1. Purpose

To provide the guidelines for appropriate management and handling of study products for use during a clinical trial.

2. Table of Contents

3. Abbreviations

CCR	Center for Cancer Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DAR	Drug Accountability Record
DFS	Drug Fact Sheet
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Documentation Practices
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IDCU	Investigational Drug Control Unit
IEC	Independent or Institutional Ethics Committee
IOR	Investigator of Record
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
NF	National Formulary
NCI	National Cancer Institute
NIH	National Institutes of Health
OSRO	Office of Sponsor and Regulatory Oversight
OSRO PM	Office of Sponsor and Regulatory Oversight Pharmaceutical Management
PI	Principal Investigator
SOP	Standard Operating Procedures
SWU	Study Write Up
USP	United States Pharmacopeia

4. Glossary of Terms

4.1. **Alternate Pharmacist:** A licensed/registered pharmacist identified to perform the same designated activities when the lead research pharmacist is absent and must be trained by the lead research pharmacist to perform activities as required of a CCR-held IND/CCR sponsored clinical trial. (See *Section 15.1 Lead Research Pharmacist Coverage*).

4.2. **Blinding:** A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).

4.3. **Chain of Custody:** The chronological documentation of an unbroken trail of accountability of authorized study personnel showing custody (responsible party), control, transfer, and disposition of the study product.

4.4. **Clinical Research Site:** Discrete locations (e.g., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) where qualified professionals conduct clinical trial research on human subjects in accordance with International Council for Harmonization (ICH) / Good Clinical Practice (GCP) (See Reference 16.7).

4.5. **Clinical Research Site Monitoring:** The act of overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements.

4.6. **Clinical Trial:** A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

4.7. **Cold Chain:** Cold chain refers to maintaining the required refrigerated or frozen conditions at or between a defined temperature range for study products according to the manufacturer's specifications.

4.8. **Drug Accountability Record (DAR):** A log of study drugs kept by an investigator running a clinical trial. It lists many things about each drug, including the drug name, lot number, expiration date, the amount of drug received, used, returned, or thrown away, and the amount left. Drug Accountability Records help make sure that a clinical trial is done safely and correctly. Drug Accountability Records are required by the U.S. Food and Drug Administration (FDA).

4.9. **Drug Fact Sheet**: A document developed by the Pharmacy to provide study drug information for specific protocols, including information related to but not limited to dosing, preparation, storage, stability, etc.

4.10. **Form FDA 1572:** A U.S. Food and Drug Administration (FDA) form serving as a statement by the investigator that he/she will abide by the Code of Federal Regulations (CFR) for the use of drugs under an Investigational New Drug Application (IND).

4.11. **Helper Page**: A document developed by Pharmacy instructing the dispenser to refer to commercially available product information sources, such as study product package inserts, when dispensing investigational products.

4.12. **Institutional Review Board (IRB):** An independent body constituted of medical, scientific, and nonscientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects recruited to participate in a clinical trial. Assurance is provided by reviewing, approving, and providing continuing review of protocols, consents, amendments, safety reports, and methods and materials to be used in obtaining and documenting informed consent of the study subjects.

4.13. **Investigator Agreement:** An agreement for an Investigational Device Exemption (IDE), which is signed by all investigators stating their commitment to comply with investigator obligations per 21 CFR 812.43(c)(4) (Reference 16.3).

4.14. **Investigator of Record (IOR) Form:** An agreement signed by the principal investigator (PI) that he/she will abide by the regulations set forth in 45 CFR Part 46 (Reference 16.4) and the requirements of the protocol. The form also lists sub-investigators, laboratories, and reviewing IRBs. It is used for IDE studies in lieu of an FDA 1572 form.

4.15. **Investigator's Brochure (IB):** A compilation of the clinical and non-clinical data on investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved with the trial information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as dose, dose frequency/interval, methods of administration, safety monitoring procedures, and possible adverse events. For marketed products, the package insert (also known as the product label) can be used for the IB.

