# HACCP: A Process Validation Tool for Ensuring Quality of Biotech and Pharmaceutical Products

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Hazard analysis and critical control points (HACCP) is a methodical and systematic application of science and technology to evaluate, plan, control, and document the safe and efficient manufacture of products, from raw materials to end use. The goal of HACCP is to ensure product safety before, during, and after manufacture (product is free of pathogens and contaminants, for example). The original concept goes back to the late 1950s and early 1960s and the space program under the U.S. National Aeronautic and Space Administration (NASA). HACCP was developed to ensure that food products utilized as part of the space program were safe for use in space travel (1, 2). *Hazards* under HACCP are defined in terms of their possible impact on the end user or customer. The *hazard analysis* provides an assessment of where and how safety risks may arise, and the *critical control points* provide verification of effective control of the process.

**As part of a NASA project, the Pillsbury Company developed the hazard analysis and critical control point (HACCP) concept to ensure against bacterial contamination.** NATIONAL AERONAUTICS AND SPACE ADMINISTRATION (WWW.NASA.GOV)

The HACCP program was developed in a combined effort between Pillsbury and the Department of Defense. It is based on failure mode analysis and considers how failures may happen, where they are most likely to occur, and how they may be prevented or mitigated. The main concern at NASA was the risk of microbial contamination (microbial hazards due to presence of pathogenic microorganisms) that could cause foodborne illness during space travel. Also considered under HACCP were chemical and physical hazards such as cross contamination, pesticides, extraneous particles, and so on.

In 1971, the HACCP program was made public during a National Conference on Food Protection. Two years later, the U.S. Food and Drug Administration (FDA) issued 21 CFR 113 and 114 (the acidified and the low-acid canned food regulations). Those sections of the CFR are examples of successful programs implementing HACCP. In 1989, a guideline on HACCP was published by the National Advisory Committee on Microbiological Criteria for

PRODUCT FOCUS: ALL FDA-REGULATED PRODUCTS

PROCESS FOCUS: MANUFACTURING

WHO SHOULD READ: PROJECT MANAGERS, QUALITY ASSURANCE AND CONTROL, MANUFACTURING

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LEVEL: INTERMEDIATE

Foods. It describes the procedure and requirements for successfully implementing HACCP (1, 2).

It is important to recognize that application of HACCP in the food industry has mainly focused on foodborne pathogen issues. In the pharmaceutical industry, however, microbial contamination is just one of several issues that can affect product quality attributes. Depending on the type of pharmaceutical product involved, other issues such as potency and stability may also be addressed through HACCP. In addition, HACCP can be used to identify critical process parameters and assess the effects of process changes and deviations on the safety, purity, and effectiveness of a given drug product.

## Elements of HACCP

The principal elements of HACCP are stepwise as follows.

**Process Mapping:** A detailed description and flow diagram of a manufacturing process including all process variables and related product quality attributes is prepared and reviewed for accuracy and completeness. The process map should indicate the types of hazards that may affect each step. The main objective of this map is to identify all possible control points along the process to prevent or minimize any hazard.

**Critical Control Points:** Once the hazards and risks have been assessed, the control points that affect product quality attributes are identified as *critical control points* (CCPs). A CCP is a process step in which a hazard can be eliminated or mitigated. Each CCP should have at least one critical process parameter (CPP) that is tied to the quality attribute(s). CPPs are process parameters in unit operations that should be maintained within predetermined ranges to achieve certain quality attributes in the final product.

**Critical limits** (CLs) define the operating range of a CPP in which the process is known to yield an acceptable product. These limits are determined for every critical process parameter on the basis of data from developmental runs. The effect of running a CPP outside the CL also could be evaluated and documented.

**Monitoring Critical Control Points:** All CCPs should be monitored to ensure that the CPPs are satisfied during the manufacturing process. Typically, CPPs are monitored through batch records and / or manufacturing process documents. The information is recorded in accordance with current Good Manufacturing Practices (cGMPs) (3, 4).

