BRIEFING

⟨1168⟩ Compounding for Phase I Investigational Studies, *PF* 39(5) [Sept.–Oct. 2013]. The current proposed chapter in *PF* 43(3) [May–June 2017] is posted online at www.usp.org/usp-nf/notices/compounding-for-phase-I-investigational-studies with line numbers. Submit comments using the form available at www.usp.org/goto/1168comments.

Due to the complexity of the drug development process, the pharmaceutical industry applies various tools to improve efficiency. One of these tools is the use of compounding to supply investigational preparations for Phase I clinical studies. The application of compounding of investigational preparations requires additional considerations because it is likely that the agents in these preparations have never been administered to humans. The purpose of this chapter is to provide guidance for compounding investigational preparations for Phase I studies.

The Compounding Expert Committee has revised this chapter based on the public comments received for the proposed chapter in *PF* 39(5). Major changes from the proposed chapter include:

1. Clarification of information that a compounder should know as part of participating in a study involving the compounding of investigational preparations
2. Clarification of personnel responsibilities on materials management

Additionally, minor editorial changes have been made to update this chapter to current *USP* style.

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Add the following:

·⟨1168⟩ COMPOUNDING FOR PHASE I INVESTIGATIONAL STUDIES

1. INTRODUCTION
    - 1.1 Scope
    - 1.2 Background
    - 1.3 Applicable Regulatory Requirements
    - 1.4 Best Practices

2. PERSONNEL TRAINING
3. BUILDINGS AND FACILITIES
4. EQUIPMENT AND COMPONENTS
    - 4.1 Equipment
    - 4.2 Components

5. STANDARD OPERATING PROCEDURES
6. PREPARATION ACTIVITIES
    - 6.1 Retention Samples
    - 6.2 Disposition of Unused Materials and Preparations

7. RELEASE OF INVESTIGATIONAL AGENT/PREPARATION
8. LABELING
9. ESTABLISHING BEYOND-USE DATES
10. QUALITY ASSURANCE AND QUALITY CONTROL
11. STORAGE, HANDLING, PACKAGING, AND TRANSPORT
    - 11.1 Storage
    - 11.2 Handling
    - 11.3 Packaging
    - 11.4 Transport

12. DOCUMENTATION
    - 12.1 Safety Data Sheets
    - 12.2 Certificate of Analysis
    - 12.3 Records Management

APPENDIX

1. INTRODUCTION

1.1 Scope

The objective of this chapter is to guide compounders in the compounding of investigational preparations and placebos that are used in investigational studies, specifically Phase I studies. For the purpose of this chapter, the terms "study" or "studies" are used to refer to investigational studies, specifically Phase I investigational studies or trials.

1.2 Background

Investigational studies are biomedical or health-related research studies that follow a predefined protocol to ensure subject protection and data integrity. Before drugs are tested in humans, usually a battery of preclinical animal studies is conducted to provide information about the medication's safety profile and pharmacokinetic parameters. Investigational preparations should be compounded in accordance with appropriate standards to ensure the quality of the preparation. Investigational studies in humans can provide a critical understanding of a medication's safety profile (i.e., adverse drug reactions and drug interactions) and pharmacokinetic parameters, and can provide insight into early indications of therapeutic efficacy. Compounding of investigational preparations may be useful 1) when only a small number of doses are needed to support the study, 2) to evaluate various dosage forms or dosage regimens before choosing one for further study, or 3) to develop age-appropriate dosage forms for certain study populations. Compounding investigational preparations may provide flexibility in evaluating dosing ranges and alternative routes of administration, and may reduce the time and cost to do so while maintaining subject safety and high product quality. Clinical studies generally are conducted in four phases, each with a different purpose to answer different questions.

