
An Ounce of Prevention: Controlling Hazards *in* Extemporaneous Compounding Practices

“Pharmacists need to focus on developing ways to prevent problems before they happen instead of watching for errors, problems or deviations after the fact.”

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Some industries have adopted different types of systems to ensure quality. These include failure mode effect analysis (FMEA), root cause analysis and hazard analysis critical control points (HACCP). This article focuses on HACCP because of the parallels in the types of products (food) on which it focuses and the compounded products that pharmacies prepare (products that are “ingested” or administered).

Introduction

Currently, within the pharmacy community, there is a significant amount of discussion about end-product testing for extemporaneously prepared sterile preparations. The United States Pharmacopeial Convention, Inc. (USP) has published, for public comment, General Chapter <797>, titled “Pharmaceutical Compounding: Sterile Preparations.”¹ *United States Pharmacopeia* General Chapter <797> has extensive quality-control and assurance requirements that pharmacists will be expected to follow. Once finalized, this new chapter may be enforceable by state boards of pharmacy. In response to recent incidents of product contamination and patient deaths, many states have revised or are planning to revise pharmacy practice acts to stipulate that pharmacies have quality-assurance

Continuing Education

GOALS AND OBJECTIVES

“An Ounce of Prevention - Controlling Hazards in Extemporaneous Compounding Practices”

Goal: To introduce, at a basic level, the principles and application of hazard analysis critical control points (HACCP) and explain how HACCP can be used as a quality tool for sterile and nonsterile preparations in various practice settings.

Objectives: After completing and studying this article, the participant will be able to:

1. Describe how and why the HACCP concept was developed.
2. List seven HACCP principles.
3. Briefly describe how to address each of the seven principles.
4. Describe how HACCP relates to quality and safety in the practice of pharmacy.
5. Identify the basic hazards in sterile and nonsterile product preparation.
6. Evaluate an HACCP-specific plan for the presence of “preliminary HACCP” steps used in the creation of the HACCP-specific plan.

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programs, many of which may rely on some form of end-product testing. Although end-product testing is valuable in batch preparation and can identify grossly unacceptable batches, it is not applicable to small-number or single-unit preparations and is certainly not the only quality indicator for pharmacy-prepared sterile preparations. Adequate quality assurance of the preparation processes used in compounding are even more important in ensuring the quality of pharmacy-compounded sterile preparations.

Pharmacists must understand that compounding processes, people performing the compounding and environmental conditions where compounding occurs all have an impact on the assurance of quality of the final product. The pharmacy profession and regulations promulgated by the state boards of pharmacy continue to focus and rely too heavily on end-product testing. Pharmacists need to focus on developing ways to prevent problems before they happen instead of watching for errors, problems or deviations after the fact.

According to a personal conversation between an inspector for the US Food and Drug Administration (FDA) and a South Carolina pharmacist (Harold Blackwood and Ray Burns, oral communication, November 2002), the shocking truth is that, statistically speaking, if 15% of a single batch of preparation is contaminated, one would have to test 30% of the batch to detect a single contaminated unit. The key to compounding quality is not retrospective end-product testing exclusively, but proactive processes that have been validated and are in control. The prevention of problems before they occur is a paramount goal in any quality system or process. As the old adage goes, “An ounce of prevention is worth a pound of cure.” Quantitative and qualitative end-product sampling plans attempt to identify or detect errors after they have occurred; however, routine end-product testing may not reveal all variations in safety and efficacy. Absolute sterility cannot be practically demonstrated without complete destruction of every finished unit.¹ Unfortunately, reliance on end-product testing alone can give a false sense of security that the process is regularly producing a high-quality and correct product when that may not be true.

The best method to ensure the likelihood of consistently producing a quality product is to know where failures can occur in a process and to control and monitor those critical control points (CCPs) of failure. Quality cannot be inspected into the final product; quality must be built in.

Historical Development of HACCP

HACCP is an overall quality system in which preventive and corrective measures are instituted at each stage of the food-production process where food-safety hazards could occur.^{2,3} HACCP is now well recognized in the pharmaceutical industry as a way of ensuring product quality.⁴

HACCP was derived from the FMEA engineering quality system. The program started in the 1960s when the National

Aeronautics and Space Administration contracted Pillsbury Foods to produce foods that would be used in the space program. Quality and safety were key requirements of this program.⁵ Milestones include the following:

- 1971—HACCP was first presented to the American National Conference for Food Protection.
- 1973—The FDA applied HACCP to low-acid canned-food regulations.
- 1988—The 1995 HACCP principles were promoted and incorporated into food-safety legislation in many western countries.

On July 25, 1996, the Food Safety and Inspection Service of the US Department of Agriculture published a final rule on pathogen-reduction HACCP systems (PR/HACCP). The PR/HACCP rule requires that meat and poultry plants under federal inspection must take responsibility for, among other things, reducing the contamination of meat and poultry products with disease-causing (pathogenic) bacteria. Reducing contamination with pathogenic bacteria is a key factor in reducing the number of deaths and illnesses linked to meat and poultry products. A number of media reports have associated deaths with ingestion of contaminated beef.⁶

The key benefits of HACCP include:

- Allowing for a more systematic, consistent approach;
- Focusing on problem prevention versus error detection and correction;
- Being proactive versus reactive;
- Increasing operational cost effectiveness when properly implemented;
- Focusing resources on “critical” areas;
- Complementing other management systems; and
- Being a nationally and internationally accepted quality system.

