Hazard Analysis and Critical Control Points (HACCP)

1 Overview

Hazard Analysis and Critical Control Point (HACCP) has been defined by the World Health Organization as "a scientific, rational and systematic approach for the identification, assessment and control of hazards.[1]" Originally developed to focus on food safety hazards, the HACCP system has been successfully applied to other applications and other industries. The intent of HACCP is to help prevent known hazards and to reduce the risks that they will occur at any point in a process through the execution of seven core action:

1. Conduct a Hazard Analysis
2. Determine the Critical Control points (CCPs)
3. Establish Target Levels and Critical Limits
4. Establish System(s) to monitoring CCPs
5. Establish an appropriate Corrective Action Plan for each CCP.
6. Establish Procedures to verify that the HACCP system is working effectively
7. Establish Documentation concerning all procedures and keep records of their application.

Background: *HACCP was conceived by NASA, the U.S. Army Laboratories at Natick and the Pillsbury Company as a means to ensure the safety of food consumed by NASA astronauts.*

Because the approach enforces procedural governance and rigorous documentation practices, HACCP serves not only as a model to assess risk, but also as an effective means to communicate risk control.

This document presents some core steps in the execution of HACCP. Successful application of any risk management model requires that tools are used in concert with the quality risk management process. This guide will present the seven principles of HACCP in the context of the ICH Q9 defined quality risk management process consisting of Risk Assessment, Risk Control, Risk Review and Communication.

1.1 Usage

The Hazard Analysis and Critical Control Point (HACCP) System:

- Is focused on safety hazards – typical safety hazards include biological, chemical or physical agents or operations that could lead to illness or injury if not controlled
- Typically, includes an entire process (e.g., for pharmaceutical manufacturing, it typically encompasses raw material receipt through distribution to the consumer)
- Is implemented through a plan that details the initial analysis and the on-going monitoring and review. The Plan is a "living" system; not a one-time assessment.
- Generates a "HACCP Control Chart" listing the potential hazards, preventive measures, critical limits, monitoring systems and corrective actions associated with each Critical Control Point.

[1] *HACCP: Introducing the Hazard Analysis and Critical Control Point System*, World Health Organization, 1997

Advantages	*Disadvantages*
+ Output is easy to understand – useful for communication + Fosters holistic and comprehensive understanding of hazards and controls for a process + Emphasis on control not detection	- Requires comprehensive process understanding – not ideally suited for little known hazards or processes - Does not quantify or prioritize risks - Does not quantify impact of additional controls on reducing risk

1.2 Quality Risk Management Applications

HACCP is well-suited for a variety of applications, including:

- To identify microbiological hazards and their controls in a process
- As an input to define Critical Process Parameters and the associated action and alert limits for those parameters
- As a structure to evaluate, support and communicate the effectiveness of cleaning and sanitization processes
- To evaluate the impact of operator actions on the quality and safety of a product.

2 Preliminary Tasks

2.1 Define Risk Question and Scope of System

The first step in any risk management effort is to define the overall risk question. Answering the risk question represents the ultimate goal of the risk assessment. Examples of risk questions include:

- How often should a manufacturing site be audited to assure GMP compliance?
- What root causes of non-conformances should we prioritize for remediation?
- What are the appropriate back-up inactivation methods that provide an appropriate level of decontamination in a fermentation suite to inactivate BL2 waste and equipment when the inactivation autoclave is unavailable?

2.2 Assemble the HACCP Team and Define Scope

Because of the complexity and variety of potential hazards with any pharmaceutical product or process, it is important to assemble a multidisciplinary HACCP team. The scope of the effort will indicate the type and level of expertise of required HACCP team members. For example, for an effort focused on patient or consumer safety concerns, a HACCP team should have available expertise in:

- Active ingredients and associated impurities and degradants
- Operations, including synthesis, manufacturing and packaging processes
- Utilities, including water systems, HVAC and electrical
- Cleaning processes, including detergents and sanitizing agents
- Process changeovers, including manual operations such as clearance practices and equipment assembly / disassembly
- Microbiological flora inherent in raw materials, products or the environment

- Product characteristics that may impact stability of the product, including packaging materials of construction, closures, and physical product robustness
- Handling of a product by the patient, consumer or caregiver, including potential misuse, including implications of label comprehension, storage, and possible off-label use
- Health implications of exposure or consumption of hazards, including concomitant medications

If the scope of the initiative includes operator safety or environmental impact, the team should also be represented by an expert in safety and industrial hygiene.