4.16. **Lead research pharmacist:** A licensed/registered pharmacist who is designated responsibility by the PI to perform the day-to-day research pharmacy activities and study product management at clinical research sites, including but not limited to the procurement, storage, preparation, dispensing, drug accountability, and final disposition of study products for CCR-held IND/CCR sponsored clinical trial(s). The main pharmacy contact for a protocol.

4.17. **Manufacturer**: Anyone who is engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a prescription drug.

4.18. **Principal Investigator:** Also known as the Investigator of Record (IOR), is responsible for the conduct of a clinical trial at a clinical research site. This individual is the signatory for the Form FDA 1572 (for IND studies) or the IOR Form (for IDE studies).

4.19. **Protocol:** A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial as well as provides the background and rationale for the trial.

4.20. **Protocol Deviations:** Any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or protocol-specific Manual of Procedures (MOP) requirement. The noncompliance may be either on the part of the subject, the investigator, or the study site staff, and may result in significant added risk to the study subject. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

4.21. **Randomization:** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. Neither the researcher nor the subject chooses which treatment or intervention the subject will receive.

4.22. **Research:** According to 45 CFR Part 46 (Reference 16.4), this is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities."

4.23. **Research Pharmacy:** For purpose of this document, any facility, building, room, or secure area used to perform one or more of the following functions: storage, preparation, dispensing, and management of study products (e.g., hospital or institutional pharmacy, dispensary, drug storage unit).

4.24. **Research Pharmacy Ancillary Supplies:** Any materials or tools that may be used in a pharmacy to perform and support the day-to-day activities and functions of the pharmacist, such as needles and syringes, oral syringes, prescription vials and lids, gowns, masks, IV solutions, or diluents.

4.25. **Research Pharmacy Equipment:** Apparatus (device or machinery) that is utilized to ensure the physical and scientific integrity of the study product during shipment, storage, handling, and preparation. Examples of pharmacy equipment are biological safety cabinets, refrigerators, -20°C freezers, -70°C freezers, air conditioners, air heaters, humidifiers, dehumidifiers, thermometers, probes, vortex machines, temperature alarm systems, limited access/security systems (security alarms, key locks), locking file and storage cabinets, shelving, counting trays for tablets and capsules, graduated cylinders, spatulas, study product containers, fax machines, computers, or printers.

4.26. **Sponsor:** Entity that oversee a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.

4.27. **Sponsor Investigational Product Preparation Form**: A form completed by sponsor or designee and provided to site pharmacy detailing the preparation instructions of a study product.

4.28. **Study Product:** A study product is defined by OSRO as any drug, biologic, device, or combination product that is provided for the study or identified in the protocol as a study product, including any diluents or placebos provided for use during the study. For the purpose of this document, the term 'study product' is used in lieu of the following terms:

- Investigational product (ICH E6(R2) GCP)
- Investigational drug (21 CFR Part 312)
- Investigational Device (21 CFR Part 812)
- Test article (21 CFR Part 50)

4.29. **Study Write Up (SWU)**: A document developed by the IDCU pharmacists to provide dispensing information for double blind studies.

4.30. **United States Pharmacopeia/National Formulary (USP/NF) Storage Conditions Definitions**[1]:

Specific instructions are stated in the clinical research protocols with respect to storage conditions at which study product must be stored and shipped. Unless otherwise stated in the protocol or by the manufacturer, current storage conditions for study products are defined by the USP in the following terms:

4.30.1. **Freezer**: A place in which the temperature is controlled between −25°C and −10°C (−13°F and 14°F). It is noted that, in some instances, articles may have a recommended storage condition below −20°C (−4°F). In such cases, the temperature of the storage location should be controlled to ±10°C.

4.30.2. **Refrigerator**: A place in which the temperature is controlled between 2°C and 8°C (36°F and 46°F).

4.30.3. **Cold**: Any temperature not exceeding 8°C (46°F).

