expectations.

Risk review - Examination or control of product/outcomes of the risk management process taking into account (if applicable) new knowledge and experience about risk.
Risk - Combination of the probability of harm occurring and the severity of that harm (ISO/IEC Guide 51).
Quality system - The sum of all aspects of a system that implements the quality policy and ensures that quality objectives are met.
Trend - Statistical term referring to the direction or rate of change of a variable.

REFERENCIAS

ICH Q8 Pharmaceutical development
ISO/IEC Guide 73:2002 - Risk Management - Vocabulary - Guidelines for use in Standards
ISO/IEC Guide 51:1999 - Safety Aspects - Guideline for their inclusion in standards
Process Mapping by the American Productivity & Quality Center 2002, ISBN 1928593739
IEC 61025 - Fault Tree Analysis (FTA)
IEC 60812 Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA)
Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983
Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press ISBN 0849319102 The
Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996 ISBN 0527763209
WHO Technical Report Series No 908, 2003 Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals
IEC 61882 - Hazard Operability Analysis (HAZOP)
ISO 14971:2000 - Application of Risk Management to Medical Devices
ISO 7870:1993 - Control Charts
ISO 7871:1997 - Cumulative Sum Charts
ISO 7966:1993 - Acceptance Control Charts
ISO 8258:1991 - Shewhart Control Charts
What is Total *Quality Control?; The Japanese Way,* Kaoru Ishikawa (Traducido por David J. Liu), 1985, ISBN 0139524339

APPENDIX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this appendix is to provide an overview of references to some of the main tools that could be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation where a quality risk management procedure is used.

I.1 Basic Methods of Facilitating Risk Management Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are: - Flow charts - Check sheets - Process Mapping - Cause and effect diagrams (also called fishbone diagrams or de Ishikawa)

I.2 Analysis of Effects and Failure Mode (FMEA)

FMEA (see IEC 60812) provides an assessment of potential failure modes of processes and their likely effect on product results and/or performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control potential failures. FMEA is based on understanding products and processes. FMEA methodically breaks the analysis of complex processes into manageable steps.

It is a powerful tool to summarize the important failure modes, factors that cause these failures and the possible effects of the same. **Potential areas of use(s)**

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and could be used to analyze a manufacturing operation and its effect on the product or process. Identifies elements/operations within the system that make it vulnerable. The FMEA product/result can be used as a basis for design or further analysis or to guide the deployment of resources.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

The FMEA could be extended to incorporate an investigation on the degree of severity of the consequences, their respective probabilities of occurrence and their detectability, thus becoming a Failure Mode, Effects and Criticality Analysis (FMECA; see IEC 60812). In order for this type of analysis to be performed, product or process specifications must be established.

The FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential areas of use(s)

The application of the FMECA in the pharmaceutical industry should mostly be used for failures and risks associated with manufacturing processes; however, it is not limited to this application.
The output of a FMECA is a relative risk “score” for each failure mode that is used to rank modes based on relative risk.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes the failure of the functionality of a product or process. This tool assesses system (or subsystem) failures one at a time, but can combine multiple failure causes by identifying causal chains. The results are graphically represented in the form of a failure mode tree. At each level in the tree, the failure mode combinations are described with logical operators (AND, OR, etc.). The FTA relies on expert understanding of the process to identify causal factors.

The FTA can be used to establish the path to the root cause of the failure. The FTA can be used to investigate complaints or deviations to fully understand their root cause and ensure that planned improvements fully resolve the issue and do not lead to other issues (i.e. fixing one issue may still cause a different issue). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given problem. The output of an FTA includes a visual representation of the failure modes. It is useful for both risk assessment and the development of monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive and preventive tool to ensure product quality, reliability and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent and control the risk of adverse consequence(s) of hazard(s) due to the design, development, production and use of products.

HACCP consists of the following seven steps:
1. perform a hazard analysis and identify preventive measures for each step in the process; 2. determine critical control points; 3. set critical limits; 4. establish a system to monitor critical control points; 5. Establish corrective measures to be taken when monitoring indicates that critical points control are not in a control state;
6. establish a system to verify that the HACCP system is working effectively; 7. Establish a registration system.

Potential areas of use(s)
HACCP could be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when the understanding of the product and process is comprehensive enough to support the identification of critical control points. The result of a HACCP analysis is risk management information that facilitates the monitoring of critical points, not only in the manufacturing process, but also in other phases of the life cycle.