Like food plants, pharmacies have many potential and significant hazards that need to be systematically addressed so that the quality of pharmacy-prepared sterile preparations can be improved. If the principles of HACCP are applied to the practice of extemporaneous compounding practices, these principles will control and reduce contamination, as well as control and reduce the incidence of errors. If the original definition of HACCP directed at food-processing applications is rewritten to make it applicable to the practice of pharmacy, the definition could read as follows: HACCP is a scientifically sound and evidence-based system for compounding process control that

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can be used for sterile and nonsterile preparation practices to prevent problems by applying controls at points in the compounding and dispensing process where hazards could be controlled, reduced or eliminated.

HACCP creates a quality-assurance system that indicates when a deviation occurs and a process control has been lost. The deviation is detected early, and appropriate steps are taken to re-establish control in a timely manner to ensure that potentially hazardous products do not reach the consumer.

To demonstrate how HACCP can be applied to extemporaneous pharmacy practices, we will use the preparation of an intrathecal pain solution as a model process in this article. The model serves as an illustration of how HACCP can be used by pharmacists to build a quality-assurance system. It is important to note that the quality-assurance practices described may differ from practices that need to be followed for other types of preparations. HACCP serves as a conceptual framework and model for building the necessary specific steps to be applied to activities actually being performed in the compounding of specific products.

Basic Principles

To use HACCP to create an effective quality system, it is necessary to address seven basic principles of an HACCP plan.⁷

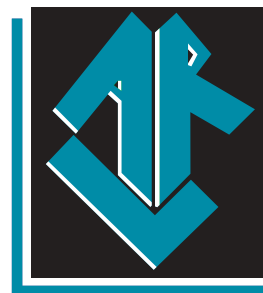
1. Conduct a hazard analysis.
 - a. Prepare a process flow diagram of the steps in the process.
 - b. Identify and list all possible hazards and specify appropriate control measures.
2. Identify CCPs.
3. Establish critical limits by specifying criteria that must be met to ensure that each hazard (that makes a process step a CCP) is under "control."
4. Establish monitoring procedures.
 - a. Implement systems to monitor the "control" status of the identified hazard.
 - b. Safeguard all monitoring documentation and records.
5. Establish corrective action plans in advance for correcting a CCP that has gone out of "control" so that actions can be taken that are effective and performed in a calm and planned manner.

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6. Establish verification procedures – make practical plans for checking whether the HACCP plan is working.
7. Establish robust record-keeping and documentation procedures and document all procedures and records.

Preliminary Steps

Some preliminary steps are recommended as a starting point to implement HACCP.

1. Assemble an HACCP team. Ideally, the HACCP team should be multidisciplinary, with an HACCP leader and secretary who records all discussions and decisions of the group. All pharmacy employees can participate in the HACCP team since each brings a different and unique perspective of the process or product to the team. Even small or family-owned pharmacies benefit from bringing together a group of people to look at the operation of this quality system. Bringing in an outside group of health professionals to assist in the quality process may be a great marketing opportunity in the community.
2. Describe each product being produced and the method used to prepare it. Table 1 furnishes a sample product description. Each product must be described in terms of its:

- Product name(s),
- Important product characteristics and specifications,
- Intended use,
- Packaging appropriate for the preparation and intended use,
- Storage conditions,
- Beyond-use date (shelf life),
- Distribution, and
- Auxiliary labeling instructions.

For the purpose of quality assurance, methods of preparation can be described by creating a flow diagram of the process. Figure 1 provides an example of a flow chart. A flow diagram is a simple schematic of the process used to produce the product; producing an accurate, clear sketch of the process is critical. In creating the flow diagram, ensure that no steps are missed and that all steps are incorporated correctly. It is also critical to ensure that all individuals involved in the compounding process follow the specified quality-assurance process each and every time.

3. After documenting the flow of the compounding process, verify the flow chart to ensure that it is a true reflection of the actual process. For example:



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Table 1. Sample Product Description for Morphine Sulfate 10-mg/mL Preservative-Free Injection.

1. Product name(s)	Intrathecal Morphine Sulfate 10 mg/mL Preservative Free
2. Important product characteristics	Near isotonic; final solution pH: 6.0 to 8.0 10 mg/mL (\pm 10%) Preservative free Nonpyrogenic Sterile Clear, colorless solution free of particles and haze
3. Intended use	Management of pain or other associated conditions
4. Packaging	Polypropylene syringe Glass vial Polyvinyl chloride/ethylene vinyl acetate plastic container Deltec cassette Other infusion container
5. Storage conditions	Refrigerate at 2 to 8°C. Do not freeze – protect from excessive heat.
6. Beyond-use date (shelf life)	X days at room temperature X days at refrigerated temperatures
7. Method of distribution and delivery	Controlled substance requiring C-II narcotic prescription Dispensed as a patient-specific product Retail, hospital or institutional Delivery via patient/authorized individual or common carrier (not US mail per statute)
8. Labeling instructions	Protect from light. Use as directed. “Federal legend” May cause drowsiness Keep refrigerated.
9. Special control and distribution	High potential for diversion and abuse Store in secured area. Maintain perpetual inventory.