**Figure 1:** Scope of HACCP for biotechnology and pharmaceutical processes

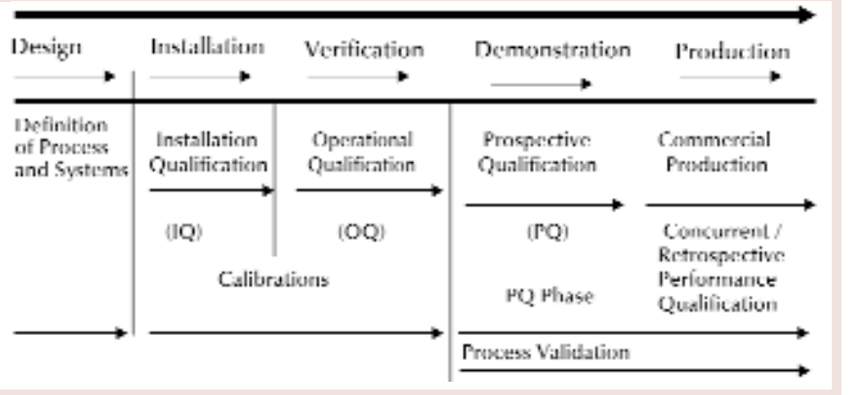



**Figure 2:** Decision tree for critical control points

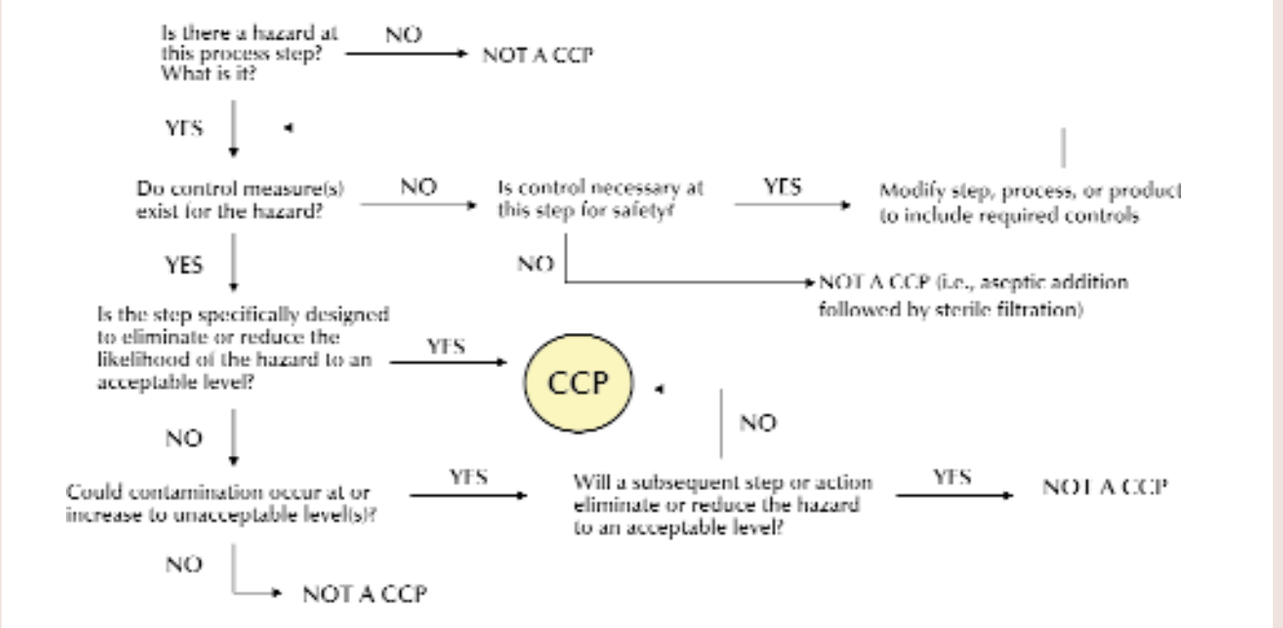