I.6 Hazard Analysis and Operability (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that hazard events are caused by deviations from design or operating intentions. It is a systematic brainstorming technique to identify hazards using so-called “guide words”. “Guide words” (eg No, More, In addition to, Part of, etc.) are applied to relevant parameters (eg contamination, temperature) to help identify possible deviations from normal use or design intentions . Often uses a team of people with expertise covering process or product design and its application. **Potential areas of use(s)**

HAZOP can be applied to manufacturing processes, including outsourced production and formulation, as well as suppliers upstream, equipment and facilities of pharmaceutical (drug) ingredients and products. It has also been used mainly in the pharmaceutical industry for the evaluation of process safety hazards. As is the case with HACCP, the result of a HAZOP analysis is a list of operations critical to risk management. This facilitates periodic monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is an analysis tool based on the application of experience or knowledge of a hazard or failure to identify future hazardous hazards, situations and events that could cause harm, as well as to estimate their probability of occurrence for an activity, facility, product or before system. The tool consists of: 1) the identification of the possibilities that the risk event occurs, 2) the qualitative evaluation of the magnitude of possible injuries or damage to health that it can cause and 3) a relative classification of the hazard using a combination of severity and probability of occurrence, and 4) the identification of possible corrective measures.

Potential areas of use(s)
PHA could be useful in analyzing existing systems or prioritizing risks when circumstances preclude the use of a more extensive technique. It can be used for product, process, and facility design, as well as to assess types of hazards for the general type of products, then the product class, and finally the specific product. PHA is most commonly used early in project development when there is little information on design details or operating procedures; therefore, it will often be a precursor to further study. Typically, the risks identified in the PHA are further assessed using other risk management tools, such as those in this section.

I.8 Risk Sorting and Filtering Risk
sorting and filtering is a tool for comparing and classifying risks.
Risk classification of complex systems normally requires the evaluation of multiple and diverse quantitative and qualitative factors for each risk. The tool consists of breaking a basic risk question into as many components as necessary to capture factors involved in risk. These factors are combined into a single relative risk score that can then be used for risk classification. “Filters”, in the form of weighting factors or cut-off points for risk scores, can be used to scale or fit the risk ranking to management or policy objectives. **Potential areas of use(s)**

Risk sorting and filtering can be used to prioritize manufacturing locations for inspection/audit by regulators or industry. Risk classification methods are particularly useful in situations where the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk classification is useful when management has to assess risks assessed both quantitatively and qualitatively within the same organizational framework.

I.9 Supporting statistical tools Statistical
tools can support and facilitate quality risk management. They can enable effective assessment of the data, aid in determining the significance of the data set(s), and facilitate more confident decision making. A listing of some of the main statistical tools commonly used in the pharmaceutical industry is provided: (i) Control Charts, for example: - Acceptance Control Charts (see ISO
7966)

- Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
- Cumulative Sum Charts (see ISO 7871)
- Shewhart Control Charts (see ISO 8258)
- Weighted Moving Average

(ii) Design of Experiments (DOE)
(iii) Histograms
(iv) Pareto Charts (v)
Process Capability Analysis

APPENDIX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This appendix is intended to identify possible uses of quality risk management principles and tools by industry and regulators. However, the selection of certain risk management tools is entirely dependent on the specific facts and circumstances. These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Addendum is not intended to create new expectations beyond current regulatory requirements.

II.1 Quality risk management as part of integrated quality management Documentation

Review current interpretations and application of regulatory expectations Determine the convenience and/or develop the content of SOPs, guides, etc.

Training and education

Determine the adequacy of initial and/or ongoing training sessions based on the education, experience and work habits of staff, as well as a periodic assessment of previous training (for example, its effectiveness).

Identify the training, experience, qualification, and physical capabilities that enable personnel to carry out reliable operation without any adverse impact on product quality Quality **Defects** Provide the basis for identifying, evaluating, and communicating the potential quality impact of a defect , complaint, trend, deviation, investigation, out-of-specification result, etc. quality suspect Facilitate risk communication and determine appropriate actions to address major product defects, in conjunction with regulatory authorities (e.g. recall)

Audit/Inspection

Define the frequency and scope of audits, both internal and external, taking into account factors such as: - Existing legal requirements - The overall compliance status and history of the company or facility - The robustness of audit activities quality risk management of a company - The complexity of the site - The complexity of the manufacturing process - The complexity of the product and its therapeutic importance

- The number and significance of quality defects (for example, recall)
- The results of previous audits/inspections
- Major construction changes, equipment, processes, key personnel
- Experience with manufacturing a product (for example, frequency, volume, number of batches)

- Results of the tests of the official control laboratories

Periodic revision
Select, evaluate, and interpret trending data results within the product quality review