4.30.4. **Cool**: Any temperature between 8°C and 15°C (46°F and 59°F). Note: An article for which storage in a cool place is directed may, alternatively, be stored and shipped as refrigerated, unless otherwise specified by the individual monograph.

4.30.5. **Room temperature** (also referred to as Ambient temperature): The temperature prevailing in a working environment.

4.30.6. **Controlled room temperature**: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C–25°C (68°F–77°F). The following conditions also apply. Mean kinetic temperature not to exceed 25°C. Excursions between 15°C and 30°C (59°F and 86°F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°C, transient spikes up to 40°C are permitted as long as they do not exceed 24 h. Spikes above 40°C may be permitted only if the manufacturer so instructs. Articles may be labeled for storage at “controlled room temperature” or at “20°C–25°C”, or other wording based on the same mean kinetic temperature (see also Reference 16.12). An article for which storage at Controlled room temperature is directed may, alternatively, be stored and shipped in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label.

4.30.7. **Warm**: Any temperature between 30°C and 40°C (86°F and 104°F).

4.30.8. **Excessive heat**: Any temperature above 40°C (104°F).

4.30.9. **Dry place**: A place that does not exceed 40% average relative humidity at 20°C (68°F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT 12 equally spaced

[1] **USP42-NF37 2S**– General Chapters <659> PACKAGING AND STORAGE REQUIREMENTS.

measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a Container validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry place.

4.30.10. **Protect from freezing**: The Container label will bear an appropriate instruction to protect the article from freezing in cases where freezing exposes an article to loss of strength or potency or to destructive alteration of its characteristics. These risks are present in addition to the risk that the Container may break if exposed to freezing temperatures.

4.30.11. **Protect from light:** Where light subjects an article to loss of strength or potency or to destructive alteration of its characteristics, the *Container* label bears an appropriate instruction to protect the article from light. The article must be packaged in a light-resistant *Container*.

In CCR sponsored protocols, unless otherwise specified by the manufacturer, for the purposes of study product storage and transport, room temperature will be defined as USP controlled room temperature at 20°C to 25°C.

Any questions regarding the storage conditions for study products used in CCR sponsored clinical trials should be directed to OSROStudyAgent@nih.gov.

5. Introduction

5.1. Background

The Office of Sponsor and Regulatory Oversight (OSRO) resides in the Office of the Clinical Director (OCD) of the Center for Cancer Research (CCR) of the National Cancer Institute (NCI) of the National Institutes of Health (NIH).

As a sponsor of CCR-held IND clinical trials, the OSRO must ensure that trials supported by the CCR are being conducted in compliance with U.S. federal regulations and any other applicable local regulations. The Principal Investigator (PI) has responsibility for all aspects of the clinical trial at his/her site, including conduct, management, and record maintenance. In addition to following the protocol and applicable regulations, the PI is responsible for assuring that the clinical trial is conducted in accordance with international standards such as the International Council for Harmonization (ICH) Good Clinical Practice (GCP) E6(R2) guidelines (see Reference 16.7).

This responsibility extends to the appropriate management and handling of study products, including ordering, receipt, storage, use, accountability, and disposition of study products procured for use during a clinical trial, and where necessary, for labeling of study products, according to the protocol and Manual of Procedures (MOP). The PI may delegate the day-to-day responsibilities of study product management to a licensed/registered pharmacist, but the ultimate responsibility lies with the PI. The licensed/registered pharmacist must be qualified to conduct the tasks delegated to them, based on appropriate experience, training, education, and licensure/registration (as applicable according to local and other requirements). For the purpose of this document, this designee will be referred to as the lead research pharmacist (see definition for *lead research pharmacist*). For the purpose of this document, all

references to the lead research pharmacist also apply to the alternate pharmacist (see definition for *alternate pharmacist*).

Study products for CCR sponsored studies must be stored in safe, secure, and appropriate locations and at correct storage conditions based on the requirements of the manufacturer and the study protocol. For the purpose of this document, this location will be referred to as the research pharmacy. For further details, see the definition for *research pharmacy*.