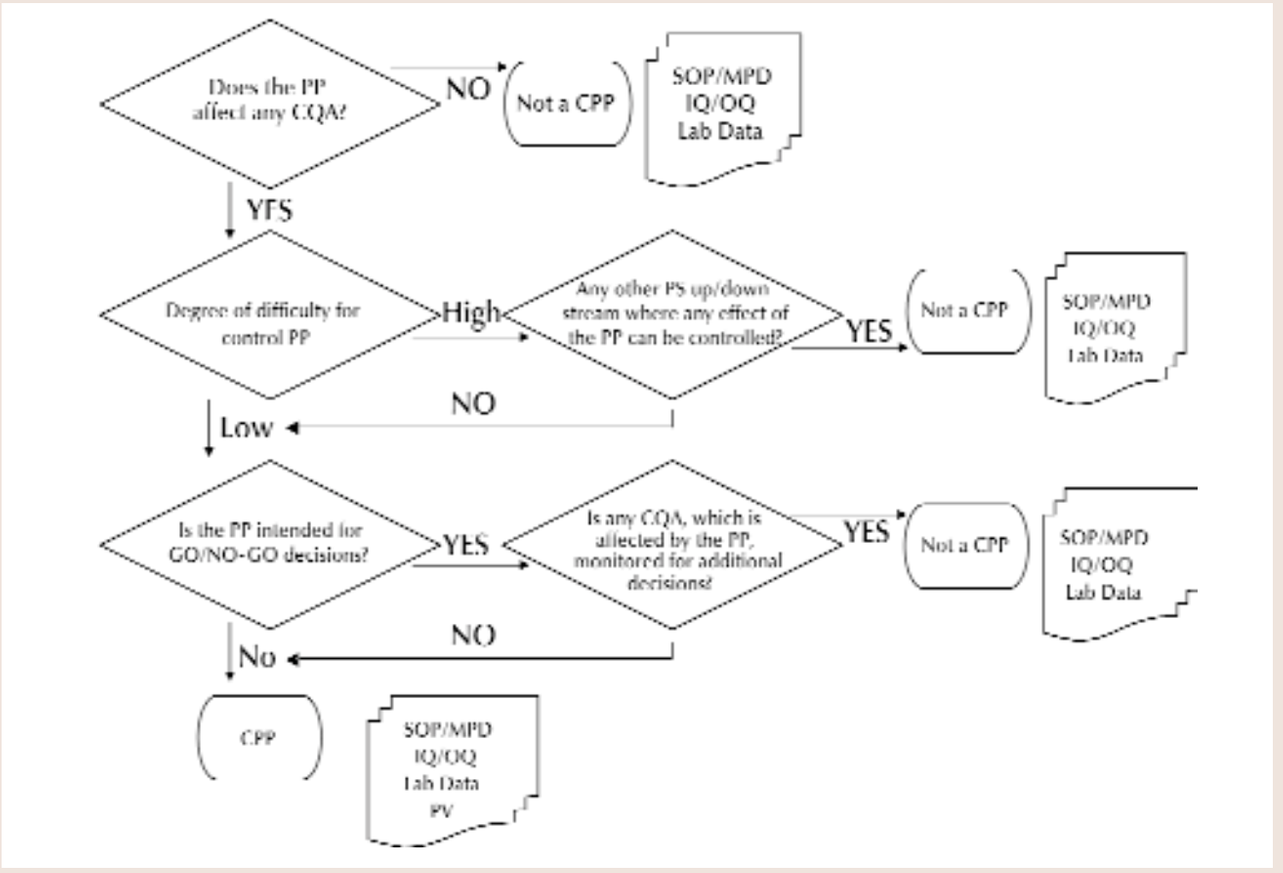


**Figure 3:** Decision tree for critical process parameters; MPD = manufacturing process description; PP = process parameter; and PS = process step.