Interpret monitoring data (for example, to support an assessment of the adequacy of revalidation or changes in sampling)
Change management/change control
Manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing
Evaluate the impact of changes on the availability of the final product
Assess the impact on product quality of changes in facilities, equipment, materials, manufacturing processes, or technical transfers
Determining the appropriate steps that precede the implementation of a change, e.g. additional testing, (re)qualification, (re)validation or communication with regulators
continuous improvement
Facilitate continuous improvement in processes throughout the product life cycle

II.2 Quality Risk Management as part of regulatory operations Assessment and inspection activities Assist in the allocation
of resources, including, for example, the planning and frequency of inspection, and the intensity of inspection and assessment (see the “Audit” section in Annex II.1)

Assess the significance of, for example, quality defects, potential recalls and Inspection findings
Determine the relevance
and type of post-inspection regulatory follow-up Assess information submitted by
industry, including information on pharmaceutical development

Assess the impact of proposed variances or changes Identify
risks that need to be communicated between inspectors and assessors to facilitate a better understanding of how risks can be or are controlled (for example, parametric release, Process Analytical Technology (PAT)).

II.3 Quality risk management as part of development Design a
quality product and its manufacturing process to consistently deliver the expected product performance (see ICH Q8)
Improve knowledge of product performance across a broad range of material attributes (for example, particle size distribution, moisture content, flow properties), processing options, and process parameters Assess critical raw material attributes , solvents,
Active Pharmaceutical Ingredients (APIs) starting materials, APIs, excipients, or packaging materials
Establish appropriate specifications, identify critical process parameters,
and establish manufacturing controls (for example, use of information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)

Reduce the variability of quality attributes: -
Reduce product and material defects - Reduce
manufacturing defects Assess the
need for additional studies (eg bioequivalence, stability) in relation to scale and technology transfer
Make use of concept of “design space” (see
ICH Q8)

II.4 Quality Risk Management for Critical Facilities, Equipment and Services Facility/ equipment design Determine
appropriate zones in the design of buildings and facilities, for example, - Flow of
material and personnel -
Minimize contamination -
Control measures for pests -
Prevention of product mixes - Open
vs. closed equipment - Clean
rooms vs. isolation technologies - Dedicated or
segregated facilities/equipment Determine
appropriate product contact materials for equipment and containers (e.g. selection of type stainless steel, seals, lubricants)

Determine appropriate services (for example, steam, gases, power supply, compressed air, heating, ventilation and air conditioning (HVAC), water)
Determine appropriate preventative maintenance for associated equipment (for example, inventory of necessary spare parts)

Hygiene aspects in the facilities

Protect product from environmental hazards, including chemical, microbiological, and physical hazards (for example, determining appropriate clothing and gowning, hygiene issues)

Protect the environment (eg, personnel, potential for cross-contamination) from hazards associated with the manufactured product

Qualification of critical facilities/equipment/services

Determine the scope and extent of qualification of production facilities, buildings and equipment and/or laboratory instruments (including proper calibration methods)

Equipment cleaning and environmental control

Differentiate efforts and decisions based on intended use (eg, multiple vs. single purpose, batch vs. continuous production)
Determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance

Establish appropriate calibration and maintenance schedules

Computer systems and computer controlled equipment

Select hardware and software design (for example, modular, structured, fault-tolerant)

Determine the extent of the validation, for example:
- Identification of critical performance parameters
- Selection of requirements and design
- Code review
- Scope of tests and test methods
- Reliability of electronic records and signatures

II.5 Quality risk management as part of Materials Management Assessment and evaluation of suppliers and contract manufacturers Provide a comprehensive assessment of suppliers and contract manufacturers (e.g. audit, supplier quality agreements)

Starting material
Assess differences and potential quality risks associated with variability in starting materials (eg age, route of synthesis).
Use of materials
Determine if it is suitable to use the quarantined material (for example, for further internal processing)

Determine the adequacy of reprocessing, reprocessing, use of the returned goods **Storage, logistics and distribution conditions** Assess the adequacy
of mechanisms to ensure the maintenance of appropriate transport and storage conditions (for example, temperature, humidity, container design)

Determine the effect on product quality of discrepancies in storage or transport conditions (for example, cold chain management) in conjunction with other ICH guidelines Maintain infrastructure (for example, the
ability to ensure adequate conditions transportation, interim storage, handling of hazardous materials and controlled substances, customs clearance)

Provide information to ensure the availability of pharmaceuticals (for example, supply chain risk classification)

