



Planning of Hazard Analysis Critical Control Point (HACCP) in Pharmaceuticals

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ABSTRACT

The FDA is considering HACCP (Hazard Analysis Critical Control Points) as the new foundation for revision of the US Food Safety Assurance Program because HACCP is considered to be a science-based, systematic approach to the prevention of food safety problems. In addition, the implementation of HACCP principles permits more government oversight through requirements for standard operating procedures and additional systems for keeping records, places primary responsibility for ensuring food safety on the food manufacturer or distributor, and may assist US food companies in competing more effectively in the world market. The maintenance of a health is essential for the overall wellbeing of an individual. As Hazard Analysis and Critical Control Point (HACCP) is a relatively new concept in the pharmaceutical industry. The methodology has been considered to be a food safety management and it is a systematic method for the identification, assessment and control of safety hazards. The (HACCP) is a federal initiative involving the FDA, WHO, GMP, GCP, GLP. The existence and effectiveness of GCP, GLP and GMP should be assessed when drawing up HACCP plans. 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. HACCP plans are focused on hazards, the overall objective being to ensure that pharmaceuticals are safe for use. This proposed review will evaluate temporal trends in identification, assessment and control of safety hazards.

Keywords: HACCP, Quality risk management, Hazard, Safety, Risk assessment.

INTRODUCTION

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

Hazard Analysis Critical Control Point System (HACCP) is even defined as a systematic approach to assure food safety by U.S. National Advisory Committee on Microbiological Criteria for Foods (NACMSF). The system was developed as an alternative to traditional control systems such as finished product analysis and process controls as shown in Figure 1. It was reported a decrease in some food borne diseases was observed between the years of 1996-1998 due to widely implementation of the system. HACCP is a preventive system and assures food safety as close to 100%. The success of HACCP depends largely on prerequisite programs including Good manufacturing practices (GMP), SOPs and SSOPs (Sanitation Standard Operating Procedure).

Potential areas of use(s)

HACCP can be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of Contains Nonbinding Recommendations 14 critical control points.

The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other lifecycle phases.

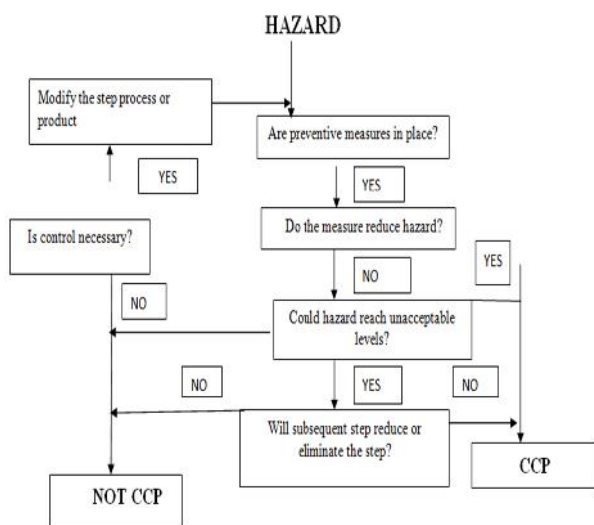


Figure 1: Flowchart of Hazard analysis critical control point.

Definitions²**Critical control point (CCP)**

A step at which control can be applied and is essential to prevent a food safety hazard or reduce it to an acceptable level.

Critical limit: A criterion which separates acceptability from unacceptability.

HACCP: A system which identifies, evaluates, and controls hazards which are significant for food Safety.

HACCP plan: A document prepared in accordance with the principles of HACCP to ensure control of hazards which are significant for food safety in the segment of the food chain under consideration.

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Hazard analysis

Assessment of risks present in particular environment and classification of exposure points according to their estimated degree of risk.

Risk assessment

A systematic process of evaluating the potential risks that may be involved in a projected activity or undertaking.

Quality risk management

A systematic process for the identification, assessment and control of **risks** to the **quality** of pharmaceutical products across the product lifecycle.