1. **Phase I studies:** Researchers test an experimental drug or treatment in a small group of people (20–80 generally healthy volunteers, sometimes including patients) for the first time to evaluate the drug's safety, determine a safe dosage range, understand the pharmacokinetic profile, and identify side effects
2. **Phase II studies:** The experimental drug or treatment is administered to a larger group of people (usually NMT several hundred subjects with the specific disease state to be treated) to see if the drug is effective and to further evaluate its safety
3. **Phase III studies:** The experimental drug or treatment is administered to large groups of people (usually several hundred to several thousand subjects with the disease state of interest plus concomitant medical conditions) to confirm the drug's effectiveness, monitor side effects, compare it to commonly used treatments, and

collect information that allows the experimental drug or treatment to be used safely

4. **Phase IV studies:** Post-marketing studies delineate additional information about the drug's risks, benefits, and optimal use

Sponsors of studies involving investigational preparations being developed for commercial use usually provide the materials to be used in Phase I studies. Sometimes, however, those materials require additional preparation before administration to patients. For example, a lyophilized powder may require reconstitution, or a vial of investigational agent may need to be combined with a solution for infusion. In some cases, a sponsor may use a compounder to prepare the investigational preparation from a bulk drug substance or approved drug that the sponsor supplies. For investigator-initiated studies, the investigator may ask a compounder to prepare the investigational preparation from either approved drugs or bulk drug substances that are available from commercial sources. It is important to differentiate between the use of compounded preparations for treating patients in clinical practice for a specific condition and the evaluation of an agent for the purposes of an investigational use in a Phase I clinical study. Additionally, handling of hazardous drugs must comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

Virtually all dosage forms can be used in investigational studies (see *Pharmaceutical Dosage Forms* ⟨1151⟩). Investigational preparations may include tablets, capsules, powdered drug substance pre-weighed in unit doses, powdered drug substance in bulk for multiple subjects, solution or suspension in unit doses, solution or suspension in bulk for multiple subjects, sterile solutions for injection or infusion, sterile lyophilized powdered drug substance, powder for inhalation, nasal spray, radio-labeled bulk and unit doses, bulk drug substance and excipients for compounding, topical preparations such as creams or lotions, and/or placebos.

The formulation to be used in the study should be based on the questions to be answered by the study and must exclude any ingredient (i.e., excipient) that may adversely affect the patient's response to the investigational preparation.

1.3 Applicable Regulatory Requirements

Regulatory bodies in many countries specify requirements for the compounding of investigational preparations as part of an investigational drug application. Personnel engaged in compounding of preparations for investigational use must comply with these requirements, which vary according to applicable laws, regulations, and guidelines of the regulatory jurisdiction.

This chapter references *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations*

⟨797⟩, ⟨800⟩, and *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩ which provide specific guidelines for compounding of sterile and nonsterile preparations. With respect to any provisions in these chapters that are inconsistent with applicable regulatory requirements, compounders must comply with the more stringent requirements.

When a third party (e.g., a compounder or a contract research organization outside the sponsor's organization) is involved in an investigational study, contractual documents should be written to clearly specify the scope, roles, and responsibilities of each party involved. If a sponsor initiates a contract with a compounder to perform part or all of the Phase I compounding of an investigational preparation, the sponsor and the compounder are both responsible for ensuring that the Phase I investigational preparation is prepared in compliance with applicable requirements. The sponsor should evaluate the compounder to ensure that effective quality control (QC) functions are in place.

1.3.1 FEDERAL REQUIREMENTS

According to the U.S. Food and Drug Administration (FDA) Code of Federal Regulations (CFR) at 21 CFR §210.2, an investigational agent for use in a Phase I study is subject to statutory current Good Manufacturing Practices (cGMP) requirements set forth in 21 U.S. Code (USC) 351(a)(2)(B), although the production of such drug is exempt from compliance with the regulations in 21 CFR part 211. However, this exemption does not apply to an investigational agent for use in a Phase I study once the investigational agent has been made available for use by or for the sponsor in a Phase II or Phase III study, or the drug has been lawfully marketed. If the investigational agent has been made available in a Phase II or Phase III study or the drug has been lawfully marketed, the drug for use in the Phase I study must comply with part 211.

1.3.2 STATE, TERRITORY, AND PROVINCIAL REQUIREMENTS

Compounding for investigational studies may be addressed differently in different states, territories, or provinces. When states do not specifically address the topic, investigators (e.g., pharmacists, physicians, veterinarians, nurses, and physical therapists) must refer to *USP–NF* standards for compounding. States may require the name of the subject (individual receiving the investigational preparation) on a prescription, and when the subject's name is not known, a unique identifier may be assigned for labeling, documentation, and traceability of all compounded investigational preparations.