As with any project, the scope should be clearly defined as part of chartering the initiative. Clearly-defined boundaries will help ensure that suitable team members are selected, representation, realistic goals are set, and that management and the HACCP team members are aligned and committed.

2.3 Describe the Product, Intended Use and Process

The HACCP team should first define the product(s) associated with the HACCP System. Because each product has a unique set of process steps and associated hazards, it is important that all products are defined through physical, chemical and biological characteristics. It is also important to consider the intended use of a product. If a product requires another device or another component as part of administration or use by the patient or consumer, it will be necessary to identify the hazards associated with that process.

At this early stage in the HACCP initiative, it may be helpful to group products by their characteristics, or by their intended use. Grouping helps to consolidate the assessment and management of risks and streamline the effort. Grouping can be done if the processes and intended use of a set of products are consistent. In cases where variations exist, the HACCP team may still choose to group products and assume the worst-case based on scientific rationale

It is at this point that the HACCP team will define the process. The process should be sufficiently detailed to highlight hazards and control points. It should depict:

- Process steps and equipment, whether manual or automated
- Direct process control elements, including on-line instrumentation, logic, manufacturing procedures and testing and inspection controls
- Indirect process controls including operator gowning, maintenance, cleaning and storage
- Quality controls supporting raw material and finished product release.

As with products, the HACCP team may choose to group similar process elements to simplify the effort.

Tip: *It is said that there are typically three different versions of a process:*
1. *What the SOP describes*
2. *What operators normally do*
3. *What operators do during both normal and abnormal conditions*

Unless your process flow encompasses the third version, you may be missing critical steps.

2.4 Challenge, Refine and Confirm the Process Flow

Once the process flow has been defined, it is important for the HACCP team to review the process with operators and/or other process experts and challenge the steps to confirm accuracy and completeness.

3 Risk Assessment

3.1 Conduct a Hazard Analysis (HACCP Core Action #1)

Once a process flow has been confirmed, the HACCP team will identify and assess hazards associated with each step of the process A comprehensive hazard analysis will capture:

- Actual and potential hazards associated with a step in the process
- The potential sources of hazards
- Whether the hazard is introduced, controlled or enhanced by this step
- The severity of harm (health effects) associated with each hazard and the impact of varying amounts or concentrations to the severity classification
- The probability of occurrence of a hazard without suitable control measures
- The survival or multiplication of organisms or presence of toxins of concern and contributing conditions, if / as applicable
- The introduction or creation of chemical impurities or degradants and contributing conditions, as applicable
- Rationale for determining that the hazard is sufficiently significant to warrant inclusion in further HACCP assessment
- Control measures in place to prevent or reduce the hazard to acceptable levels

For a large, complex HACCP scope, a phased approach to hazard analysis may be warranted. The first step may be to catalog all hazards for each step. The next phase may involve assigning hazards as "significant" based on scientific rationale for severity and probability of occurrence. The next phase may include revisiting each process step and identifying the controls associated with each step targeted at reducing or preventing the inventoried hazards.

Ultimately, the hazard analysis should be itemized in a table to clearly memorialize the analysis. The table below provides and example of an entry in a Hazard Analysis table.

Process Step	***Potential Hazard***	***Introduced, Controlled or Enhanced***	***Significant Hazard?***	***Rationale***		***Control Measures***
				Sev.	***Occ.***	
1) Mixed Trash is packed and prepared for autoclave.	BL2 Host Organism	Introduced	Yes	H	M	• Physical containment • Ethanol spray and wipe-down

3.2 Determine the Critical Control Points (HACCP Core Action #2)

One of the most problematic steps in a HACCP effort is determining the Critical Control Points (CCPs). The Hazard Analysis performed as Principle #1 typically yields a great deal of control measures that are ultimately not deemed to be CCPs. Determining which steps and controls are CCPs is aided by the use of a decision tree. The Codex CCP decision tree shown in Figure 1 below is a traditional starting point for developing a decision tree. The tool may be used as is or may be modified to meet the specific operations in question.