mg = milligram

mL = milliliter

- Does the flow chart reflect the nuances that different personnel exercise (professional compounding discretion), the time of day (Friday vs. Monday, morning vs. afternoon), vacation and time of the year, eg, Christmas rush?
 - Was everyone that was involved at each of the steps questioned to ensure that the flow diagram reflects his or her responsibility at each step?
4. To apply the program to the broad array of extemporaneously prepared products in the pharmacy, categorize preparations into groups with similar characteristics. Similar preparations having the same process characteristics can use the same or similar HACCP plan. Examples of some product categories may include:
- Topical ointments, creams, lotions;
 - Capsules and tablets;
 - Injectables/inhalations/ophthalmics;
 - Prepared from nonsterile components;

- Prepared from sterile manufactured injections;

- Suppositories;
- Lollipops (suckers); and
- Nonsterile liquids and suspensions.

Conducting a Hazard Analysis

Conducting a hazard analysis is generally considered to be a two-step process involving (1) the identification and analysis of hazards (threats) and their control measures and (2) the identification of the CCPs, the establishment of critical limits and the monitoring of procedures.

Identify and Analyze Hazards and Their Control Measures

The hazards (threats) that might be introduced into pharmacy-prepared sterile preparations must be identified as the preparations are produced. These hazards are grouped into three broad categories: (1) biological (including microbiological), (2) chemical and (3) physical.

Biological Hazards. Biological hazards (living organisms) can make any pharmacy-prepared preparation unsafe to use. Generally, pharmacies have two types of preparations that are compounded; (1) sterile and (2) clean. Among those required to be aseptically prepared and sterile would be the injectables (including intrathecal), ophthalmics and respiratory inhalation medications. Other preparations, such as orals, topicals, etc., should be prepared in a clean manner. While there is no requirement for sterility of products prepared in a clean manner, they should be devoid of hair, dirt and other extraneous foreign matter. Ideally, formulations prepared in a clean manner should be prepared close to aseptically, including using hand-washing, gloving and gowning procedures.

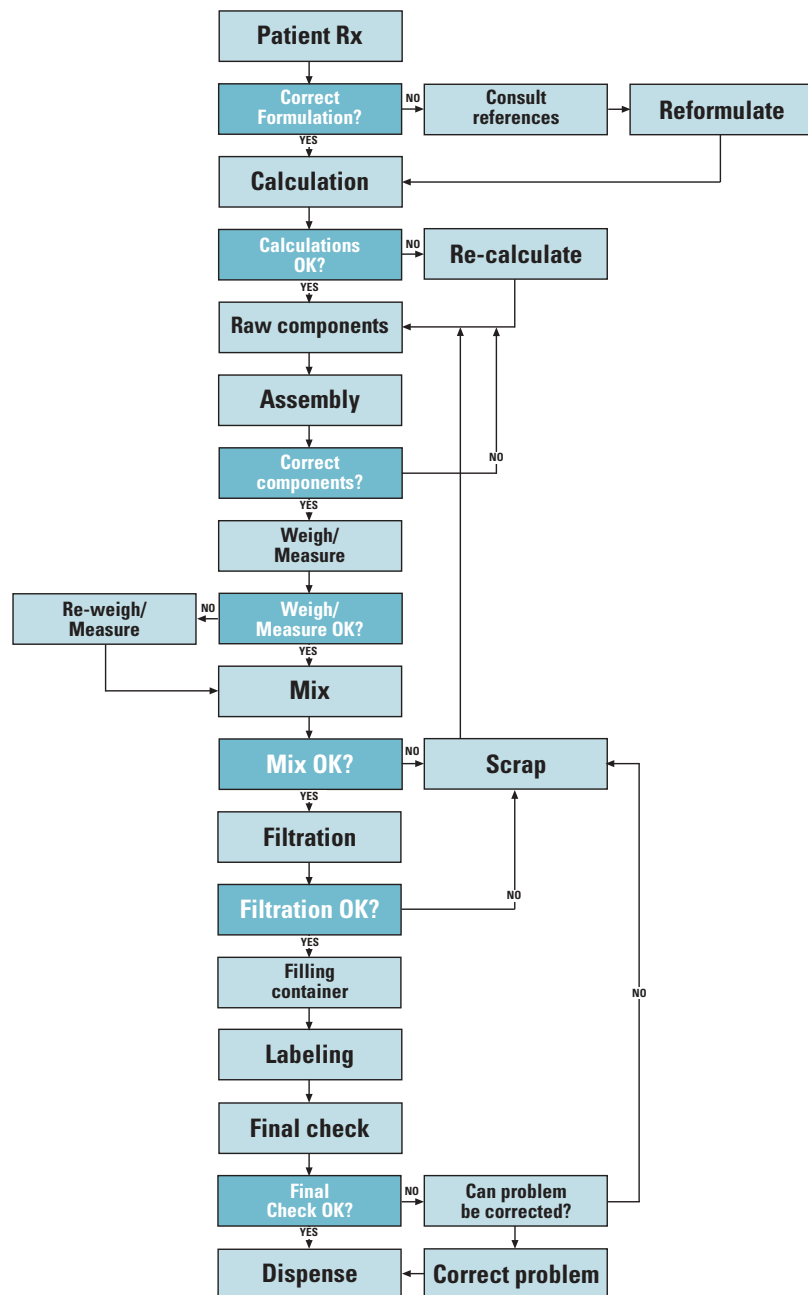
Biological hazards include bacteria, fungi, viruses and parasites. Identifying the biological hazards to which production processes might be subjected is a challenging task. Biological hazards can be best addressed through the following processes:

- Personnel controls (personal hygiene, hand and arm washing, absence of jewelry, using face masks when needed, gowning and gloving procedures);
- Process controls (personnel aseptic technique and compounding process testing using tryptic soy broth growth medium);
- Validated process methods (the process used to prepare the product should consistently yield a final product with acceptable identity, quality and purity, established through qualitative and quantitative evaluation); and
- Environmental controls (use of Class 100 compounding environments and limited-access support areas; daily, weekly and monthly cleaning procedures; air and surface microbiological testing).