For most CCR sponsored studies, product is supplied directly from the manufacturer, purchased commercially through a wholesaler, or obtained through the hospital/institutional pharmacy.

The OSRO Pharmaceutical Management (PM) team has lead responsibility for communication with the manufacturer for product/pharmacy-related issues regarding shipping, storage, and preparation/administration of study product. The OSRO PM is the primary contact to address study product-related issues (send email queries to OSROStudyAgent@nih.gov).

If the clinical site believes that any of the OSRO guidelines outlined in this document cannot be met, the protocol team must discuss with OSRO PM to determine how best to proceed. In addition to these guidelines, non-U.S. or international sites must also adhere to in-country guidelines/requirements. If any differences exist between these guidelines and in-country requirements, the most stringent regulations must be followed. For any questions or clarifications, the protocol team must contact the OSRO PM to determine how best to proceed.

5.2. Scope and Objectives

The purpose of this document is to outline OSRO guidelines related to the appropriate management and handling of study products (see definition for *study product*) at the clinical research sites in order to comply with applicable regulations. These guidelines apply to clinical trials sponsored by the CCR, regardless of funding mechanism or clinical research site location.

The guidelines described in this document are not all inclusive. If there are more specific instructions relating to a study product, the study team should ensure instructions are included either in the protocol, MOP, Investigator's Brochure (IB)/package insert, and/or any other relevant study specific standard operating procedures (SOPs). In addition, certain protocols may include study product that, due to the nature of the product or unique management and handling requirements, may fall outside of the general guidance as described in this document (e.g., investigational devices or challenge material). Additional information for the management of these products should be provided in protocol-specific documents.

Unless otherwise stated within the protocol, MOP, or any other protocol-specific material, the scope of this document does not extend to therapies or treatments administered as part of standard-of-care or to those used for the management of a study-related intervention (e.g., rescue therapy, challenge study treatment management, toxicity management).

5.3. Resources

5.3.1. E-mail: OSROStudyAgent@nih.gov

5.3.2. Documents Applicable to Research Pharmacies

Refer to Section 16, References for documents that may be applicable to research pharmacies.

5.4. Research Pharmacy SOPs

Sites are expected to have research pharmacy SOPs in place prior to the initiation of a clinical trial. The lead research pharmacist/designee is responsible for establishing internal policies and procedures for the safe and proper ordering, receipt, storage, preparing, dispensing, disposing, accountability, inventory, and quarantine of study products. For some protocols, the lead research pharmacist may be required to generate protocol-specific SOPs, as indicated, based on the requirements in the protocol or study-specific MOP.

Examples of some applicable SOPs may include, but are not limited to, the following:

- Accountability of Study Product
- Chain of Custody of Study Product
- Cold Chain Management of Study Product
- Communication between Pharmacy and the Clinic
- Destruction of Study Product
- Dispensing of Study Product
- Emergency Plan for Equipment Failure or Prolonged Power Failure
- Inventory and Expiration Date Review of Study Product
- Management of Damaged, Expired, or Recalled Study Product
- Management of Study Product Essential Information and Related Documents
- Ordering and Receipt of Study Product
- Prescriptions for Study Product
- Quality Assurance and Quality Management for Study Product
- Quarantine of Study Product
- Return of Study Product
- Storage and Security of Study Product
- Temperature Alarm Notification Process
- Temperature Monitoring and Documentation
- Unblinding Procedures for Routine and Emergent Situations

6. Essential Information Required for Study Products

6.1. The PI or designee is responsible for providing any study-related documents with essential information on study products to the lead research pharmacist.

6.2. Documents with essential information on study products should include but are not limited to the following:

- IRB-approved Protocol (most recent and current version)
- Manual of Procedures (if applicable)
- Pharmacy Manual (if applicable)
- Product Package Insert (PPI) or Investigator's Brochure (IB)

The lead research pharmacist must have detailed knowledge of and must adhere to the requirements as outlined in the above documents. The lead research pharmacist must maintain all essential information, pertaining to study products being used in the CCR sponsored clinical trials, in the pharmacy files.