1.3.3 INTERNATIONAL AND GLOBALIZATION ISSUES

Many countries require information on the investigational preparation as part of the investigational drug application. These requirements vary according to the respective laws, regulations, and guidelines of the country.

Where guidance documents are available, the latest version should be obtained and followed.

1.4 Best Practices

Compounding an investigational preparation requires additional consideration beyond that of other types of compounding. Designated personnel at compounding facilities should work closely with the sponsor and understand the following considerations:

1. Is this a Phase I study?
2. Is an Investigational New Drug (IND) application in place for this investigational agent?
3. Is an Institutional Review Board (IRB) approval in place for this investigational agent/preparation?
4. Would cGMP standards apply to this investigational agent or preparation?
5. Is there an established triad relationship between the pharmacist, investigator, and patient?
6. Are all the materials supplied by the sponsor or being used to compound the investigational preparation appropriate for human use as determined by the study sponsor?
7. Are the necessary checks and balances in place to ensure subject safety and the compounding of a high-quality preparation?
8. Does the investigational preparation interact with any of the dosing devices that are being used in the study?
9. How is the investigational agent going to be dosed and is the investigational preparation appropriate for that route of administration?
10. Would the investigational preparation require additional release testing?
11. What is the dosage form and what type of testing criteria is specified for this dosage form?
12. Will this preparation be sent to other sites/facilities/locations participating in the clinical study?
13. Has the sponsor provided clear preparation instructions supported by stability and in-use data?
14. Are the available stability data adequate to support the beyond-use date (BUD) of the preparation?
15. Is the investigational agent or any components of the final compounded preparation hazardous as defined by the National Institute for Occupational Safety and Health (NIOSH) criteria (see ⟨800⟩)?

2. PERSONNEL TRAINING

In general, all personnel should have the education, experience, and training—or any combination thereof—to enable each individual to perform their assigned function. In particular, personnel should have the appropriate experience to prepare the Phase I compounded investigational preparation and be familiar with QC principles and acceptable methods for complying with applicable regulatory requirements. Additionally, personnel must be knowledgeable with regard to the standards in ⟨795⟩, ⟨797⟩, ⟨800⟩, and ⟨1163⟩. In addition to the training described in ⟨795⟩ and ⟨797⟩, training for compounding for investigational studies should be described in standard operating procedures (SOPs) and should include, but is not limited to, the following (as appropriate for specific protocols):

- Overview of new drug development
- Investigator obligations in FDA-regulated clinical research
- Managing investigational agents and preparations
- Detection, evaluation, and reporting of adverse events
- Audits and inspections in clinical studies
- Monitoring of clinical studies by industry sponsors
- Health Insurance Portability and Accountability Act (HIPAA) privacy rules for human and animal subject protection
- IRB roles
- Recruitment for participation in research studies and informed consent
- Good clinical practice (GCP)
- Human subjects protection (HSP)

3. BUILDINGS AND FACILITIES

Facilities should be properly designed and constructed for compounding of the investigational preparations. The design should include special controls to ensure that the investigational agents/preparations are not commingled with approved drugs used for treatment. The areas used for labeling (see *8. Labeling*), storage, handling, packaging, and transport (see *11. Storage, Handling, Packaging, and Transport*) should be secure, with restricted access. Facility design and use considerations must comply with ⟨795⟩, ⟨797⟩, ⟨800⟩, and applicable regulatory requirements. Additionally, facilities should comply with *Physical Environments That Promote Safe Medication Use* ⟨1066⟩ and ⟨1163⟩. Sponsors should conduct an audit to ensure compliance. Facilities should consider the value of being accredited by a national accreditation agency or organization.