Consider the following model practice guidelines and compare them against current practice as a means of identifying the gaps, which will assist in elucidating the risk of biological hazards in the pharmacy:

- Do all compounding employees who prepare sterile products wear the appropriate attire consistent with USP Risk level guidelines (based on the type of compounding being

Figure 1. A Sample Intrathecal Pain Medication Preparation Flow Chart.



performed) when working in the controlled compounding environments?

- Do all compounding employees undergo aseptic technique verification via media fill or other comparable methods to ensure that each employee has good aseptic technique?

- Are all compounding employees trained in aseptic technique, do they know compounding risk levels, and have this training and knowledge been documented?
- Have all types of sterile compounding processes for all USP Risk levels undergone verification via media-fill challenge or comparable methods to ensure that each type of process is adequately controlled?
- Has the method of preparing each sterile preparation been verified through an adequate process-verification study?
- Are all representative product samples over several different batches that are prepared by all personnel being evaluated and analyzed or sent for analysis to a qualified laboratory on a regular and ongoing basis?
- Are the critical compounding environments routinely cleaned with the appropriate types of cleaning agents?
- Is environmental monitoring (air and surface testing) being routinely performed and documented?
- Are the monitoring data used to affect changes in personnel activities (gowning or movement) or processes (cleaning, etc.)?

Chemical Hazards. Chemical hazards may be the result of mislabeled components (wrong product from the manufacturer), component impurities, incompatibilities with other active or inactive components, improper component mix order (incompatible components reacting in the compounding process) or other process errors (calculation or weighing

Table 2. Steps in the Intrathecal Pain Medication Preparation Flow Chart and Questions Related to Each Step.

<i>Flow-Chart Steps</i>	<i>Questions Related to Each Step</i>
1. Raw components	<p>Is the chemical purity of each component acceptable for the clinical application?</p> <p>Do the raw components present any pyrogenic or microbiological hazards, chemical hazards (eg, incorrect component, impurities) or physical hazards (foreign matter)?</p>
2. Intrinsic factors of raw components	<p>Are there physical characteristics (eg, pH, temperature, exposure to light) of the component during and after compounding that can cause or prevent a hazard?</p> <p>Which intrinsic factors of the final pharmacy-prepared sterile preparation must be controlled to produce a safe and effective product?</p> <p>Does the final pharmacy-prepared sterile product permit survival or multiplication of pathogens and/or pyrogen formation before or during preparation?</p> <p>Will the sterile product permit the survival or multiplication of pathogens and/or pyrogen formation during subsequent steps of preparation, storage or consumer possession?</p>
3. Procedures used for preparation/processing	<p>Is the product formulation correct for both the active pharmaceutical ingredients and inactive ingredients?</p> <p>Are the final formulation calculations correct? Have they been double-checked by a second person?</p> <p>Is there documentation that clearly identifies the compounder, lot numbers and expiration date of products used in the preparation?</p> <p>Do the compounding procedures or processes include controllable steps that prevent contamination (eg, 0.22-μm filtration or sterilization via autoclave) from remaining in the final preparation?</p> <p>Is the product subject to recontamination between the compounding processes and final product packaging?</p>
4. Microbiological bioburden of components and sterile preparation environment	<p>Are the raw components and final pharmacy-prepared sterile product processed in a manner that should ensure sterility?</p> <p>Is the bacterial endotoxin burden of each raw material acceptable?</p> <p>Is it likely that raw components and final pharmacy-prepared sterile product will contain viable spore-forming or nonspore-forming pathogens?</p> <p>What are the normal microbial status of the sterile preparation environment and microbial content of the final pharmacy-prepared sterile product stored under proper conditions?</p> <p>What is the potential for microbial population growth during processing in the preparation environment?</p>
5. Facility design	<p>Does the layout of the facility provide an adequate separation of raw materials, in-process materials and quarantined materials from final pharmacy-prepared sterile products?</p> <p>Is positive air pressure maintained in sterile preparation areas? Is this essential for final pharmacy-prepared product safety? (Cytotoxics have their own requirements and are not the focus of this article.)</p> <p>Is the traffic pattern for people and moving equipment a potential source of contamination?</p>

errors). Time, temperature and storage conditions can also negatively contribute to chemical hazards in final products.