History of HACCP³**Initial development**

NASA's Zero Defects program

- ✓ Testing materials
- ✓ Natick's Failure Mode program
- ✓ Hazard Analysis and Critical Control points

Introduced during the National Conference on Food Protection, 1971

Three principles:

- Identification and assessment of hazards
- Determination of critical control points to control any identified hazard
- Establishment of systems to monitor critical control points

National Research Council - 1985

- An Evaluation of the Role of Microbiological Criteria for Foods and Food Ingredients
- ✓ Microbiological hazards not controlled by testing

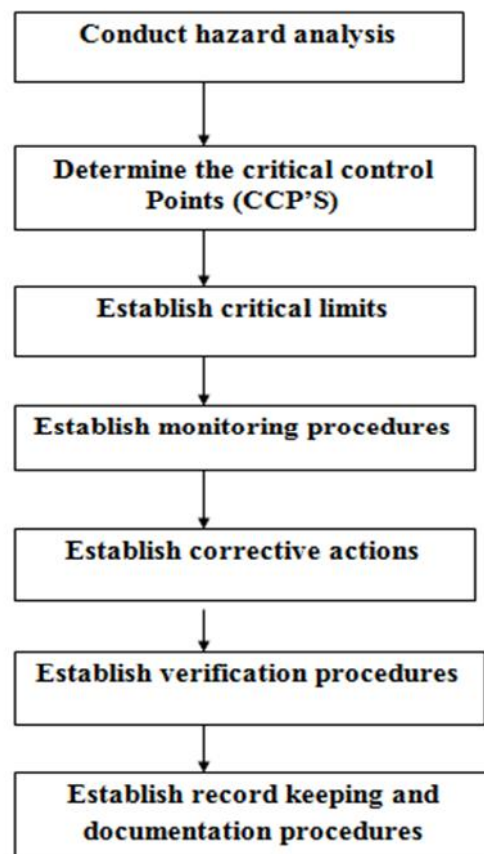
- ✓ Recommended using HACCP for food safety assurance

National Advisory Committee on Microbiological Criteria for Food (NACMCF)

- ✓ 1988
- ✓ Encourage adoption of HACCP
- ✓ Develop a consensus for HACCP application

NACMCF proposed 7 principles of HACCP application

- ✓ Published in 1989
- ✓ 1st. Revision in 1992
- ✓ 2nd. Revision (latest) in 1997
- ✓ Released immediately on the Internet
- ✓ Published in 1998 (Journal of Food Protection)

MATERIALS AND METHODS**Principles of HACCP System****Prerequisite programs and HACCP⁴**

Before developing the HACCP program, one prerequisite program is required. The minimum allowable sanitary conditions for the equipment and facilities are identified as Sanitation Standard Operating Procedures. SSOPs consist of written cleaning and sanitizing procedures, validation procedures, and records regarding sanitary

conditions both pre-processing and during processing. The SSOP verifications is carried out daily.

Examples of these are shown in Table 1, along with the relevant portion of the Sanitation regulations. It is

important to note that when FSIS verifies the regulatory requirements, it will only examine those records required by 9 CFR 416.

Table 1: Examples of common prerequisite programs

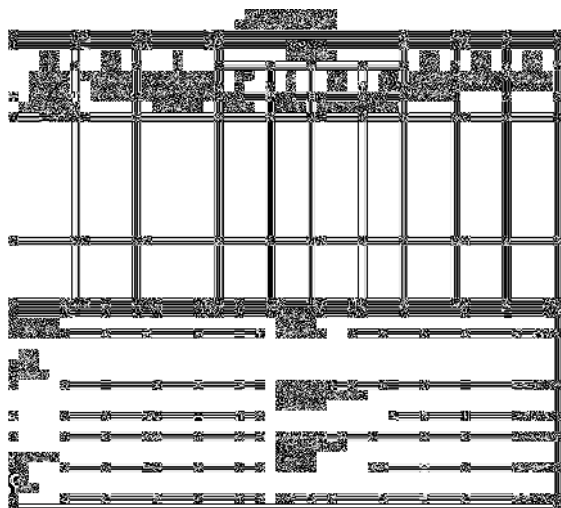
Maintenance	416.1–3. 416.6	Equipment is designed and constructed with sanitary practices in mind. Preventive maintenance and calibration schedules established and documented.
Personal hygiene	416.1, 416.5	All employees and other persons who enter and work in the manufacturing plant must follow the proper hygienic practices.
Pre-operational Sanitation	SSOPs 416.1, 416.11–17	This program documents that food is produced using sanitary practices in a sanitary facility using sanitary equipment prior to the start of daily operations.
Pest control	416.2	Effective pest control programs should be in place and monitored.
Storage and Shipping	416.1–416.4	All raw materials and products should be stored under sanitary conditions and proper environmental conditions to assure their safety.
Traceability and Recall	Requirement of the Bioterrorism Act of 2002, Section 306	All raw material and finished products should be lot-coded and a recall system in place so that rapid and complete traces and recalls can be done when a product retrieval is necessary.
Supplier control	Requirement of the Bioterrorism Act of 2002, Section 306	Facility should ensure that supplier has in place effective Good Management Practices
Personal Safety (not part of HACCP)	Requirement of the Bioterrorism Act of 2002, Section 306	This program discusses all non food safety issues including repetitive stress injuries, general health, MSDS (Material Safety Data Sheets), etc. Inspections performed by Occupational Safety and Health Administration.