4. EQUIPMENT AND COMPONENTS

4.1 Equipment

Equipment must meet the standards in ⟨795⟩, ⟨797⟩, and applicable regulatory requirements. Additionally, equipment should comply with applicable standards in ⟨1163⟩ and *Prescription Balances and Volumetric Apparatus Used in Compounding* ⟨1176⟩. A number of technologies and resources are available to facilitate and streamline compounding of investigational preparations. Some examples include:

- Disposable equipment and process aids to reduce cleaning burden and risk of cross contamination
- Commercial, prepackaged materials (e.g., *Sterile Water For Injection*, and presterilized containers and closures) to eliminate the need for sterilization of additional equipment
- Closed processing equipment (e.g., robotic compounding systems)

The compounder should consider and understand the impact of drug delivery devices (e.g., infusion tubing, pumps, and syringes) used to deliver investigational preparations on the stability and systemic availability of the investigational agent. Information should be evaluated to ensure that the investigational preparation does not interact with or create stability issues when used with the drug delivery device such that it could impact the safety or effectiveness of the preparation (e.g., investigational agent, excipient, or vehicle binding to the IV tubing).

4.2 Components

For sponsor-initiated studies, all materials (e.g., drug substance, excipients, commercial product, packaging components, and in-process material) will likely be supplied by the sponsor. All materials must comply with the standards in ⟨795⟩, ⟨797⟩, available monographs, and applicable regulatory requirements. Additionally, materials should comply with applicable standards in ⟨1163⟩. Any materials not supplied by the sponsor must be appropriate for human use as determined by the study sponsor.

4.2.1 BULK DRUG SUBSTANCES AND EXCIPIENTS

Compounders must have SOPs in place that describe the receipt, handling, review, acceptance, storage, and control of materials to be used to compound preparations for investigational studies. Receipt records should be maintained, and the materials used should be traceable to the individual patient. Bulk investigational agents preferably should be official compendial articles, but noncompendial ingredients and substances may be used if they are approved or provided by the sponsor, are evaluated for safety, and the evaluation is appropriately documented. A Certificate of Analysis (COA) or similar product/substance release document confirming the identity, strength, purity, and quality should accompany the bulk drug substance. For

human- and animal-derived material, documentation should include information about sourcing and test results for adventitious agents. All bulk investigational agents and other ingredients should be examined for any physical damage and should be quarantined until examined or tested, as appropriate, before they are released for use. Storage and handling conditions for investigational agents (bulk drug substances), other ingredients (excipients), and the final preparation should be described in SOPs and should be maintained to prevent degradation or contamination and to ensure preparation quality. Temperature, humidity, light protection, and other specifications should be provided by the sponsor or supplier. Investigational agent labeling and other ingredient-container labeling should be displayed prominently and understandably with respect to the requirements for proper storage and retest date. If required, in-package temperature-monitoring devices should be used during transport and their information recorded after the package is received at the study site.

4.2.2 CONVENTIONALLY MANUFACTURED PRODUCTS AS DRUG SOURCE MATERIAL

Conventionally manufactured approved drug dosage forms (e.g., tablets, capsules, injectables, or liquids) may be used in investigational studies if they are approved or provided by the sponsor. Examples of compounding with conventionally manufactured dosage forms may include, but are not limited to, reconstitution of injectable preparations, over-encapsulation, and incorporating comminuted tablets into an oral liquid or capsule preparation. Generally, immediate-release tablets should be used. Controlled-release tablets can be used if the sponsor determines they are acceptable after careful consideration of the controlled-release mechanism.

4.2.3 IN-PROCESS MATERIALS

In-process materials include any item or preparation that is prepared in advance and held for use during the compounding of the investigational preparation (e.g., premixes, triturations, stock solutions, primary emulsions, and gel components).

5. STANDARD OPERATING PROCEDURES

Appropriate SOPs must be in place to facilitate the compounding of the investigational preparation. Compounding procedures must follow ⟨795⟩, ⟨797⟩, and any applicable regulatory requirements. The procedures should be written clearly and should contain sufficient detail to allow reproducibility of the compounding process and traceability of materials. In addition, the procedures should take into account the complexity of the process and a risk assessment of the material to be prepared. For instance, weighing and compounding a nonsterile preparation starting with a nonsterile powder is less complex and has fewer associated risks compared to preparing and

dispensing a sterile preparation from nonsterile ingredients, which is highly complex and entails high associated risks.