Consider the following model practice guidelines and compare them against current practice as a means of identifying the gaps, which will assist in elucidating the risk of chemical hazards in the pharmacy:

- Is the appropriate grade of each raw component being used in each formulation (USP or NF grade versus technically or chemically pure)?
- Is the raw component vendor registered with the FDA as a manufacturer, and is this registration documented in writing?
- Does each lot of raw component come with or have available on demand a certificate of analysis (CoA) and Material Safety Data Sheet?
- Is a CoA of each lot of raw component kept on file in the compounding pharmacy?
- Have independent verification and analysis of the raw component/vendor been performed by a qualified laboratory as required?
- Is the weighing, measuring and compounding equipment calibrated at least annually by a qualified vendor/individual?
- Is the weighing, measuring and compounding equipment calibrated daily prior to use; and is the equipment routinely cleaned, serviced and documented per the manufacturer's recommendations?
- Has the method used to compound the sterile preparation been qualitatively and quantitatively checked to ensure that

Flow-Chart Steps

Questions Related to Each Step

6. Equipment design	<p>Will the equipment to be used (eg, autoclave, filters, magnetic mixer, automated compounder) provide the aseptic control necessary to meet critical limits?</p> <p>Is the equipment properly sized for the volume of sterile products that will be prepared?</p> <p>Can the equipment be controlled so that the variation in performance will be within the tolerances required to produce a safe pharmacy-prepared sterile product?</p> <p>Is the equipment reliable, or is it prone to frequent breakdowns?</p> <p>Is the equipment designed so that it can be cleaned and sanitized?</p> <p>Is product contamination with hazardous or extraneous substances (eg, glass, hair, skin fragments, airborne organisms from talking and/or coughing, other components being prepared in adjacent or surrounding areas) likely to occur?</p>
7. Packaging	<p>Does the method of final product packaging permit the multiplication of microbial pathogens and/or the formation of pyrogens or other types of viable or nonviable contamination?</p> <p>Is the packaging material resistant to damage, thereby preventing the entrance of microbial contamination?</p> <p>Is the package clearly labeled with the proper storage conditions (eg, "Keep Refrigerated," "Store at Room Temperature") if this is required to ensure product stability and sterility?</p> <p>Do the final product and packaging include instructions for the safe storage and use by the consumer as well as any other pertinent information?</p> <p>Are tamper-evident packaging features used?</p> <p>Is each package legibly and accurately labeled to indicate date/time of preparation for traceability purposes?</p> <p>Does each final pharmacy-prepared sterile product package contain proper labeling that can be understood by everyone?</p>
8. Cleaning/sanitation	<p>Can the sanitation practices employed affect the safety of the final product being prepared?</p> <p>Can the facility and the compounding areas be effectively cleaned and sanitized?</p> <p>Are the cleaning and sanitizing measures performed frequently enough?</p>
9. Employee health, hygiene and education	<p>Can employee health or personal hygiene practices impact the safety of the pharmacy-prepared sterile product being compounded?</p> <p>Do the employees understand the sterile product preparation process and the factors they must control to ensure that a sterile and accurate preparation is compounded?</p> <p>Do the employees take the necessary steps to ensure that their activities do not inadvertently introduce contamination into products?</p> <p>Will the employees inform management of a problem that could impact safety of pharmacy-prepared sterile products?</p>
10. Storage conditions, packaging and the patient	<p>What is the likelihood that the final pharmacy-prepared sterile product will be improperly stored at the wrong temperature?</p> <p>Would storage at improper temperature lead to a microbiologically or chemically unstable product?</p> <p>Are the patient and/or caregiver able to effectively manipulate the preparation and its packaging?</p>
11. Intended use	<p>Will the consumer clearly understand how and when to properly use the pharmacy-prepared sterile product?</p>

the preparation will meet its characteristics of identity, strength, quality and purity?

- Will time, temperature and/or storage conditions negatively contribute to a compounded preparation's solubility, stability and pharmacological activity?

Physical Hazard. An unexpected physical component of a pharmacy-prepared sterile preparation that may not be pharmaceutically elegant or cause illness, injury or death to the consumer is considered a physical hazard. Foreign materials such as glass, metal, plastic and simple dust or dirt are physical hazards that have been found in compounded preparations. They are introduced because a material, process or piece of equipment has not been properly controlled during the compounding process or because the compounder was not following proper policy and procedure.

A number of situations can contribute to physical hazards in pharmacy-compounded preparations, including:

- Contaminated raw materials;
- Extraneous foreign matter, eg, plastic shards or threads from plastic boats;
- Poorly designed or poorly maintained facilities and equipment;
- Contaminated packaging materials; and
- Inattention to details by employees with key responsibilities.

At this stage in the hazard analysis, a series of questions should be asked about the appropriateness of each step in the flow diagram. The hazard analysis should question the effect of a variety of factors on the safety of the pharmacy-prepared sterile preparation. Table 2 provides a list of steps in the flow diagram and a series of questions related to each step. Table 3 provides a list of hazards that might be encountered when preparing morphine sulfate injection.

Identify the CCPs, Establish Critical Limits and Monitor Procedures

To identify the CCPs, it is important to understand what they are. A CCP is a step in the process at which a control measure is applied to eliminate a hazard or to reduce it to an acceptable level. A control measure is the application of some action or activity required to reduce or eliminate a hazard, or its possible cause, to a safe level.

