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Annex 7
Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals

1. Introduction

Traditionally, the Hazard Analysis and Critical Control Point (HACCP) methodology has been considered to be a food safety management system. It aims to prevent known hazards and to reduce the risks that they will occur at specific points in the food chain. The same principles are also increasingly being applied, in other industries, such as the car industry, aviation and the chemical industry.

This text provides general guidance on the use of the HACCP system to ensure the quality of pharmaceuticals, while recognizing that the details of its application may vary depending on the circumstances (see Appendix 1). It does not provide detailed information on major hazards.

Hazards affecting quality are controlled to a certain extent through the validation of critical operations and processes in the manufacture of finished pharmaceutical products in accordance with Good Manufacturing Practices (GMP). However, GMP do not cover the safety of the personnel engaged in manufacture, while both aspects are covered by HACCP.

Procedures, including GMP, address operational conditions and provide the basis for HACCP. HACCP is a systematic method for the identification, assessment and control of safety hazards. Such hazards are defined as biological, chemical, or physical agents or operations that are reasonably likely to cause illness or injury if not controlled. In the manufacture of pharmaceuticals,[1] these may include the manufacture of certain antibiotics, hormones, cytotoxic substances or other highly active pharmaceuticals, together with operations such as fluid-bed drying, granulation is an example of hazard unit operations. The use of inflammable solvents (solutions) and certain laboratory operations may also constitute hazards.

[1] Safety hazards are common in the manufacture of active pharmaceutical ingredients; e.g., dangerous chemical conversions such as catalytic hydrogenation or nitration, or handling reactions with extremely hazardous chemicals such as phosgene or methyl-isocyanate require special precaution and control measures.

The following elements of the HACCP methodology are integral parts of the validation master file:

— development of a flow diagram of the process;
— verification of the flow diagram on site.

In addition, HACCP will extend this concept to include an analysis of the critical quality variables as well as the assessment of hazards affecting the safety of workers and environmental pollution hazards directly related to the process (in particular in open systems) concerned.

GMP for pharmaceutical products require the validation of critical processes as well as of changes in the manufacturing process which may affect the quality of the final product. Experience shows that most manufacturing processes contain steps that are "critical" from the point of view of variations in final product quality.

HACCP should not be confused with validation since its approach is broader; it thereby helps to identify matters on which validation should concentrate. It is science-based and systematic, and identifies specific hazards and measures for their control, as well as providing information on environmental protection and labour safety. HACCP is a tool to assess hazards and establish, control systems that focus on prevention rather than relying on corrective action based on end-product testing. All HACCP systems are capable of accommodating changes, such as advances in equipment design and processing procedures or technological developments.

HACCP should not replace GMP; however, its application may be used as a first step towards GMP.

In countries where appropriate regulations exist and are enforced, compliance with GMP (including validation), drug regulatory activities and inspections provide good assurance that risks are largely controlled. In countries where control is less effective, however, patients may be put at risk through the production of drugs of inadequate quality. The assessment of individual risks related to specific pro-ducts and starting materials, and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve drug control by increasing the effectiveness of their activities within the limits of the available resources.

The present guidelines are aimed at assisting industry to develop and implement effective HACCP plans covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing and distribution.

2. Links with other programmes

In each stage of the manufacture and supply of pharmaceuticals, the necessary conditions should be provided and met to protect the pharmaceuticals concerned. This has traditionally been accomplished through the application of Good Clinical Practice (GCP), Good Laboratory Practice (GLP), GMP and other guidelines, which are considered to be essential to the development and implementation of effective HACCP plans. HACCP plans are focused on hazards, the overall objective being to ensure that pharmaceuticals are safe for use. The existence and effectiveness of GCP, GLP and GMP should be assessed when drawing up HACCP plans.

3. Definitions

The following definitions apply to the terms as used in these guidelines. They may have different meanings in other contexts.

control (verb)
The taking of all necessary actions to ensure and maintain compliance with the criteria established in the HACCP plan.

control (noun)
The state wherein correct procedures are being followed and criteria are being met.

control measure
Any action and activity that can be used to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

corrective action
Any action to be taken when the results of monitoring at the CCP (see below) indicate a loss of control.

critical control point (CCP)
A step at which control can be applied and is essential to prevent or eliminate a pharmaceutical quality hazard or reduce it to an acceptable level.

critical limit
A criterion which separates acceptability from unacceptability.

deviation
Failure to meet a critical limit.

flow diagram
A systematic representation of the sequence of steps or operations used in the production, control and distribution of a particular pharmaceutical.