6.3. The PI and lead research pharmacist/designee should establish a system to ensure that the current document versions are on file for reference and are being followed when preparing and dispensing the protocol-specific product.

6.4. The OSRO PM team should be contacted for any study-product related questions. If there is any question regarding the content or instructions contained in any other study-related documents, the OSRO Regulatory team should be contacted for clarification.

6.5. If the study is blinded, a treatment assignment list may be used by the lead research pharmacist. Access to this information must be limited to only the unblinded authorized personnel per the protocol or MOP. The treatment assignment list must be stored in a locked and secure location with limited accessibility.

6.6. The names of the investigator(s), study coordinator, and product supplier, along with an authorized prescriber list, should be maintained for each protocol, as applicable. This list should be kept current, with updates whenever individuals are added or deleted.

6.7. The information contained within the study-related documents may be proprietary and should not be reproduced or distributed to individuals outside of the clinical research site team.

7. Accountability and Inventory Control

The PI is responsible for maintaining study product accountability. The PI may designate or delegate this task to a lead research pharmacist who will maintain accountability, documentation and control of the study product inventory used from the time the study product is first received at the site until final disposition. Refer to ICH E6(R2) GCP section 4.6 (Reference 16.7) for additional information.

7.1. Ordering and Receipt of Study Product

For most CCR sponsored studies, product is supplied directly from the manufacturer, purchased commercially through a wholesaler, or obtained through the hospital/institutional pharmacy.

The following section describes expectations regardless of the supplier.

7.1.1. Study Product Ordering

7.1.1.1. OSRO must be provided with the following documents before study product can be shipped to a clinical research site:

- IRB approval and IRB approved Informed Consent
- Form FDA 1572 / Investigator Agreement or Investigator of Record (IOR) Form
- PI curriculum vitae (CV)

OSRO or its designee will issue a site activation memorandum, if applicable, once all the documentation and internal approvals are in place.

7.1.1.2. An appropriate communication plan must be developed between the product supplier and the study site/pharmacy to facilitate study product ordering and receipt. This plan should include contact individuals, phone numbers, fax numbers, and e-mail addresses, as appropriate. This information is usually included in the MOP.

7.1.1.3. Personnel responsible for ordering of study product(s) must establish a written procedure to ensure that sufficient product supply is available to meet anticipated recruitment and subject needs for the duration of the study per a specific protocol and include estimates for any product loss due to suspected waste or compromise.

7.1.1.4. The lead research pharmacist (or designee, as determined by the PI) is responsible for ordering of study product(s). If the PI (or designee, as determined by the PI) must be notified of inventory levels, the lead research pharmacist (or designee) must do so without breaking the blind. This process will be established by the PI and lead research pharmacist (or designee) based on current and forecasted usage patterns and storage capacity.

7.1.1.5. When investigational study product is provided by a manufacturer and the supply is not covered by an agreement between the manufacturer and CCR:

7.1.1.5.1. OSRO will approve any manufacturers chosen by the pharmacy.

7.1.1.5.2. Testing and retesting plans for the time period the product will be used must be provided by the PI or the lead research pharmacist. OSRO shall approve/disapprove the plan.

7.1.2. Study Product Receipt

7.1.2.1. If needed, arrangements must be made between the product supplier and the study site to determine the most appropriate time, place, and individual to receive study product at the site. These arrangements will be agreed upon prior to shipment or delivery of study product(s).

7.1.2.2. Upon receipt of study product(s) (from the supplier or another location), the lead research pharmacist must ensure that the information on the packing slip matches what has been sent to the site and that study product(s) sent are appropriate for the trial as described in the protocol and MOP.

7.1.2.3. At a minimum, the lead research pharmacist/designee should verify the following:

- Product identification
- Date of shipment and date of receipt
- Quantity of product received
- Lot number(s)
- Unique code numbers assigned, if applicable
- Expiration dates or re-test dates, if available
- Physical product is in good condition

- Storage conditions, especially temperature control, have been maintained

7.1.2.4. The lead research pharmacist must notify the supplier of the receipt and condition of the study product(s), according to the manufacturer's specified instructions. Temperature monitoring device(s) may be included with the shipment, along with instructions for reading and returning the device(s).