As illustrated in the previous tables, several CCPs were identified while conducting the hazard analysis. For each of these CCPs, critical limits need to be established. Critical limits are safety metrics for the preventive measures used at each of the CCPs. A critical limit will be a reading or a direct observation such as a temperature, a time or a chemical property, ie, pH. Critical limits for CCPs are pass/fail parameters, meaning that they must be met to ensure that product safety is maintained. In addition to the CCPs and critical limits, monitoring procedures are included in this section.

Monitoring procedures are activities done routinely that measure the process at each CCP. They can be achieved by an

employee, eg, observation or documentation check, or by mechanical means, eg, automatic autoclave temperature recorder.

It is very important to note that employees performing monitoring activities, eg, recording refrigerator or freezer temperatures, must record exact values where exact values are indicated and not "yes/no" or "okay" observations. When weighing powders, the actual weight from the scale should be recorded next to the target weight listed on the compounding document. All documentation should also be signed and dated by the person performing the monitoring or recording the activity.

In the example of compounding Intrathecal Morphine Sulfate 10-mg/mL Preservative-Free Injection (Table 1), some of the critical limits for the process CCPs are shown in Table 4.

What to Do in the Event of a Failure

It is important not only to have a monitoring procedure but also to have a corrective action plan in the event that the monitoring plan identifies a deviation from the critical limit. Several considerations can be incorporated into a corrective action plan, as follows:

1. Has the cause of the deviation been identified and eliminated?
2. Will the CCP be under control after the corrective action plan has been taken?
3. Have measures to prevent recurrence of the deviation been established?
4. Do the corrective action procedures ensure that no product that is harmful, contaminated or incorrect will be dispensed to the patient?

There needs to be a consistent set of actions for employees to follow whenever a process deviation occurs from the critical limit. The following questions help identify and elucidate how to develop a corrective action plan:

- How will everyone be informed and/or alerted when a deviation occurs? If a person identifies the deviation while performing a monitoring procedure, who will be the key contact for that person?
- Who will be responsible for controlling and/or quarantining all product that may be affected by the deviation?
- Who will be involved in deciding what to do about the product that might have been affected by the deviation?
- How will the causes of deviation be determined? By whom will the causes of deviation be determined? If technical experts or outside resources are needed, how will they be contacted?
- Who will be responsible for keeping the records of all activities and actions taken in response to the identified deviation from the critical limit?
- Is the set of corrective actions feasible at all times?

Document and Verify

To understand why proper documentation practices are important, it is helpful to understand what the word *document* means: as a verb, *to document* means to record an observation or an action; as a noun, *document* means the written or electronic record of an observation or an action. When documentation occurs as a result of an action or process during the preparation of pharmacy-prepared sterile products, it becomes a permanent record of that product's history. Anyone reviewing the documentation should be able to tell what occurred during all phases of the preparation process.

Proper documentation practices ensure that all processes and actions performed before, during and after the procedure actually occurred. They are proof that written policies and procedures were followed. They are a critical component of the HACCP system or any type of quality system and provide a means of tracing or recreating a set of events that can be investigated and acted upon. Documentation also serves as proof that the HACCP system is working properly. By incorporating routine and daily documentation practices (temperature, calibration, cleaning and dispensing logs) into daily workflow, the critical data necessary to evaluate the HACCP system are created. In too many cases, little or no thought is put into daily workflow practices; therefore, any quality system data become an end-of-the-month chore that is rarely accomplished properly or consistently. The old adage, "If it isn't documented, it didn't happen," is pretty accurate, especially in this day and age of greater regulatory and legal scrutiny.

Conclusion

The example provided in this article can be used as a template to model other compounding procedures used in pharmacy practices. Understanding and controlling the critical points of failure in pharmacy compounding procedures are a good first step and also serve as an excellent risk-management tool.

By carefully considering each of the hazards, CCPs, critical limits and monitoring plans, one will find that the development of a corrective action plan is not as difficult or overwhelming as the adverse impact of a contaminated or incorrectly compounded preparation that harms or kills a patient.

When such events occur, they are devastating, not just to the patient and the patient's family and friends, but also to the pharmacy and its employees. Although it may take a persistent effort to implement HACCP as a quality system, it will become a self-monitoring and self-perpetuating process that will build quality into the final product.

To ensure quality, it is absolutely critical that everyone in the organization knows about the processes performed and what the CCPs and the supporting critical limits, and monitoring and documentation procedures are for each of the processes. The best defense is a good offense, and the use of HACCP as a guide to establish a pharmacy quality-assurance system will provide great piece of mind and, even more important, a better and safer extemporaneously prepared product.

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Table 3. Hazards in the Preparation of Morphine Sulfate 10-mg/mL Preservative-Free Injection.