HACCP plan
A document prepared in accordance with the principles of HACCP to ensure the control of hazards which are significant for pharmaceutical quality in the production and supply chain.

hazard
Any circumstance in the production, control and distribution of a pharmaceutical which can cause an adverse health effect.

hazard analysis
The process of collecting and evaluating information on hazards which should be addressed in the HACCP plan.

monitor
The act of conducting a planned sequence of observations or measurements of control parameters to assess whether a CCP is under control.

pharmaceuticals
All products related to pharmacy, including starting materials (active pharmaceutical ingredients and excipients), finished dosage forms, and biological and other specific products.

validation
The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes — including equipment, buildings, personnel and materials — are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

verification
The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the HACCP plan.

4. Principles

The HACCP system is based on seven principles. In applying these principles, 12 stages are recommended and are discussed in section 7.

Some stages are linked to specific principles while others serve as an introduction to the concept.

The seven principles are:

1. Conduct a hazard analysis.
2. Determine the critical control points (CCPs).
3. Establish target levels and critical limit(s).
4. Establish a system to monitor the CCPs.
5. Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control.
6. Establish procedures to verify that the HACCP system is working effectively.
7. Establish documentation concerning all procedures and keep records appropriate to these principles and their application.

5. Guidelines for the application of the HACCP system

The following guidelines will be found useful in applying the HACCP system:

- Before HACCP is applied to any sector, that sector should be operating in accordance with the principles of good practices and the relevant legislation.
- Management commitment is necessary if an effective HACCP system is to be implemented.
- HACCP should be applied to each specific operation separately.
- CCPs identified in any given example in any reference document (including GMP guidelines) may not be the only ones identified for a specific application or may be of a different nature.
- The HACCP application should be reviewed and necessary changes made when any modification is made in the product or process, or in any step.
- It is important, when applying HACCP, to take into account the nature and size of the operation.
- There should be a HACCP plan. The format of such plans may vary, but they should preferably be specific to a particular product, process or operation. Generic HACCP plans can serve as useful guides in the development of product and process HACCP plans; however, it is essential that the unique conditions within each facility are considered during the development of all components of the HACCP plan.

6. Training and education

As HACCP is a relatively new concept in the pharmaceutical industry, training of personnel in industry, government and universities in

HACCP principles and applications is essential for its effective implementation.

In developing specific training to support a HACCP plan, working instructions and procedures should be drawn up which define the tasks of the operating personnel to be stationed at each critical control point. Specific training should be provided in the tasks of employees monitoring each CCP.

Cooperation between producers, traders and responsible authorities is of vital importance. Opportunities should be provided for the joint training of industrial staff and the control authorities to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of HACCP.

The success of a HACCP system depends on educating and training management and employees in the importance of their role in producing safe pharmaceuticals. Information should also be provided on the control of hazards at all stages of production and supply.

Employees must understand what HACCP is, learn the skills necessary to make it function properly, and must also be given the materials and equipment necessary to control the CCPs.

7. Application

The application of HACCP principles consists of the following 12 stages, as identified in the logic sequence for application of HACCP.

7.1 *Assemble a HACCP team*

The pharmaceutical manufacturer should assure that product-specific knowledge and expertise are available for the development of an effective HACCP plan. This may be best accomplished by assembling a multidisciplinary team. Team members should therefore represent all the relevant disciplines, such as research and development, production, quality control, quality assurance, microbiology, engineering and distribution or others as applicable.

Team members should have specific knowledge and expertise regarding the product and process. Where such expertise is not available on site, expert advice should be obtained from other sources.

Team members should be able to:

(a) conduct a hazard analysis;
(b) identify potential hazards;
(c) identify hazards which should be controlled;
(d) recommend controls and critical limits;

(e) devise procedures for monitoring and verification;
(f) recommend appropriate corrective action where deviations occur;
(g) verify the HACCP plan.

The scope of the HACCP plan should be defined. The scope should describe the segment of the process involved and the classes of hazards to be addressed should be identified.

7.2 *Describe the product and process*

A full description of the product and the process should be drawn up, including relevant quality information such as the composition, physical/chemical properties, structure, pH, temperatures, method of cleaning, bactericidal/bacteriostatic treatments (e.g. heat-treatment), drying, screening, mixing, blending, packaging, and the storage conditions. The method of distribution and transport should also be described, especially where products are thermolabile.

7.3 *Identify the intended use*

The intended use should be based on the expected uses of the product by the end user or consumer. In specific cases, vulnerable population groups, e.g. geriatric patients, infants and immunocompromised patients, may have to be considered.