7.1.2.5. The study product(s) can be placed in active inventory if it does not appear damaged or if there are no discrepancies or temperature deviations/excursions.

7.1.2.6. If there are any discrepancies discovered upon receipt of the study product(s), the supplier, OSRO PM and PI will be promptly notified by the lead research pharmacist. The notification must be dated and documented by the lead research pharmacist in the shipping records.

7.1.2.7. If there is any evidence of breakage, compromised storage or cold chain conditions (e.g., refrigerated items that are not refrigerated upon receipt), or suspicion of product tampering, OSRO PM should be notified promptly and details of the incident must be documented in the shipping records. The study product(s) must be quarantined (see *Section 8.4 Quarantine of Study Products*) and maintained under the correct storage conditions until further instructions are given.

7.1.2.8. If there are any discrepancies with the study product(s), the affected study product(s) may not be placed into active inventory or dispensed until notification is received in writing, by email, or fax, that the study product(s) may be safely used.

7.1.2.9. The following shipping and receipt documentation should be retained:

- Order forms
- Packing slips, invoices and/or receipts upon delivery from the product supplier
- Any correspondence with the product supplier relating to the condition of the product upon receipt
- Temperature recording printouts, if applicable

7.1.2.10. The date/time and condition of the study product upon arrival and before being placed into active inventory should be noted and documented in the shipping records.

7.1.2.11. Study product(s) must not be dispensed until they are properly inventoried, and the quality of the product is verified by authorized pharmacy personnel.

7.2. Study Product Accountability

7.2.1. Although the PI is responsible for ordering and accountability of all study products in his/her clinical trial, the lead research pharmacist can be delegated this responsibility when he or she accepts/receives the study product.

7.2.2. Accountability should be maintained for study products supplied for a study-specific protocol, whether they are investigational or commercially obtained. Accountability of study product must be documented from the time of initial product receipt through final disposition.

7.2.3. Depending on the protocol and with prior authorization from OSRO, for a product that is obtained from commercial sources, the requirements for that product to be dispensed without tracking accountability on a Drug Accountability Record (DAR) are as follows:

7.2.3.1. No agreement exists that covers a specific quantity or supply to be used for the protocol.

7.2.3.2. When requested by sponsor or a regulatory body, a list could be generated that details the product dispensed by participant number and notes date of dispensing and lot number.

7.2.4. Each time a study product is received from the supplier or other source, dispensed to a subject, returned, or destroyed, the occurrence must be documented on the accountability log or DAR. All entries on the accountability log must match the corresponding documentation (e.g., study product received should match the invoice or packing slip, study product dispensed should match the prescription or prescribing order for that entry). Unused supply and empty containers should be returned to the study team for documentation of the unused study product returns from subjects and its final disposition. The date and quantity of study product returned should be recorded on the DAR.

7.2.5. The study product accountability log/DAR may take the form of a continuous electronic record or a paper document.

7.2.6. If a paper document is used, all entries must be made in dark ink (blue or black indelible ink). Never use pencil to write an entry. Never use correction fluid or obliterate entries that require correction. Never destroy or re-write original comments, even if they require error correction.

7.2.7. Entries/corrections should be made consistent with Good Documentation Practices (GDP). For any change or correction to an entry or document, draw a single line through the incorrect information, initial, date, and insert the correct information. If necessary, an explanation of correction, or other relevant comment, may be written in an appropriate comment section on the form or in the page margins, clearly defining which entry the comment refers to or addresses. In addition, the original entry should not be obscured.

7.2.8. If an electronic record is used, it must have an audit trail for all entries and/or corrections and should be retrievable upon request for monitoring or auditing.