<i>Process Step</i>	<i>Safety Hazard</i>	<i>Reasonably Likely to Occur?</i>	<i>Basis</i>	<i>If Yes in Column 3, Measures That Could Be Applied To Prevent, Eliminate or Reduce the Hazard to an Acceptable Level</i>	<i>CCP</i>
Receiving-Patient prescription: Formulation	Biological: None				
	Chemical: Improper formulation and calculations	No	Formulation is from published references, and all calculations have been validated. Retrospective feedback from patient use that there has been no incidence of subtherapeutic response		
	Physical: None	No			
Receiving - Raw, nonsterile ingredients	Biological: Microbial or bacterial endotoxin contamination	Yes	Ingredients come from FDA-registered chemical suppliers. Ingredients meet <i>USP-NF</i> specifications.	Validate that ingredients do not have unacceptable levels of endotoxin.	1B
	Chemical: Not acceptable for intended use	Yes	Ingredients meet <i>USP-NF</i> specifications.	Order only <i>USP-NF</i> -grade chemicals.	1C
	Incorrect ingredient	Yes	CoA on file for each lot number received	Validate CoA through independent laboratory.	
	Physical: Foreign materials	No	Ingredients meet <i>USP-NF</i> specifications. CoA on file for each lot number received.	Verify that no hazardous foreign materials are present in components.	
Assembly (of ingredients and compounding documents)	Biological: Introduction of microbial contamination	Yes	Inappropriate environmental exposure can lead to introduction of organisms.	Ensure the integrity of component packaging and adequacy of environmental conditions.	2B
	Chemical: Incorrect ingredients assembled for formulation	Yes	Errors can occur in pulling the wrong ingredients.	All assembled ingredients should be double-checked by another person before any processing is performed. Consider color coding often-used drugs that look similar.	2C
	Physical: Introduction of foreign matter	No	Inappropriate exposure to foreign materials	Ensure the integrity of component packaging and adequacy of environmental conditions.	
Weighing/measuring ingredients	Biological: Personnel, equipment or environmental contamination introduced into ingredients	Yes	The literature is replete with incidences of external contamination of compounded products.	Written policies and procedures for hand washing, gloving and gowning Written policies and procedures for equipment and facility cleaning and sanitization	3B
	Chemical: Incorrect amounts of ingredients weighed for formulation	Yes	Quantities of ingredients weighed or measured could be more or less than desired amounts.	Use electronic equipment with attached printers to record the amount of ingredients weighed or measured.	3C

<i>Process Step</i>	<i>Safety Hazard</i>	<i>Reasonably Likely to Occur?</i>	<i>Basis</i>	<i>If Yes in Column 3, Measures That Could Be Applied To Prevent, Eliminate or Reduce the Hazard to an Acceptable Level</i>	<i>CCP</i>
Weighing/ measuring Ingredients <i>Cont.</i>			Many pieces of equipment used are sensitive electronic devices that require routine calibration and service per manufacturer's guidelines.	Were the weighed ingredients double-checked by a second person? Routinely calibrate scales to ensure proper operating functionality. Service equipment through authorized and certified vendors.	
	Physical: Introduction of foreign matter	No	Inappropriate exposure to foreign materials	Ensure adequacy of environmental conditions.	
Mix/compound	Biological: Personnel, equipment or environmental contamination introduced into ingredients	Yes	The literature is replete with incidences of external contamination of compounded products.	Written policies and procedures for hand washing, gloving and gowning Written policies and procedures for equipment and facility cleaning and sanitization Biannual certification of controlled engineered environments (eg, Class 100 hoods) Only controlled environments should be used to mix or compound parenteral/aseptic formulations.	4B
	Chemical: Ingredient incompatibilities, incorrect pH, presence of preservatives, antioxidants or other ingredients	Yes	Due to the complexity of many formulations, mixing errors have led to patient injuries and deaths. There have been reports in the media of pain pumps' clogging due to product sludge and precipitates.	Written compounding directions should exist for each formulation. Do not exceed published solubility concentrations. Titrate pH as needed to achieve desired ranges.	4C
	Physical: Plastic, glass or metal contamination	Yes	Glass shards, rubber cores or metal shavings can be introduced during the compounding process.	Visually inspect solution during the compounding process.	3P
Filtration sterilization	Biological: Filter failure or incorrect type to achieve desired SAL of 10^{-3} via membrane filtration or an autoclave cycle adequate to achieve desired SAL of 10^{-6}	Yes	The literature is replete with incidences of external contamination of compounded products.	Written policies and procedures for final product filtration procedures and filter integrity testing (bubble-point testing) Written policies and procedures for the use of an autoclave and the use of biological indicators Semiannual concentration of controlled engineered environments (eg, Class 100 hoods) Only controlled environments should be used to mix or compound parenteral/aseptic formulations.	5B

Process Step	Safety Hazard	Reasonably Likely to Occur?	Basis	If Yes in Column 3, Measures That Could Be Applied To Prevent, Eliminate or Reduce the Hazard to an Acceptable Level	CCP
Filtration sterilization <i>Cont.</i>	Chemical: Ingredient incompatibilities, incorrect pH, presence of preservatives, antioxidants or other ingredients	Yes	Due to the complexity of many formulations, mixing errors have led to patient injuries and deaths. There have been reports in the media of pain pumps' clogging due to product sludge and precipitates.	Written compounding directions should be available for each formulation. Do not exceed published solubility concentrations. Titrate pH as needed to achieve desired ranges with acids or bases compatible with the ingredients.	4C
	Physical: Plastic, glass or metal contamination	Yes	Glass shards, rubber cores or metal shavings can be introduced during the compounding process.	Visually inspect the solution during the compounding process.	3P
Filling final container	Biological: Product packaging is not intact to maintain sterility.	No			
	Chemical: Incompatibility with container/closure	No			
	Physical: Final container is damaged or leaking, or integrity has been compromised.	No	Periodically, final containers have leaks or packaging has been damaged, potentially compromising the sterility of the final container.	All containers should be visually inspected prior to use.	
Labeling	Biological: None				
	Chemical: None				
	Physical: None				
	Other: Correct information as required by Pharmacy Practice Acts	Yes	Incorrect information or incorrect label	Visual inspection of the label copy before moving the final prepared product into stock or dispensing to the patient	10
Final Check	Biological: None				
	Chemical: None				
	Physical: None				
	Other: Were all of the CCPs checked, and were all of the necessary documented steps signed and dated by the compounder?	Yes	Attention to detail regarding critical compounding documentation is typically overlooked, leading to incomplete and ambiguous data.	All completed products and their supporting compounding documentation require a final review and release by a person licensed to check the final product.	4P
Dispense	Biological: None				
	Chemical: None				
	Physical: None				
	Other: The right preparation is dispensed to the right patient.	Yes	Product verification is a critical point in the dispensing process to ensure that the correct patient receives the correct medication.	Verify that the correct preparation is dispensed to the correct patient.	