Table 2: Steps in HACCP plan [10]

Features	Descriptions
Preliminary Steps	<ol style="list-style-type: none"> 1) Assemble HACCP team 2) Describe product 3) Identify intended use 4) Construct flow diagram 5) Verify flow diagram onsite
Principles of HACCP	<ol style="list-style-type: none"> 1) Conduct hazard analysis 2) Determine CCP'S 3) Establish critical limit for each CCP 4) Establish monitoring system for each CCP 5) Establish corrective actions 6) Establish verification procedures 7) Establish documentation and record



The HACCP Plan form⁵



This guidance document is designed to walk you through a series of 18 steps that will yield a completed (HACCP) plan. Note that this is a double-page form, with the second page to be used if your process has more critical control points than can be listed on one page. However, using this standardized form may help you develop an acceptable plan and will expedite regulatory review. The HACCP plan form is given above.

The Hazard Analysis Worksheet

To complete the HACCP plan form, perform hazard analysis. FDA has found that the use of a standardized Hazard Analysis Worksheet assists with this process. Note that this is also a two-page form, with the second page to be used if your process has more processing steps than can be listed on one page.

However, FDA expects that a written hazard analysis will be useful when you perform mandatory HACCP plan reassessments and when you are asked by regulators to justify why certain hazards were or were not included in your HACCP plan.

RESULTS AND DISCUSSION

Hazard analysis critical control point plan^{6,7}

The implementation of the HACCP Plan

Prior to beginning the development of a HACCP plan, have to undertake a thorough gap analysis of its existing prerequisite programmed and good manufacturing practices (GMPs).

As shown in Table 2, five preliminary steps were then taken to facilitate the smooth and quick application of the seven basic HACCP principles.

Preliminary Steps

Assemble the HACCP team

The team consists of individuals, who have specific knowledge and expertise appropriate to the product and process. Other team members include the person(s) responsible for plan maintenance. One person on the

HACCP team must be HACCP-trained. A team can be as few as one or two people.

Describe product

This provides an information on the ingredients, processing methods, and distribution methods. Classification of the product into a process allows the processor to focus on likely hazards associated with this type of product.

Identify the intended use and consumer

Identify the intended consumer or user of the product. The intended consumer may be the general public or a particular segment of the population, such as infants or the elderly. The intended user may also be another processor that will further process the product.

Develop a flow diagram describing the process

This diagram provides a clear, simple outline of the steps involved in the making the product. A block flow diagram is usually sufficient.

Verify the flow diagram

The HACCP team should perform an on-site review of the operation to verify the accuracy and completeness on the flow diagram. Perform a walk-through of the process to make sure all process steps are covered.

Once those preliminary tasks are completed, can develop the actual HACCP plan by taking the following steps.

HACCP Principles

Principle I

The first principle involves conducting a hazard analysis, which involves assessing certain risks involved in production of a product. "Hazard Analysis is defined as 'the process of collecting and evaluating information on hazards and conditions leading to their presence to decide which are significant for food safety and therefore should be addressed in the HACCP plan'. The first part of conducting a hazard analysis involves identifying all possible hazards that could occur within the product. The HACCP team should hold a brainstorming session to identify every possible hazard. During this session, the team should not consider the significance of a particular hazard. That will be dealt with during the risk assessment. The Hazard Analysis is probably the key principle in the whole HACCP system and the one people find to be the most difficult."