II.6 Quality risk management as part of production Validation
Identify the
scope and extent of verification, qualification and validation activities (for example, analytical methods, processes, equipment and cleaning methods Determine the extent of
quality control activities). follow-up (for example, sampling, monitoring and re-validation)

Distinguish between critical and non-critical process steps to facilitate the design of a validation study
Sampling
and in-process testing Assess
the frequency and extent of in-process control testing (for example, justify reduced testing under proven control conditions)
Evaluate and justify the use of process analysis technologies (PAT) in conjunction with real-time and parametric release time

Production planning
Determine appropriate production planning (for example, concurrent, dedicated, and campaign production process sequences)

II.7 Quality risk management as part of stability and laboratory control studies Out-of-specification

results Identify potential root causes
and corrective actions during investigation of out-of-specification results **Retest period / expiration date** Assess adequacy
of storage and examination of intermediate products,
excipients and starting materials **II.8 Quality risk management as part of packaging and labeling Packaging design**
Design secondary packaging for the protection of primary packaged product (for
example, guarantee
the authenticity of the product, label legibility)

Selection of container closure system
Determine critical parameters of the container closure system **Label**
controls Design label
control procedures based on the potential for product mix-ups involving different product labels, including different versions of the same label

GLOSSARY

The definitions below apply to words as used in this Guide. They may have different meanings in other contexts.

Action Limit

Established criteria that require immediate monitoring and corrective measures if exceeded.

Trap

An enclosed space with two or more doors and placed between two or more rooms, for example, of different cleanliness, for the purpose of controlling the flow of air between those rooms when they need to enter. A trap is designed and used by people or products.

Alert Limit

Established criteria that give early warning of the possibility of deviation from normal conditions that are not necessarily the ultimate corrective action, but do require follow-up investigation.

Authorized person

Person recognized by the authority as having the necessary scientific and technical training and basic experience.

Batch A defined quantity of starting material, packaging material, or product processed in a process or series of processes in such a way that it might be expected to be homogeneous.
Note: To complete certain stages of manufacturing, it may be necessary to divide a batch into a number of sub-lots, which are later joined to form a final homogeneous batch. In the case of continuous manufacturing, the batch must correspond to a defined fraction of the production, which is characterized by the desired homogeneity.
For finished product control, a batch of medicinal products comprises all units of a dosage form that are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all the units have been manufactured in a certain period of time.

Lot number A

distinctive combination of numbers and/or letters that specifically identifies a lot.

Biogenerator

A contained system, such as a fermenter, into which biological agents are introduced along with other materials for the purpose of effecting their multiplication or their production of other substances by reaction with the other materials.
Biogenerators are generally equipped with regulation, control, connection, material addition and material removal devices.

Biological agents
Microorganisms, including genetically modified microorganisms, cell cultures and endoparasites, whether pathogenic or not.
Bulk Product Any
product that has completed all stages of processing up to, but not including, final packaging.

Calibration

The set of operations that establish, under specified conditions, the relationship between the values indicated by a measuring instrument or system, or the values represented by a materialized measurement, and the corresponding known values of a reference standard.
Cell Bank Cell

Bank *System:* A cell bank system is a system whereby successive batches of a product are manufactured by culturing cells derived from the same master cell bank (fully characterized for identity and freedom from contamination).). A number of vessels from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a step level or number of population doublings beyond that achieved during routine production.

Master Cell Bank: A culture of cells (fully characterized) distributed into vessels in a single operation, processed together in such a manner as to ensure uniformity, and stored in such a manner as to ensure stability. A master cell bank is typically stored at -70°C or below.

Working cell bank: A cell culture derived from the master cell bank and intended for use in the preparation of production cell cultures. The work cell bank is normally stored at -70°C or below.

Cell culture

The result of in vitro growth of cells isolated from multicellular organisms. **Clean Area**
An area with
defined environmental control of particulate and microbial contamination, constructed and used in a manner that reduces the introduction, generation, and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the manufacture of sterile drugs. **Clean /**

Contained Area An area
constructed and operated in such a way as to meet the objectives of both a clean and a contained area at the same time.

Containment

The action of confining a biological agent or other entity within a defined space.
Primary Containment: A containment system that prevents the release of a biological agent into the immediate work environment. This involves the use of closed containers or biological safety cabinets in conjunction with safe operating procedures.
Secondary containment: A containment system that prevents the release of a biological agent into the external environment or other work areas. This implies the use of rooms with specially designed air treatment, the existence of air traps and/or sterilization for the exit of materials and safe operating procedures. In many cases it can contribute to the effectiveness of primary containment. **Contained area** An area constructed and operated in such a way (and equipped with adequate air treatment and filtration) that contamination of the external environment by biological agents within the area is prevented. **Controlled area** An area constructed and operated in such a way that some attempt is made to control the introduction of potential contamination (an air supply approaching grade D may be the case), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the agency employed in the process. As a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for effective removal of small amounts of airborne contaminants.