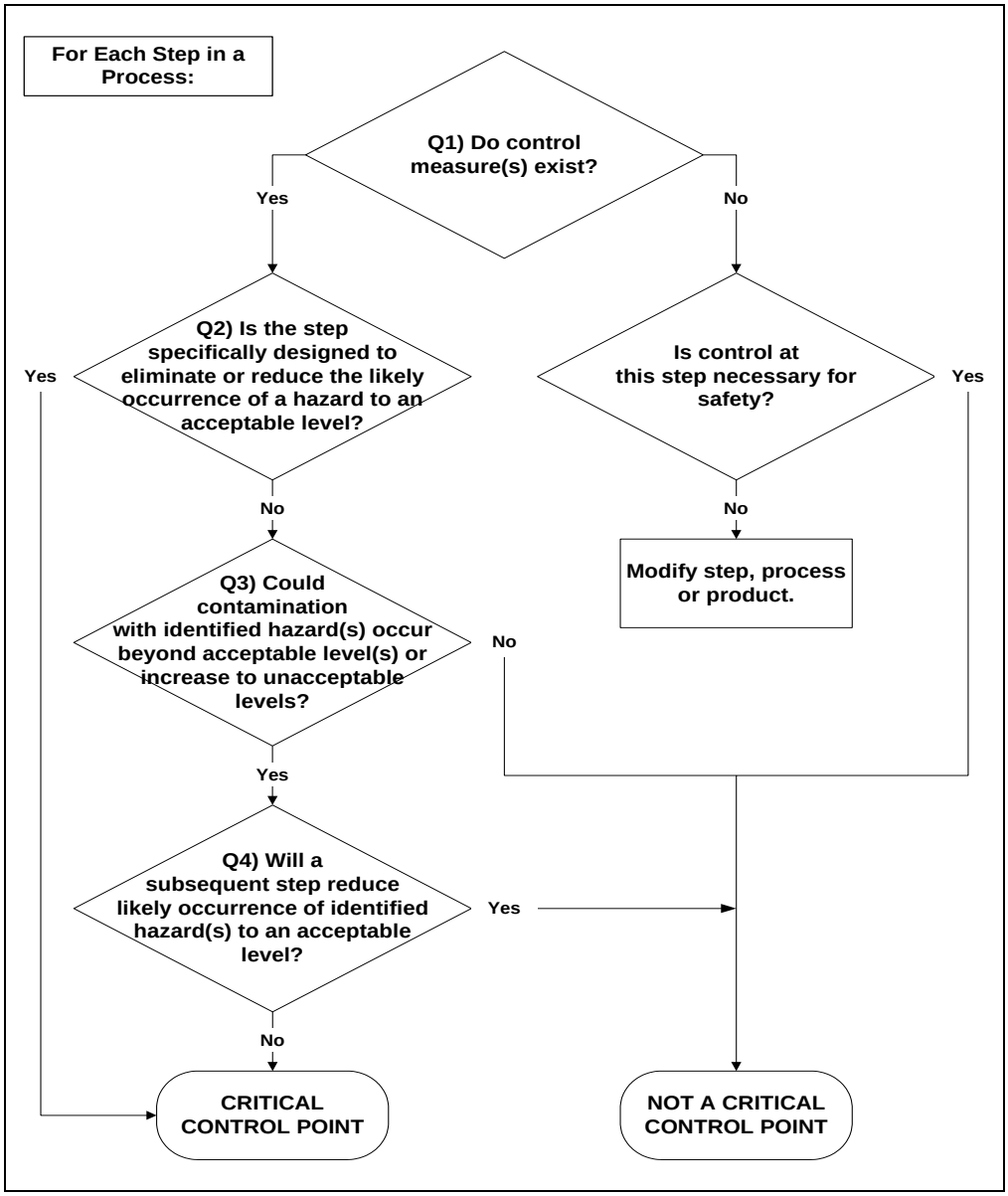

Figure 1 – Codex Critical Control Point Decision Tree[2]

[2] Codex Alimentarius Commission, *Report of the Twenty-Second Session of the Codex Alimentarius Commission*, Geneva, June 1997

The first question in the Codex Decision tree addresses whether or not there is a measure in place to control physical, chemical or biological hazards at this step. This information may be easily found from the Hazard Analysis table developed in Principle #1. If no control measures are in place then the step is not a CCP, but stronger control may be warranted.

The second question asks if the step is specifically targeted at hazards. Examples of such steps include sterilization, cleaning, distillation, or polishing operations. If this step is in place to target hazards, then the step is clearly a CCP.

The third question essentially asks whether or not a control measure is necessary. If contamination with an identified hazard in excess of unacceptable levels is impossible, then there is no need for a control measure and this step is deemed to be not a CCP.

Lastly, if significant contamination could occur then the fourth question asks if there are downstream controls in place to make any controls at this step seem superfluous. This last question typically is the most difficult to answer, but will yield powerful insight into the rationale for controls.

Some HACCP teams use a simple table to document the determination of a step as a CCP. An example of a CCP determination table is shown below.