7.4 *Construct a flow diagram*

The flow diagram should be constructed by the HACCP team, and should cover all operations and decisions in a process.

When applying HACCP to a given operation, the steps preceding and following that operation should also be considered.

A block-type diagram may be sufficiently descriptive.

7.5 *On-site confirmation of flow diagram*

The HACCP team should confirm the processing operation against the flow diagram during all stages and hours of operation. Amendments to the flow diagram may be made where appropriate, and should be documented.

7.6 *List all potential hazards associated with each step, conduct a hazard analysis, and consider any measures to control identified hazards (Principle 1)*

When hazard analysis is conducted, safety concerns must be distinguished from quality concerns.

The HACCP team should list all the hazards that may be reasonably expected to occur at each step from production, testing and distribution up to the point of use. It should then conduct a hazard analysis to identify for the HACCP plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential.

A thorough hazard analysis is required to ensure an effective control point. A two-stage hazard analysis is recommended. During the first stage, the team should review the materials, activities, equipment, storage, distribution and intended use of the product. A list of the potential hazards (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up.

In the hazard analysis, the following should be included wherever possible:

— the probable occurrence of hazards and the severity of their adverse health effects;
— the qualitative and/or quantitative evaluation of the presence of hazards;
— the survival or multiplication of microorganisms of concern;
— the production or persistence in drugs of toxins, chemicals or physical agents;
— the conditions leading to the above.

During the second stage, a hazard evaluation should be conducted, i.e. the severity of the potential hazards and the probability of their occurrence should be estimated.

The team should then decide which potential hazards should be addressed in the HACCP plan, and what control measures, if any, exist that can be applied for each hazard. More than one control measure may be required to control a specific hazard(s) and more than one hazard may be controlled by a specified control measure.

Potential hazards in relation to at least the following should be considered:

— materials and ingredients;
— physical characteristics and composition of the product;
— processing procedures;
— microbial limits, where applicable;
— premises;
— equipment;
— packaging;
— sanitation and hygiene;
— personnel;

— risk of explosions;
— mix-ups.

Common examples of failures are given in Appendix 2.

7.7 *Determine critical control points (Principle 2)*

A CCP in the HACCP system can be more easily determined by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packing, reprocessing, storage, distribution. Training in the use of decision-trees should be given.

If a hazard has been identified at a step where control is necessary for safety, and no control measure exists at that step, or any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure.

7.8 *Establish critical limits for each CCP (Principle 3)*

Critical limits must be specified and verified, if possible, for each critical control point. More than one critical limit may sometimes be elaborated at a particular step. The criteria used often include measurements of temperature, time, moisture level, pH, and sensory parameters, such as visual appearance and texture. Critical limits should be scientifically based.

7.9 *Establish a monitoring system for each CCP (Principle 4)*

Monitoring is the scheduled measurement or observation of a CCP relative to its critical limits. Monitoring should be recorded.

The monitoring procedures used must be able to detect loss of control at the CCP, and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the critical limits. Where possible, process adjustments should be made when monitoring results indicate a trend towards loss of control at a CCP. These adjustments should be made before a deviation occurs.

Data derived from monitoring must be evaluated by a designated person with the knowledge and authority to carry out corrective actions when indicated.

If monitoring is not continuous, the amount or frequency of monitoring must be sufficient to guarantee that the CCP is under control.

Most monitoring procedures for CCPs will need to be done rapidly because they relate to on-line processes and there will not be time for

lengthy analytical testing. For this reason, physical and chemical measurements are often preferred to microbiological tests because they can be done rapidly and can often indicate the microbiological control of the product.

The personnel conducting the monitoring of CCPs and control measures should be engaged in production (e.g. line supervisors, maintenance staff) and, where appropriate, staff from quality control. They should be trained in monitoring procedures.

Where continuous monitoring is possible, a reliable monitoring procedure and frequency should be identified. Statistically designed data collection or sampling systems should then be used.

All records and documents associated with monitoring CCPs must be signed and dated by the person(s) carrying out the monitoring and by a responsible reviewing official(s) of the company.

7.10 *Establish corrective actions (Principle 5)*

Specific corrective actions should be developed for each CCP in the HACCP system in order to deal with deviations when they occur. These actions should ensure that the CCP is brought under control. Corrective actions should include at least the following:

(a) determination and correction of the cause of non-compliance;
(b) determination of the disposition of the non-compliant product;
(c) recording of the corrective actions that have been taken.