The three types of hazards that must be considered during a hazard analysis are biological, chemical and physical. When determining the likelihood of a hazard, the HACCP team must research each hazard and identify any trends. If the literature indicates that this hazard does not occur often, the team can indicate that the likelihood of occurrence is low. The team must also research a hazard to understand the severity if it is not properly controlled.

Principle II

When the hazard analysis is complete, the HACCP team must go over the flow diagram and decide which steps are critical control points (CCPs). A CCP can be a point in the process where a significant hazard can be eliminated or reduced to an acceptable level. A CCP is also a point where loss of control will lead to a significant hazard. CCPs require a lot of careful development and extra documentation and that is why they should be limited to only those that are truly critical.

When determining the steps are critical control points, some companies use what is called the shotgun approach. This is a method is not based on any true reasoning; rather CCPs are chosen based on the opinions of the team. This may lead to an excessive number of CCPs resulting in problems for the plant. A more accurate and feasible method that can reduce the number of CCPs is use of the decision tree. This approach asks several questions about each processing step where a hazard is significant. The questions are in "yes or no" format, and will eventually determine whether that step is a CCP.

Principle III

Once the CCPs are determined, critical limits are required for each step that is a CCP. A critical limit is a maximum or minimum value to which a specific parameter must be controlled at each CCP. Common critical limits are temperature, time, moisture, pH and salt concentration. Critical limits are rarely a range of values.

Principle IV

The next step is to monitor each CCP and critical limit. Monitoring of each critical limit is very important because it helps to ensure that the CCPs are in compliance and the critical limits are not exceeded.

Critical limits can be monitored continuously or non-continuously. If a critical limit were monitored continuously, a temperature monitoring system would be a good investment.

If non-continuous monitoring is utilized, a member of the HACCP team must conduct checks at regular increments (i.e. every 30 minutes or every hour). Because non - continuous monitoring is being used, it is important that the frequency of monitoring be adequate to ensure control of the CCP.

Principle V

If there is a deviation from the set standards of a critical limit, corrective actions must be taken. Corrective actions are procedures carried out when a loss of control has occurred at a particular CCP.

Suggested that all corrective actions as well as responsibilities should be clearly outlined before HACCP is implemented. All records and corrective actions should be documented to prove that corrective actions are being conducted.

Principle VI

The principle addresses this verification. Verification is the application of methods, procedures and tests to determine the company's compliance with the HACCP plan. Verification covers all internal daily activities with regards to HACCP. A few verification procedures include a review of the HACCP system and records, any deviations and product dispositions, and confirmation that the CCPs are kept under control. The only way to be confident that a safe product is being produced is to verify that the personnel have control at each step. Verification can be performed by plant audits with the use of microbial, physical and chemical tests. Government agencies will sometimes review HACCP plans to ensure compliance with standards. The frequency of such audits should be sufficient to verify that the HACCP program is functioning properly. There is often some confusion about how validation differs from verification. Verification determines compliance with the HACCP plan, where validation merely determines that the end results can be achieved.

Principle VII

The seventh principle of HACCP is to establish adequate record keeping procedures. Without records, there is no proof that a plant is doing what their HACCP plan indicates. Records are useful in providing a basis for trends and for systematic improvement of the process over time. All forms pertaining to monitoring results, corrective action logs, or training records must be kept on file for at least 1 year. Any modifications to, or audits of, the HACCP plan must be documented as well.

Complete the HACCP Plan Form

After finishing these steps for all significant hazards that relate to the product, you will have completed the HACCP Plan Form. One should then sign and date the first page of the HACCP Plan Form. The signature is must.

CONCLUSION

HACCP is a management system in which food safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution and consumption of the finished product. For successful implementation of a HACCP plan, management must be strongly committed to the HACCP concept. A firm commitment to HACCP by top management provides company employees with a sense of the importance of producing safe food. HACCP is designed for use in all segments of the food industry from growing, harvesting, processing, manufacturing, distributing, and merchandising to preparing food for consumption. Prerequisite programs such as current Good Manufacturing Practices (GMPs) are an essential foundation for the development and implementation of successful HACCP plans. The seven principles of HACCP have been universally accepted by government agencies,



trade associations and the food industry around the world.

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