7.2.9. Information in the study product accountability log/DAR should include, but is not limited to the following:

- NIH/CCR protocol number (and local facility identification number if applicable)
- Name, dosage form, strength of the study product
- Manufacturer or other source
- Control, lot number, or other identification number

- Expiration or retest date (memo from the OSRO or noted on the protocol indicating that the expiration is centrally managed is acceptable)
- Date of receipt of the study product
- Quantity received from supplier
- Subject identification number
- Quantity dispensed as amount or dose per subject
- Date study product dispensed to subject
- Balance of study product currently available
- Disposition of drug if not dispensed to a study subject (e.g. disposed/destroyed or returned to supplier as per protocol or MOP or as directed by OSRO)

7.2.10. This log should be accessible only to the lead research pharmacist/designee, PI, study coordinator, OSRO monitors, OSRO representatives, and regulatory agency representatives. If the study is blinded, the blinding must be maintained.

7.2.11. Accountability may be performed through verification of inventory per section 7.3 and during monitoring. The inventory balance documented on the accountability log should match the actual study product inventory, on hand, at all times.

7.3. Systematic Reviews

7.3.1. Product Inventory Review

7.3.1.1. Routine inventory counts of study product inventory should be conducted monthly, at a minimum, to ensure that the physical quantity on hand corresponds to the quantities recorded on the DAR. These procedures should include a cross-check of quantity on hand with the amounts recorded on the DAR, dispensing or preparation dates, expiration dates/retest dates, and lot numbers. The inventory balance documented on the accountability log should match the actual physical inventory, on hand, at all times.

7.3.1.1.1. More frequent reviews may be indicated (i.e., running balance) at a frequency concurrent with dispensing and storage indications.

7.3.1.2. If there are discrepancies between the accountability records and the physical quantity on hand, the lead research pharmacist must attempt to reconcile them. The attempt to reconcile discrepancies must be documented.

7.3.1.3. If the attempt to reconcile a discrepancy is unsuccessful, the actions attempted by the lead research pharmacist must be documented on the accountability records and the OSRO PM and PI for the protocol must be notified immediately by the lead research pharmacist. If the study is blinded, the blinding must be maintained.

7.3.2. Product Expiration Review

7.3.2.1. The lead research pharmacist should establish written procedures for the process of study product expiration date/retest date review, including when non-routine reviews may be required.

7.3.2.2. Expiration/retest dates should be made clear in the available documentation.

7.3.2.3. A routine review of study product expiration/retest dates should be conducted.

7.3.2.4. Expiration review must be conducted quarterly.

7.3.2.5. Expired products must be separated from active study products and placed in quarantine (see *Section 8.4 Quarantine of Study Products*) until they are reconciled and, upon receipt of written authorization, destroyed on site or returned to the supplier. Instructions regarding storage of expired study product(s), such as whether storage conditions need to be maintained, will be provided by OSRO. If there are any questions, OSRO PM and PI should be contacted.

7.3.2.6. Before dispensation of study product, the lead research pharmacist must review the expiration/retest date information provided for the study product. If applicable, the lead research pharmacist must also ensure that the study product dispensed will not reach the expiration date before the subject's next collect visit.

7.4. Study Product Disposition

7.4.1. Unused study product (e.g., expired study product, unexpired study product upon completion of the study) will be destroyed or returned to the product supplier, unless otherwise specified in the protocol or MOP. Study product designated for destruction or return must be separated from active study products and placed in quarantine (see *Section 8.4 Quarantine of Study Products*) until they are reconciled and then destroyed on site or returned to the supplier upon written authorization of final disposition.

7.4.2. Site must have destruction SOP which will be reviewed and approved by OSRO prior to authorization to destroy study product. If approved by the sponsor, study product should be destroyed per the institutional policy.

7.4.3. The method and timing of study product disposition is at the discretion of OSRO. The arrangements may be outlined in a protocol, in a MOP or conveyed in a written document from OSRO.

7.4.4. Accountability records will be monitored before authorization of final disposition.

7.4.5. The lead research pharmacist must provide written documentation of study product disposition on the accountability records, either before or at study completion (as applicable to the protocol).