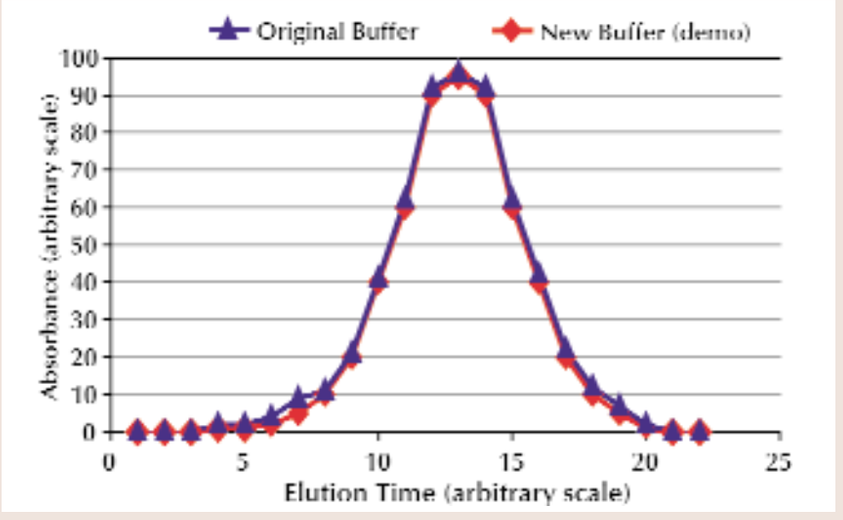



**Evaluation of Corrective Actions:** A corrective action (CA) describes a predetermined response to a lack of adequate control at a CCP, or the deviation of a CPP from its CL. This is a key element of HACCP because it represents a proactive approach to preventing possible problems during the manufacturing process.

**Verification of HACCP:** This step identifies appropriate auditing requirements to ensure the effectiveness of the implemented procedures in a manufacturing process.

**Documentation:** Appropriate procedures and records are developed and implemented as part of the HACCP initiative. The documents ensure that each lot of product is manufactured as intended and that the product meets all specified quality attributes.

**Figure 4:** Elution profiles of new and original buffers (initial demonstration)




## Application to Biopharmaceutical Processes

Figure 1 shows the intended scope of HACCP for biotech and pharmaceutical processing. HACCP should begin during the design phase of a new product and continue through scale-up, demonstration, and full-scale operation. Successful implementation of HACCP as a tool for process development, scale-up, demonstration, and validation in biotech and pharmaceutical applications involves the following.

**The HACCP Team** should include participants from all groups involved in the development and implementation of a manufacturing process (e.g. Research and

Development, Engineering, Technology, Operations, Quality, Validation, and Safety). The main difference between a HACCP team and a regular technology transfer team is that all members are involved from the early stages in development to assess properly the requirements for scale-up, to understand the effects of various process conditions on product quality, and to provide feedback for the design and development of process equipment.

**Hazard Analysis and Risk Assessment** are conducted on each process step taking into consideration microbiological, chemical, and physical hazards (and their impact on product potency, purity, sterility, and stability). These assessments facilitate the identification of critical quality attributes and critical process parameters related to raw materials, equipment, and the process itself.

Key elements of these assessments are a thorough understanding of the process and the interaction between its parameters, as well as the ability to develop effective strategies to minimize potential hazards. Hazard analysis identifies the most likely problems (microbial, chemical, and physical) that could be encountered or that may happen at any particular step. Risk assessment defines the likelihood that these hazards will occur and helps identify the most appropriate step where each hazard may be reduced or eliminated. It should be noted that hazards in HACCP are defined in terms of their possible impact on product quality (purity, potency, and safety). The "Hazard and Risk Assessment" box provides an example of hazard analysis for a hypothetical manufacturing step.

**Quality Attributes and Process Parameters.** Quality attributes are defined as product characteristics or properties that could potentially affect the potency, safety, and effectiveness of a product. Typically, they include pH, conductivity, concentration of active ingredient or protein of interest, column clearance, and purity. Quality attributes that must lie within predetermined ranges to ensure potency, safety, and effectiveness are defined as critical quality attributes (CQAs). Similarly, process conditions and parameters that must lie within predetermined ranges to ensure that the CQAs are met are defined as critical process parameters (CPPs). Typically, CPPs include flow rate, pressure, temperature, agitation rate, and hold time. In some instances, input parameters such as pH, conductivity, and salt concentration may be considered as CPPs in specific unit operations such as a chromatography step. CPPs and CQAs are generally determined through developmental studies designed to understand the relationship between process parameters and quality attributes. At every critical control point, at least one CPP that controls a CQA should be identified. From a GMP standpoint, it is imperative that all CPPs and CQAs lie within their predetermined ranges (3–5).