The compounding of Phase I investigational preparations should follow written procedures that provide for the following:

- A record that details the materials, equipment, procedures used, and any problems encountered during compounding. Compounders should retain records sufficient to replicate the compounding process. Similarly, if the compounding of a Phase I investigational preparation is initiated but not completed, the record should include an explanation of why compounding was terminated.
- Records for handling, compounding, packaging, storage, and transporting investigational agents and final preparations.
- A document that identifies procedures for reviewing, approving, and monitoring investigational agents and final preparations.
- A record of changes in procedures and processes used for subsequent batches along with the rationale for any changes.
- A record of the microbiological controls that have been implemented (including written procedures) for the production of sterile-processed Phase I investigational preparations.

6. PREPARATION ACTIVITIES

Before compounding the investigational preparation, the responsible person designated by the sponsor should review the protocol and the intended use of the investigational preparation to ensure that adequate space, facilities, equipment, and trained personnel are available to compound the investigational preparation.

The compounder should do a trial run (compound the investigational preparation in accordance with the compounding record) and have the compounded preparation tested per the sponsor protocol to ensure that a high-quality preparation is produced. This trial run will serve to verify that the compounding process produces a high-quality finished preparation. Based on the results of the trial run, the compounding record may need to be changed and additional trial runs conducted to confirm that a high-quality preparation can be compounded by the site using the compounding record.

In addition, based on these verification studies, appropriate tests (e.g., measurement of final pH of preparation, weight checking all over-encapsulated products) and acceptable limits should be selected, and all future batches evaluated using these agreed upon tests, which should be incorporated into the compounding record. The finished preparation includes the dosage form, package, labeling, and any other required items. Based on the nature of the final preparation (e.g., simple dilution as compared to a powder-filled capsule), the final preparation should be analyzed for

conformance to the specifications provided by the primary investigator or sponsor. Additionally, sufficient quality assurance measures should be incorporated in the process to ensure that the actual yield matches the theoretical yield of finished preparation or that any deviation is accounted for and documented.

Compounded investigational preparations require: correct ingredients and calculations; accurate and precise measurements; and appropriate formulation, facilities, equipment, and procedures. As a final release check, and after obtaining the results of any release testing conducted in accordance with the compounding record and *7. Release of Investigational Agent/Preparation*, the compounder should review each step of the compounding process in the compounding record to ensure that it was completed appropriately and should examine the finished preparation to ensure that it appears as expected. The compounder should investigate any deviations and discrepancies identified during the release check and take appropriate corrective action. Based on information gathered during the investigation, a decision on the outcome of the final preparation should be made and documented. The decision could range from rejection and disposal of the compounded preparation to the release of the preparation for use.

6.1 Retention Samples

A representative sample from each lot of investigational agent and each lot of compounded investigational preparation (finished preparation in the container used in the investigational study) must be retained and properly stored according to the study protocol for at least 2 years following study termination or withdrawal of the IND application. An alternative approach may be needed for unstable samples. Sponsors must have access to signed compounding records and individual retained components of the compounded preparation. These individual components must be kept according to the study protocol and retention policies. The sample must consist of a quantity adequate for the performance of additional testing or investigation if required at a later date (twice the quantity necessary to conduct release testing, excluding testing for pyrogens and sterility).

6.2 Disposition of Unused Materials and Preparations

If permitted, unused investigational preparations can be reallocated from one subject to another or from one site to another in accordance with the sponsor's protocol. Unused investigational agents, excipients, or finished preparations must be accounted for and disposed of in accordance with SOPs and sponsor requirements. The disposition (i.e., dispensed, returned to the sponsor, or destroyed) of all investigational preparations must be documented. Any discrepancies must be noted (e.g., preparation of doses not dispensed or that were in broken or breached containers). At the completion of the study, the sponsor should visit the compounding facility to

account for all used and unused supplies of the investigational agent. The sponsor should verify the accountability and note the quantity returned for reconciliation and destruction. The compounding facility should verify the quantity returned for destruction or destroyed on-site, and should complete and sign the necessary forms.