Process Step	***Q1***	***Q2***	***Q3***	***Q4***	***CCP?***
1) Mixed Trash is packed and prepared for autoclave.	Yes: • Physical containment • Ethanol spray and wipe-down	No	Yes	No	**YES**

Finally, it is worth noting that, regardless of the decision model used, a HACCP team should focus on realistic hazards and reasonable controls. There may be times when a HACCP team has to make the assumption that good manufacturing practices are being followed and that these practices will control most extraordinary hazards.

3.3 Establish Critical Limits (HACCP Core Action #3)

To fully define a Critical Control Point, its critical limits must be defined. Loosely defined, critical limits are criteria which separate acceptability from unacceptability. These are typically combinations of measurable factors, such as time, temperature, pH or visual observation that have been validated to demonstrate effectiveness of the control in eliminating or reducing hazards to acceptable levels.

Establishing critical limits supports the implementation of suitable monitoring and control systems. The HACCP team should be careful to establish critical limits that are as practical as possible for the given process. It should also be noted that not all critical limits will be routinely monitored. Some critical limits and the abilities of control mechanisms to operate within these limits are established through validation and are not routinely monitored. Nonetheless, they should be captured as part of the HACCP effort.

3.4 Establish a System to Monitor Control of the CCP (Core Action #4)

The next step for the HACCP team is to define how a CCP will be monitored with respect to its critical limits. Using the established critical limits as a guide, the team should define the control parameters with an associated critical limit. In practical terms, the team should understand how an operator will know if a control limit has been reached. The monitoring system should be used primarily as a verification of the process control of hazards. Monitoring Systems are defined by defining the associated **Procedures**, **Frequency** and **Responsibilities**.

Typical monitoring systems include:

- On-line Systems – usually capable of providing frequent, semi-continuous data
- Off-line Systems – typically involving a great deal of human involvement to operate the monitoring device(s)
- Observational Procedures – visual inspections

Tip: *A simple way to document monitoring control systems is to define:*

- ***What** will be monitored*
- ***How** it will be monitored*
- ***How Often** will it be monitored*
- ***Who** is responsible*

If a control process is validated and will not be routinely monitored, this should be supported by the validation study and through maintenance and change control practices.

As part of defining the system to monitor control, the level of monitoring frequency must be defined. This must be scientifically-based to provide assurance that the CCP is under control.

Finally, any monitoring control system must be governed by standard procedures defining the accountable roles and the necessary steps. Recorded values from monitoring of CCPs must be documented in accordance with Good Manufacturing Practices.

4 Risk Control

4.1 Establish a Corrective Action Plan for each CCP (HACCP Principle #5)

Establishing a corrective action plan for each CCP involves defining the necessary actions to bring a CCP into control in case of a deviation. Typically, this includes defining **Action Limits** and **Alert Limits** in addition to the Critical Limits previously defined. Action Limits are those limits that indicate performance within control limits, but outside of trend. Reaction to these limits is typically by way of normal adjustment and does not constitute a deviation. Alert Limits are indicated when a CCP is trending toward failure. While still within Critical Limits, an Alert Limit should trigger non-routine corrective action to avoid a deviation. In the case that a Critical Limit has been reached, the organization's deviation management practices are usually initiated to investigate and resolve.

The HACCP system should document all three scenarios and the types of actions that will be taken to manage each. In the final case of a true deviation, the HACCP system will document the standard procedures governing deviation management and any systems that support investigations and resolution of deviations.

5 Risk Review

5.1 Establish Procedures to Confirm that the HACCP System is Working (HACCP Principle #6)

On a long-term basis, operational feedback should confirm that the assessment and control steps are adequately addressing the risk question. If this is not the case, it may be necessary to review all applicable assumptions. Feedback should correspond to ensuring that assumptions made about the level of residual risks are still valid. It is also important to evaluate any new risks that may arise from risk control strategies. Sometimes risks that were not originally identified or may have been filtered out during the initial risk assessment can become aggravating factors due to the implementation of risk control measures.

6 Risk Communication

6.1 Establish Documentation Concerning All Procedures and Records (HACCP Principle #7)

HACCP is a powerful communication tool. The output of the tool should always be presented at a level of detail appropriate for the various stakeholders. This is important not just for presenting results, but also for obtaining early buy-in on the approach.

In cases where the HACCP approach is used as the basis for a "GxP" decision or some other regulated authorization, the approach should be documented in a Standard Operating Procedure. It may not be necessary to include detailed scoring steps or algorithms in the procedure, but they should be documented in a controlled report. Updates to the portfolio should also be controlled.