**Critical Control Points.** As mentioned above, a critical control point is defined as a process step in which a particular hazard is reduced

## Hazard and Risk Assessments

**Step:** buffer formulation

**Detailed Description:** Raw materials are transferred from Room A to Room B. WFI is the first ingredient charged to Tank A using a dedicated inlet. The other ingredients are charged into Tank A one at a time while mixing occurs. Once all the ingredients are charged, the mixture is sterile-filtered using a 10-inch cartridge installed in a transfer line from Tank A to Tank B. Tank B and the transfer line are steam-in-place sterilized prior to the transfer operation.

### Process Conditions

WFI: 94 kg
NaCl: 2 kg
$Na_2PO_4$: 4 kg

Steam-in-place: 123 °C, 40 min.
Clean-in-place: 50 °C, 60 min.

Filter: 10-inch cartridge, Model A

Mixing: minimum 15 minutes at 50 rpm

Temperature: 25–30 °C (both tanks)

### Hazards

**Microbial:** Tank A bioburden exceeds capacity of filter; microbial contamination of WFI (pathogens) or other raw materials.

**Chemical:** Cross contamination of raw materials; improper dispensing of a raw materials; precipitation of salts due to supercooling

**Physical:** Extraneous particles

### Risk Mitigation

**Microbial:** Continuously monitor temperature, flow rate, and pressure of WFI system. Perform bioburden testing on every batch. Ensure that all raw materials are dry and no evidence of microbial contamination (e.g. atypical appearance/odor).

Test integrity of sterilizing filter before and after use. Validate SIP procedure to deliver an $F_o$ twice the theoretical minimum (overkill approach).

**Chemical:** Verify CoA and perform ID testing on every batch of raw material. Control batch temperature between 25 °C and 30 °C. Eliminate all sources of cold water to the manufacturing tanks.

**Physical:** Visually inspect tanks before use. Validate filtration step, verifying that filter can retain worst-case particle loads.

**Figure 5:** Process yields for new and original buffers (initial demonstration)

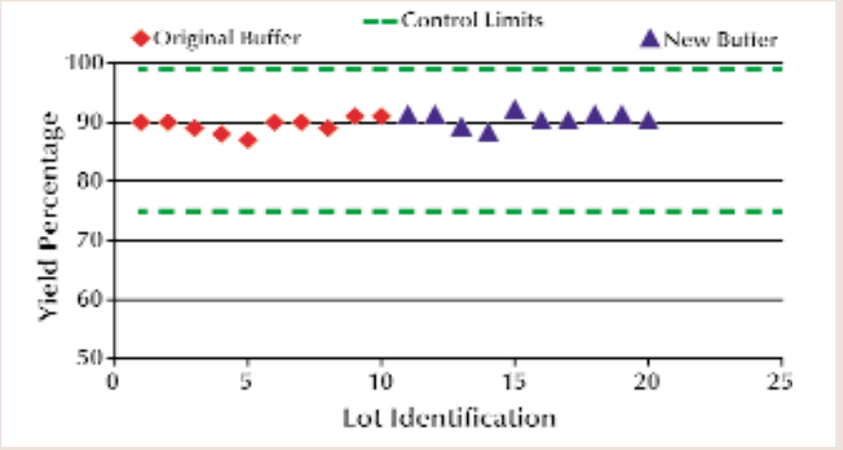
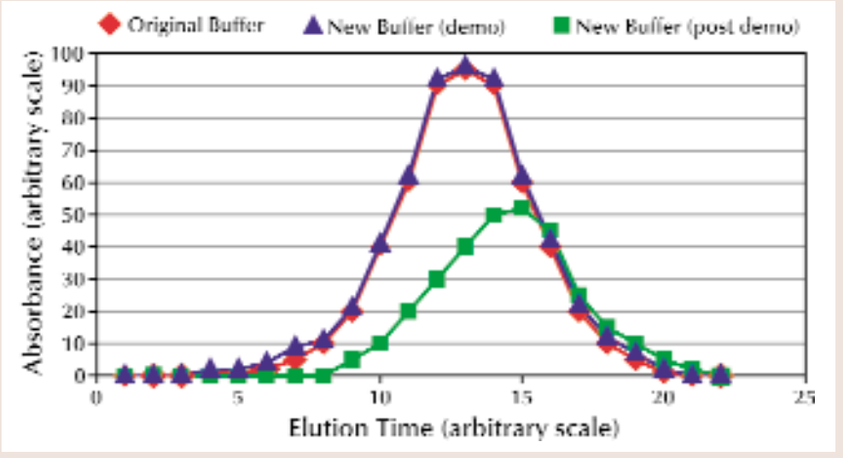