7. RELEASE OF INVESTIGATIONAL AGENT/PREPARATION

The final investigational preparation used for subject dosing should be released according to sponsor procedures, which are usually identified in the sponsor-provided study manual or study protocol. Integral to release is the assurance that preparation activities have been conducted in accordance with the appropriate quality requirements and as defined by the sponsor, including receipt, handling, preparation, dispensing, labeling, blinding (when necessary), and storage. Any discrepancies should be documented and discussed with the sponsor to determine possible effects and appropriate steps that should be taken. The sponsor is responsible for approval of the final investigational preparation prior to subject dosing, or the responsibility may be delegated to qualified personnel according to the study protocol.

Sponsors may require the evaluation of one or more quality attributes (e.g., physical, chemical, and microbiological testing) before the investigational preparation is released. Each release test should include one or more procedures, usually with well-defined acceptance criteria. Investigative and corrective actions associated with any specific failure or discrepancy should be documented. Regardless of the source, each investigational preparation and excipient should have predetermined acceptance criteria.

The qualified personnel designated by the sponsor or sponsor-investigator is responsible for either implementing an in-house testing program or working with a contract laboratory to confirm performance of appropriate testing methods for the investigational preparations. Results of any testing that is undertaken on an investigational preparation should be shared with and discussed with the sponsor of the study. If testing will be done at the compounding facility, appropriate equipment should be obtained and qualified either by the manufacturer upon sale or by the compounder upon receipt, and should be properly maintained, calibrated, and used. All personnel conducting in-house testing should be trained, skilled, and proficient in the procedure(s) necessary for testing.

If a compounding facility has the necessary equipment, supplies, and personnel who are skilled and qualified, many QC tests can be conducted on-site. Appropriate SOPs should be developed and implemented to ensure that equipment and instruments are working satisfactorily and that preparations are tested properly. Compounders can perform physical QC tests to ensure the uniformity and accuracy of compounded preparations. These tests

address individual dosage unit weights (including the average), total preparation weight, pH, and physical attributes such as appearance, taste, and smell.

If testing is outsourced, the sponsor and the qualified personnel designated by the sponsor should determine what to outsource and how to select a laboratory, and should develop an ongoing relationship with the laboratory chosen. Contract laboratories must follow standards set forth in *USP* chapters, as appropriate, and preferably should be registered with the FDA.

Factors to coordinate and consider in testing requirements include:

- Quantity of preparation being compounded according to the study protocol for a specific prescription
- Number of samples needed
- Destructive or nondestructive testing
- Appropriate methods for obtaining representative samples
- Physical state of the samples (solid, liquid, or gas)
- Type of container required for collection and storage
- Any special handling and shipping requirements or restrictions (e.g., controlled drug substances, dangerous or hazardous chemicals, hazardous drugs, flammable or caustic substances, and refrigerated or frozen preparations)
- Sponsor-specified storage requirements for samples including type of container, temperature, humidity, and light resistance (see *Packaging and Storage Requirements* ⟨659⟩)

8. LABELING

The term "labeling" encompasses all the written, printed, and graphic material accompanying the preparation, including information on the immediate container received by the patient. Labeling also includes the instructions to the investigators involved in the study, package inserts, cartons, outer wrapping (if used), and any other materials accompanying the investigational preparation. Labeling control is vitally important, and only the exact number of labels required should be printed. An example label must be affixed to the compounding record.

The label includes all written, printed, or graphic matter on the immediate container received by the patient. Appropriate labels should be selected after consideration of the font type and size as well as the adhesive to be used. The printed label must be legible and must adhere to the investigational preparation container during short-term storage and use. The label adhesive should not come in direct contact with the dosage form (e.g., tablet, capsule), leach into packaging materials, or contaminate the investigational preparation.

There should be complete agreement among all of the labeling materials in terms of the information provided. Information on the label should be verified for accuracy by a second person prior to application of the label to the final packaging of the investigational preparation.

Labeling of investigational agents and preparations should follow applicable requirements of the regulatory agency and sponsor.