FDA = US Food and Drug Administration
CoA = Certificate of Analysis

USP-NF = United States Pharmacopeia-National Formulary
SAL = Sterility assurance level

CCP = Critical control point

Table 4. HACCP Plan Development Form for Monitoring Procedures and Frequency for the Compounding of Morphine Sulfate 10-mg/mL, Preservative-Free Injection.

<i>Process Step/CCP</i>	<i>Critical Limits</i>	<i>Monitoring Procedures (Who/What/When/How)</i>
Receiving: Raw, nonsterile ingredients	A CoA is received with each ingredient shipment, USP-NF grade, and meets USP-NF specifications for the ingredient. Appropriate appearance and absence of foreign matter	Who: Employee receiving the ingredient from the chemical company What: Every ingredient received in a raw, nonsterile form When: Every time; ingredients received without a CoA should be quarantined until the manufacturer, wholesaler or repackager sends the documentation. How: Inspect the packaging slip or other attached shipping documentation. Obtain CoA. Inspect material.
Weigh/measure ingredients	All measuring equipment is calibrated and "sealed" by an official organization (to document proper functionality).	Who: Owner/PIC or designee responsible for quality What: Each piece of equipment that measures, weighs, dispenses or is part of a critical system (eg, autoclave) When: No less than annually or per manufacturer's specifications or as required by local, state or federal law How: An authorized, trained individual; may be from local governmental "weighs and measures" department
	All measuring equipment is calibrated daily to ensure proper functionality.	Who: Owner/PIC or designee responsible for quality What: Each piece of equipment that measures, weighs, dispenses or is part of a critical system used to prepare compounded product (eg, pH meter) When: Daily How: Per manufacturer's recommendations and documented on a Daily Equipment Calibration Log
	Personnel are properly trained in and knowledgeable about the policies and procedures to ensure that they are properly gowned, masked and gloved before performing any compounding activities.	Who: All employees involved in performing activities What: Visual inspection of employees who compound to ensure they are properly attired When: Any time sterile product preparation occurs How: Documented training on organizational policy and procedure
	Aseptic technique of personnel is properly verified before they compound any sterile preparations.	Who: All employees involved in performing activities What: Zero growths in media-fill units prepared as part of the aseptic technique verification program When: Initially, for 3 consecutive days and then every 6 to 12 months How: Per organizational policy and procedure
	Critical compounding areas have been properly cleaned and sanitized, and the microbial environmental bioburden is monitored and within acceptable limits.	Who: Owner/PIC or designee responsible for quality What: Each compounding area (eg, Class 100 hood and surrounding area) When: Per schedule detailed in policy and procedure (Class 100 hoods should be cleaned between batches [with bleach or alcohol] and at least daily; floors no less than weekly; walls and ceiling on a monthly basis with a germicidal detergent.) Environmental microbial bioburden (air and surface) monitoring should occur at least weekly or as required by pharmacy regulations. How: Designate mops, buckets, sanitizing detergents and wipes. Air and surface monitoring should be performed and collected on TSB plates.

<i>Process Step/CCP</i>	<i>Critical Limits</i>	<i>Monitoring Procedures (Who/What/When/How)</i>
Filtration/sterilization	Ensure that the desired SAL for cold sterilized (eg, 0.22- μ m filtered product) or terminally sterilized (eg, autoclaved) product has been achieved prior to dispensing the final product to the patient.	<p>Who: Each employee performing the compounding activity and the owner/PIC or designee responsible for quality</p> <p>What: Each compounded product having the requirement of being sterile (injectable, inhalation solutions, ophthalmics)</p> <p>When: Per batch of compounded product; It is critical to perform validation studies to ensure that the desired method of sterilization is capable of achieving sterility. It may be necessary to use an outside laboratory to perform the sterility studies before using the procedures routinely. Once validated, the compounding procedures will be able to achieve the desired sterility results. It will be important, however, to routinely use biological indicators or some other temperature-sensitive monitoring system to ensure that the autoclave worked properly. In the event of cold sterilization methods, it is important to perform a filter integrity test (bubble-point test) on the final filter to ensure that the filter functioned properly.</p> <p>How: Per written policy and procedure, appropriate biological indicators and properly licensed and credentialed analytical laboratories</p>

CCP = Critical control point

CoA = Certificate of Analysis

USP-NF = *United States Pharmacopeia-National Formulary*

PIC = Pharmacist in charge

TSB = Tryptic soy broth

SAL = Sterility assurance level