Computerized system A system that includes data input, electronic processing, and output of information to be used for notification or automatic control purposes.

Cross contamination

Contamination of a starting material or product with another material or product.

Raw vegetable (vegetable medicine)

Fresh or dried medicinal plants or parts thereof.

Cryogenic Vessel A vessel designed to contain liquefied gas at an extremely low temperature.

cylinder

A container designed to hold gas at high pressure.

Alien organism A biological agent in which the corresponding disease does not exist in a particular country or geographic area, or where the disease is the subject of prophylactic measures or an eradication program undertaken in the country or geographic area.

Finished product

Drug that has undergone all stages of production, including packaging in its final container.

Herbal medicines Medicines that
contain, as active ingredients, exclusively plant material and/or preparations of plant drugs.

Infected

Contaminated with foreign biological agents and therefore can spread infection.

In-process control

Controls carried out during production in order to monitor and, if necessary, adjust the process to ensure that the product conforms to its specification. Control of the environment or equipment can also be considered as a part of process control.

Intermediate material

Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Liquefiable

gases Those which, at normal filling temperature and pressure, remain as a liquid in the cylinder.

Manifold

Equipment or apparatus designed to allow one or more gas containers to be filled simultaneously from the same source.

Manufacturing All operations of purchase of materials and products, production, quality control, release, storage, distribution of drugs and related controls.

Manufacturer

Holder of the manufacturing authorization.

Media Fill Method

for evaluating an aseptic process using a microbial growth medium.
(Media fills are synonymous with simulated product fill, broth assays, broth fill etc.).

Medicinal plant

Plant in whole or in part of which is used for pharmaceutical purposes.

Medicines Any

medicine or similar product intended for human use, which is subject to control in the health legislation in the State of manufacture or import.

Packaging All
operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product.
Note: Sterile filling is not normally considered as part of packaging, bulk product being the primary containers filled, but not ultimately packaged.

Packaging Material
Any material used in the packaging of a drug, excluding any outer packaging used for transportation or shipping. Packaging materials are known as primary or secondary depending on whether or not they are intended to have direct contact with the product.

Procedures
Description of the operations to be carried out, precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicine.

Production
All the operations involved in the preparation of a drug, from receipt of materials, through processing and packaging, to completion as a finished product.

Qualification
Action to prove that any piece of equipment works correctly and really leads to the expected results. The word validation is sometimes expanded to incorporate the concept of qualification.

Quality control
See Chapter 1.

Quarantine
The state of starting or packaging materials, intermediate, bulk, or finished products in isolation physically or by other effective means, pending a decision on authorization or denial.

Radiopharmaceutical “Radiopharmaceutical” means any type of drug that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.

Reconciliation
A comparison, allowing for normal variation, between the theoretical and actual quantity of products or materials produced or used.

Registration Refer to Chapter 4.

Salvage The
introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing The
reprocessing of all or part of a batch of product of unacceptable quality from a defined stage of production so that its quality can be rendered acceptable by one or more additional operations.

Return

The shipment back to the manufacturer or distributor of drug products that may or may not have a quality defect.

Seed Lot Seed

Lot System: A seed lot system is a system whereby successive lots of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the primary seed lot. The final product is derived from the working stock lot and has not been further passaged from the master stock lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and passage history of the master seed lot and the working seed lot are recorded.

Master Seed Lot: A culture of a microorganism distributed from a single bulk into containers in a single operation in a manner that ensures uniformity to avoid contamination and ensure stability. A master seed lot in liquid form is generally stored at or below -70°C. A lyophilized master seed lot is stored at a known temperature to ensure stability.

Working seed lot: A culture of a microorganism derived from the master seed lot and intended for use in production. Working seed lots are dispensed into containers and stored as described above for master seed lots.

Specification

Refer to Chapter 4.

Starting material

Any substance used in the production of a drug, but excluding packaging materials.

Sterility

Sterility is the absence of living organisms. The conditions of the sterility tests are shown in the European Pharmacopoeia (or other relevant one).*

* The procedures and precautions employed should be such that a theoretical level of no more than of a live microorganism in 106 units in the final product.

Validation

Action of proving, in accordance with the principles of Good Manufacturing Practices, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).