The investigational protocol or the compounding facility manual should provide labeling instructions as well as label content. Labels may be provided by the sponsor or may be produced on-site at the compounding facility. If labels are provided by the sponsor, the site may be required by laws, regulations, or guidelines of the regulatory jurisdiction, or internal procedures, to provide additional separate and unique labeling. The compounded investigational preparation must be labeled with a unique identifier that allows traceability and recall, if necessary, and a BUD.

However, in the case of investigational preparations, there may be instances when including this information on the preparation labeling might have an adverse effect on blinding. Regulatory bodies may permit exclusion of control numbers and BUDs from the preparation labeling for blinding purposes, provided this information is made available separately (e.g., to the clinical investigator) in case the blinding or randomization code needs to be broken. An auxiliary label for supplying additional information may need to be affixed to individual compounded investigational preparations or a bag that holds a supply of vials or containers of the same drug strength or concentration. Such labels should supply information that is missing on the preparation label or information that is poorly visible on the label. A highlighter pen can be used to focus attention on key information on the label.

9. ESTABLISHING BEYOND-USE DATES

A BUD should be established for compounded investigational preparations. Due to the lack of data on investigational agent stability (e.g., if it is a new chemical entity) or stability of the final compounded preparation, the compounder must not rely on the default BUDs established in ⟨795⟩ and ⟨797⟩. A contract analytical laboratory can help establish an appropriate BUD by performing either real-time or accelerated stability testing. Stability studies may be ongoing simultaneously with the investigational study. In such situations, the compounder is responsible for ensuring regular communication with the sponsor regarding updated stability data and how those data affect a previously identified BUD. New stability data could lead to an increase or decrease in a previously identified BUD. Additionally, compounders should notify the sponsor of any stability issues which may lead to treatment failures in study subjects. The available data should

support material storage for as long as intended during the investigational trial.

10. QUALITY ASSURANCE AND QUALITY CONTROL

A quality assurance (QA) program for compounding investigational preparations is important for the integrity of a study. QA encompasses all of the processes and procedures undertaken to ensure that compounded preparations are of the quality required for their intended purposes, and also the proper documentation of all steps taken and data obtained. The effectiveness and suitability of the QA program should be assessed regularly, no less than annually. A QC program for investigational agents and preparations should address the following five components:

1. Bulk drug substances and other ingredients
2. In-process items
3. Packaging materials (e.g., container and closures)
4. Labels
5. Finished preparations

QA for compounding investigational preparations ensures the following:

- Compounded investigational preparations are designed and prepared according to the methods and procedures in the study protocol, applicable regulatory requirements, and *USP–NF* standards
- Compounding and control operations are clearly specified and implemented according to the regulatory requirements, and *USP–NF* standards
- Compounded investigational preparations are dispensed only if they have been correctly prepared, verified, and stored in accordance with the procedures and parameters defined by the sponsor
- Adequate measures are in place to ensure that the compounded investigational preparations are released, stored, and handled in such a way that the required quality can be ensured until the BUD
- Required documentation is maintained

A qualified person should be assigned overall responsibility for the establishment and execution of the quality program. Responsible personnel are essential in ensuring the identity, strength, quality, and purity of investigational agents and their components (see ⟨1163⟩).

A QA program for compounded preparations should include testing during the compounding process and of the finished compounded preparation as determined by the study sponsor.

Internal inspections should be performed at least annually to ensure compliance with SOPs, policies and procedures, and both internal and regulatory quality requirements. In a compounding facility, someone other than the compounder should be responsible for the inspections.

Sponsors, or their contract facilities including pharmacies or clinics, should conduct audits according to the study requirements. The audit should verify that the qualified personnel designated by the sponsor are performing quality inspections.

11. STORAGE, HANDLING, PACKAGING, AND TRANSPORT

11.1 Storage

Storage conditions (see ⟨659⟩) in all storage areas for investigational agents and preparations must be carefully monitored and controlled, and the data must be documented throughout the entire study process as specified by the study protocol. Any temperature deviations that are outside the sponsor's indicated storage conditions should be investigated, recorded (with duration), and reported to the sponsor. A root cause analysis (RCA) must be performed to identify the cause(s) of deviation(s). The compounder must discuss with the sponsor the impact of these deviations on the quality of the investigational agent or preparation, and a decision must be made, and documented, on whether it is acceptable to use the investigational agent or preparation. Electronic monitoring and recording devices are recommended because they can provide a detailed record of storage conditions.