Specific corrective actions should be developed in advance for each CCP and included in the HACCP plan. As a minimum, this plan should specify what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken. Individuals who have a thorough understanding of the process, product and HACCP plan should be assigned the responsibility for the oversight of corrective actions.

As appropriate, experts may be consulted to review the information available and to assist in determining the disposition of non-compliant product. Actions taken must also include the proper disposition of the affected product.

Deviation and product disposition procedures must be documented in the HACCP records.

7.11 *Establish verification procedures (Principle 6)*

Procedures should be established for verification.

Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the HACCP system is working correctly. The frequency of verification should be sufficient to confirm the proper functioning of the HACCP system.

Examples of verification activities include:

— review of the HACCP system and its records;
— review of deviations and product dispositions;
— confirmation that CCPs are kept under control.

Initial verification of the HACCP plan is necessary to determine whether it is scientifically and technically sound, that all hazards have been identified, and that, if the HACCP plan is properly implemented, these hazards will be effectively controlled.

Information reviewed to verify the HACCP plan should include:

(a) expert advice and scientific studies;
(b) in-plant observations, measurements and evaluations. For example, verification of the moist heat sterilization process for sterile injectables should include the scientific justification of the heating times, pressure and temperatures needed to obtain an appropriate destruction of pathogenic microorganisms (i.e. enteric pathogens) and studies to confirm that the sterilization conditions ensure that the whole load is kept at the required temperature for the time required.

Subsequent verifications should be performed and documented by a HACCP team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, a significant change in product, process or packaging occurs, or new hazards are recognized.

In addition, a periodic comprehensive evaluation of the HACCP system by an unbiased, independent third party is useful. This should include a technical evaluation of the hazard analysis and each element of the HACCP plan as well as an on-site review of all flow diagrams and appropriate records of the operation of the plan. Such a comprehensive verification is independent of other verification procedures and must be performed in order to ensure that the HACCP plan is resulting in the control of the hazards. If the results of the comprehensive verification identify deficiencies, the HACCP team should modify the HACCP plan as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

Where possible, verification should include actions to confirm the efficacy of all elements of the HACCP plan.

7.12 *Establish documentation and record keeping (Principle 7)*

Efficient and accurate documentation and record keeping are essential to the application of a HACCP system and should be appropriate to the nature and size of the operation.

Examples of activities for which documentation is required include:

— hazard analysis;
— CCP determination;
— HACCP plan;
— critical limit determination.

Examples of activities for which records are required include:

— CCP monitoring activities;
— process steps;
— associated hazards;
— critical limits;
— verification procedures and schedule;
— deviations;
— associated corrective actions;
— modifications to the HACCP system.

Appendix 1

Illustrative examples of major industrial hazards that may form part of a HACCP plan

The increasing use of hazardous chemicals in industry and trade further influences the quality and safety of processes and the personnel responsible for production. It is important that both on-site and off-site safety should be considered in all projects involving the storage and use of such chemicals.

This Appendix is intended only as a reminder of the major hazards that may be associated with the production, control and distribution of pharmaceuticals. Other relevant literature should be consulted, depending on the type of pharmaceuticals concerned (e.g. active pharmaceutical ingredients, vaccines).

1. Explosions and fires

Explosions can cause damage to buildings, injuries to personnel and hazards to products. Types of explosions that should be considered include detonations, gas and dust explosions, and confined and unconfined vapour-cloud explosions. Because of the possibility of explosions and fires, industry is required to control operations to prevent such hazards. An appropriate hazard-control system should therefore be in place at each site where such hazards are identified.

2. Workers' safety

3. External environment

3.1 Hazardous waste

3.2 Spillage

Appendix 2
Examples of common failures

Common failures should be identified and suitable control measures implemented.

1. **Component failures**

   Causes of such failures include bad design, pressure, corrosive media, high temperatures, mechanical failure of pumps, blowers and stirrers, failure of control systems, such as sensors, failure of welds and flanges, and failure of safety systems (e.g. valves).

2. **Deviations from normal operating conditions**

   Deviations from normal operating conditions include failures in the monitoring of crucial process parameters (e.g. pressure, temperature), failures in utilities such as steam, cooling, electricity and compressed air, failures in shut-down and start-up procedures, and formation of by-products, residues and impurities.

3. **Human and organizational errors**

   A wide variety of errors can be made by operating personnel. Common errors include operator error, pressing wrong buttons, disconnecting alarms, mix-ups of materials, communication errors, and incorrect maintenance and repairs.

4. **Natural forces**

   External impacts may be caused by natural forces such as wind, water, sunlight and lightning.

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