**Figure 6:** Abnormal elution profile of new buffer lot received following demonstration




or eliminated through effective control of process conditions. This is identified as the last point in manufacturing where that particular hazard can be controlled. Flow charts for identifying CCPs and CPPs are provided in Figures 2 and 3, respectively.

**Critical Limits.** Once the critical control points are defined along the manufacturing process, each CCP will have critical limits defined for its critical process parameters.

**Documents** (Batch Records and SOPs). The batch records, standard operating procedures (SOPs), and any other documents intended to describe a manufacturing process and collect process-related data (raw material charges, mixing times, filtration times, process pressures, process temperatures, pH of solutions, and so on) must be designed while considering information compiled from the initial design phase, hazard analysis, risk assessments, and experimental runs. These documents should be easy to follow, step-specific, and should provide readers (ultimately the technicians or operators executing each task) with all the necessary information to prevent any error while executing the operation. Each document should provide guidance to those technicians or operators on what could go wrong and how to respond in such cases. All critical control points and critical process parameters should be highlighted in SOPs and batch records.

**Validation.** The main goal of validation is to demonstrate the robustness, control, and consistency of a process. The HACCP evaluation helps you better understand the impact of each input on the possible outcomes of your manufacturing process. Also, it allows a thorough evaluation of all intended inputs and expected outcomes, including process conditions and microbial, chemical, and physical hazards. HACCP provides a systematic approach whereby the rationale for selection or omission of parameters as critical is thoroughly documented. Documents provide the technology transfer team with a comprehensive source of technical information in which the entire history behind a product is thoroughly documented.

**Auditing.** The manufacturing process should be compared routinely with related validation records to identify any possible trend that could represent an unnoticed change in raw materials, environmental conditions, equipment performance, or overall operator's practices.

**Assessment of Changes.** Another important component of HACCP is the assessment of process changes. This is accomplished by reevaluating the hazard analysis and risk assessment through the steps above to assess the possible effects that a proposed change may have on the CQAs and CPPs.

## Case Study: Outsourcing a Buffer

This case study is intended to demonstrate the use of HACCP to evaluate a change on an existing process. The underlying principles would also apply to the design of new processes. The case study considers the outsourcing of a buffer used to elute the protein of interest from a chromatography column. The buffer that is to be outsourced was originally manufactured in-house. A supplier was identified and approved on the basis of typical quality attributes such as composition, sterility, and stability. Initial shipments of several thousand gallons were received to cover production until the next year. The Certificate of Analysis (CoA) showed that the composition and product profiles obtained with the new

buffer were identical to those of the original buffer (the purity, activity, and yields were comparable).

Figures 4 and 5 compare the elution profiles and yields for the original buffer and the new buffer when the change was introduced. However, the initial inventory was consumed sooner than expected in the fourth quarter, and additional material was ordered at that time. Immediately after receiving the new shipment, a sudden change was observed in the performance of the buffer, as shown in Figures 6 and 7. The elution process showed an abnormal profile, and a significant drop in yield was observed when new lots of buffer were used. Once the problem was observed, an investigation was initiated. The investigation identified the following issues:

- Buffer temperature must be maintained above 20 °C to prevent precipitation of solutes.
- The risk of precipitation is much greater in winter when ambient temperatures fall below 20°C.
- Trucks used to ship the buffer did not have a temperature control system.
- The CoA data were based on samples taken before shipping.