11.2 Handling

All materials used in compounding should be handled appropriately and in accordance with information from the Safety Data Sheets (SDS). When compounding with hazardous drugs, compounders must pay careful attention to all aspects of handling these substances to protect personnel and the environment, and must also comply with ⟨800⟩ and all applicable laws, regulations, or guidelines of the regulatory jurisdiction.

11.3 Packaging

All packaging materials—including the immediate container and closure—should be supplied or specified by the sponsor. Packaging materials should meet *USP–NF* standards and should be sourced and selected based on physical and chemical characteristics and compatibility with the final preparation to avoid possible preparation–container interactions. They should also be accompanied by documentation of their composition and size specifications. The packaging may include, but is not limited to, glass or plastic bottles, metal or plastic caps, paper, cardboard, plastic parts and film, metal foil, drums, cans, tubes, vials, or jars.

The packaging should protect and ensure the stability of the preparation. Specifically, the investigational preparation should be packaged to protect it from alteration, contamination, and damage during storage, handling, and transport (see *Storage and Transportation of Investigational Drug Products ⟨1079.1⟩*). If the investigational preparation is sensitive to temperature fluctuations and will be transported to another facility, consideration should be given to using an in-package temperature monitoring device. If used, the information from this device should be recorded immediately after the package is received at the study site.

11.4 Transport

Distribution and dispensing are potentially the least controllable part of the overall scheme from compounding to administration. If distribution and dispensing occur within the same facility, the potential problems are reduced. However, if distribution and dispensing occur in different locations, and external carriers are used, the potential problems can be substantial, especially if overnight delivery is required or distribution needs to occur during weather extremes.

12. DOCUMENTATION

After study termination, records of investigational agents and preparations must be maintained by the compounding facility according to the sponsor's requirements. This includes records pertaining to the preparation, release, and disposition of each lot of material (e.g., drug substance and excipients) used, as well as source documentation and release testing, as appropriate, for bulk materials. Records pertaining to reference standards, if any, that are used to support investigational agents or preparations must be retained according to study requirements.

12.1 Safety Data Sheets

SDS should be available on-site or should be readily retrievable electronically. They should be reviewed by all personnel who will be working with the compounding materials.

12.2 Certificate of Analysis

A COA, or equivalent document if outside the U.S., must be obtained for every ingredient used in the compounding of an investigational preparation, and should be maintained throughout the study. It is recommended that the sponsor supply all clinical materials. If all materials are supplied by the sponsor, the sponsor is responsible for maintaining COAs for the ingredients and supplying these to the compounding facility if requested.

However, if some or all of the clinical materials are supplied by the compounding facility, a COA or equivalent document should be collected from the supplier of the material being used, and the COA should be

maintained by the compounding facility and should be provided to the sponsor at the end of the study if requested.

12.3 Records Management

Documentation should include a record of all aspects of the compounding of investigational preparations. Information must be entered on appropriate record forms (paper or electronic) as the tasks are performed. Compounding records should be reviewed for accuracy and completeness and should be approved by the responsible person before release of the preparation.

At a minimum, the required documentation for investigational preparations includes the original study specifications, the compounding records, test results, and the COAs. Sponsors must retain all records for at least 2 years after approval of an IND application, according to the study protocol and applicable regulatory requirements, or, if an IND application is not submitted or approved, for 2 years after discontinuation of shipment and delivery of the investigational agent and FDA notification.

APPENDIX

See *Table A-1* for the list of acronyms included in this chapter.

Table A-1. Acronyms Included in ⟨1168⟩

Acronym	Description
BUD	Beyond-use date
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
COA	Certificate of analysis
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human subjects protection
IND	Investigational New Drug
IRB	Institutional Review Board
NIOSH	National Institute for Occupational Safety and Health
QA	Quality assurance
QC	Quality control
RCA	Root cause analysis
SDS	Safety Data Sheets
SOPs	Standard operating procedures
USC	U.S. Code