These issues would have been identified prior to the outsourcing if a systematic approach such as HACCP had been employed. Because the first step in implementing HACCP is to conduct a thorough evaluation of the process while considering all possible hazards (microbial, chemical, and physical), the need for additional controls during transport, storage, and handling of the buffer would have been identified. Thus an

**Figure 7:** Change in yield with new buffer (post demo)

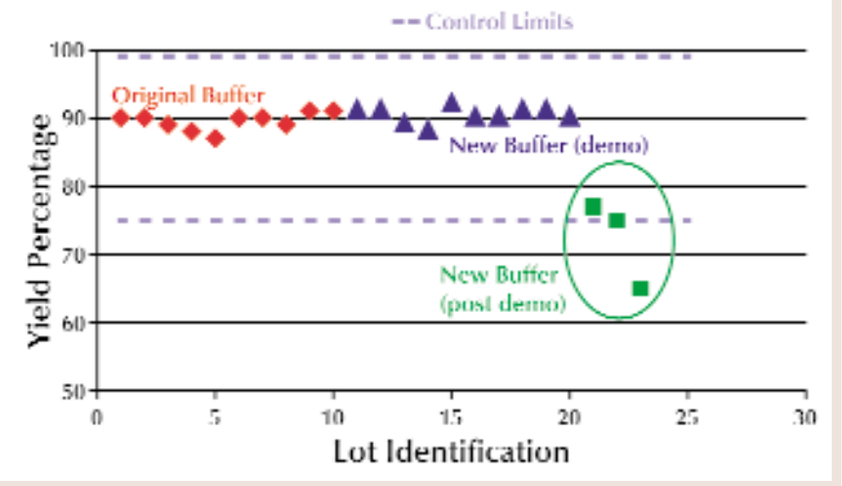
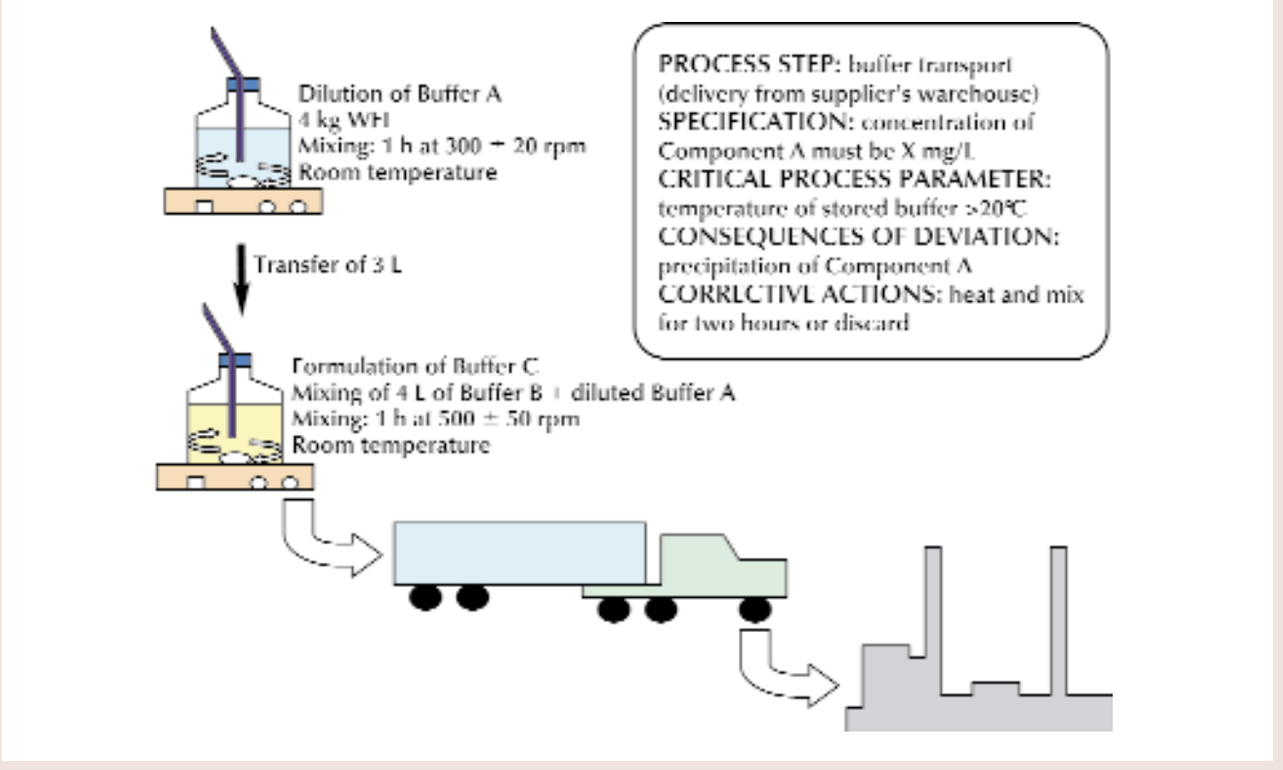



**Figure 8:** HACCP assessment (summary) showing transport conditions identified as a CCP. The buffer is manufactured by a qualified supplier. Once the product is formulated, it is packaged in plastic bags that are validated for container closure. The buffer is stored under controlled temperature conditions. It is then shipped from the supplier's warehouse to the manufacturing facility under controlled temperature conditions. The transport conditions are monitored during the entire process of transportation.



## The Origins of HACCP

When NASA started planning for manned space travel in 1959, the myriad challenges of sustaining life in space included a seemingly mundane but vitally important problem: How and what do you feed an astronaut? There were two main concerns: preventing food crumbs from contaminating the spacecraft's atmosphere or floating into sensitive instruments, and ensuring complete freedom from potentially catastrophic disease-producing bacteria, viruses, and toxins.

To solve these concerns, NASA enlisted the help of the Pillsbury Company. It quickly solved the first problem by coating bite-size foods to prevent crumbling. People at Pillsbury developed the hazard analysis and critical control point (HACCP) concept to ensure against bacterial contamination. Hazard analysis is a systematic study of product, its ingredients, processing conditions, handling, storage, packing, distribution, and directions for consumer use to identify sensitive areas that might prove hazardous. Hazard analysis provides a basis for blueprinting the Critical Control Points (CCPs) to be monitored. CCPs are points in the chain from raw materials to the finished product where loss of control could result in unacceptable food safety risks.

In early 1970, Pillsbury plants were following HACCP in production of food for earthbound consumers. Pillsbury's subsequent training courses for the Food and Drug Administration (FDA) personnel led to the incorporation of HACCP in the FDA's Low Acid Canned Foods Regulations, set down in the mid-1970s to ensure the safety of all canned food products in the United States.

National Aeronautics and Space Administration (www.nasa.gov)

HACCP analysis would have identified and solved the problem proactively, eliminating the need for a lengthy investigation. So it would have been apparent that temperature control during transportation and storage of the buffer was critical if HACCP had been used to assess the change in the first place (Figure 8).

### A Proactive Strategy

HACCP is a strategic tool that facilitates the development and implementation of new manufacturing processes. It is a systematic and proactive approach to identifying and solving possible problems that may affect the quality and yield of a product. Applying HACCP to biotech and pharmaceutical manufacturing requires some adaptations to address the unique needs of these related industries (see the "Adaptations" sidebar). The most important benefit of using HACCP is that it contributes to a thorough understanding of the manufacturing process and facilitates the identification and solution of potential problems that ordinarily might be overlooked.

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### For Further Reading


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## Adaptations

Applying HACCP to biotech and pharmaceutical manufacturing requires adaptations to address the unique needs of these related industries. Among these are identification/consideration of

- Readiness (checklist)
- Critical process parameters (CPPs)
- Potency/activity
- Stability
- Yields


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