7.4.6. After study completion, study product must not remain at the site unless authorized by OSRO.

7.4.7. The following information should be included for record keeping:

- Name of PI and contact information
- Total quantity
- Information specific to the drug including but not limited to the drug name, strength, dosage form, quantity of drug per container, quantity of containers, manufacturer, and lot/control number.

- Method and date(s) of final disposition
- Name and signature of personnel responsible for destruction if destroyed on site.

7.4.8. Study Product Return

7.4.8.1. Reasons for which study products may be returned include, but are not limited to, the following:

- The clinical protocol has been completed or terminated at a site;
- The study product was damaged when received at the pharmacy/ clinical research site;
- The study product has been stored improperly and can no longer be used safely;
- The study product has expired;
- Return of the study product has been requested by the supplier; or
- The manufacturer or sponsor has recalled the study product.

7.4.8.2. A study product recall system must be in place for the identification, retrieval, quarantine, and return of recalled study products. The lead research pharmacist must respond immediately to recall notices and return study agent as directed by OSRO.

7.4.8.3. If there are additional instructions regarding return of study product, those instructions must be specified in a protocol-specific document(s) or be conveyed by OSRO.

7.4.9. On-site Destruction

7.4.9.1. OSRO will provide written authorization for the destruction of study products. The study products to be destroyed must be quarantined in a separate area from the active stock.

7.4.9.2. Destruction should follow instructions in the protocol and MOP. If instructions are not provided in the protocol and MOP, the site should defer to their institutional policies and procedures for destruction of study product. Any applicable medical waste standards must be strictly adhered to.

7.4.9.3. Destruction of study product must be documented in the accountability log. OSRO and/or the supplier may request a copy of this documentation.

8. Storage of Study Product

The PI or designated lead research pharmacist is responsible for the storage of study product(s) in the research pharmacy, ensuring that the proper storage conditions are maintained, and that documentation is adequate. Study product(s) should be stored appropriately, including segregation in a secure location and under controlled storage conditions as specified in the protocol, MOP or by the manufacturer and in accordance with applicable regulatory requirements. Refer to ICH E6(R2) GCP section 4.6.4 (Reference 16.6) for additional information.

8.1. Space, Security, and Segregation

8.1.1. Space

8.1.1.1. Upon receipt, all study products supplied for a specific protocol must be stored in the research pharmacy (see definition for *research pharmacy*).

8.1.1.2. Adequate pharmacy space, facilities, equipment, and supplies for storage, preparation, packaging, and dispensing of study products must be assessed prior to receiving study product(s) at the site to guarantee appropriate storage, ensuring protection from vermin, extreme temperature, and humidity.

8.1.1.2.1. The research pharmacy facilities must be in compliance with all local laws and regulations and be of adequate size, organization, and ample lighting. Hand washing and cleaning facilities must be available for cleaning purposes and work spaces should be adequate for the preparation of study products, study product accountability, and record management.

8.1.1.2.2. Study product(s) requiring special storage, handling, or preparation (for example, hazardous drugs, non-standard temperature requirements, protection from light, sterile or aseptic conditions) should be identified and availability of space and equipment for storage should be determined by the lead research pharmacist prior to receiving study product(s) at the site.

8.1.2. Security

8.1.2.1. Study products and supplies must be kept under the custody of the lead research pharmacist/designee until dispensed for the subject or upon final disposition.

8.1.2.2. The storage area for study products and supplies must have limited and secured access and must be locked when not in use.

8.1.2.3. Access to study product is limited to essential and authorized personnel only with approved access to the research pharmacy, such as the designated lead research pharmacist or his/her designee.

8.1.2.4. Systems must be in place to prevent unauthorized entry and unauthorized access to study products and for identifying and alerting staff when proper security conditions have been compromised.

8.1.2.4.1. If security has been compromised, the PI and OSRO must be notified. This breach of security, along with additional correspondences, must be documented.

8.1.3. Segregation

8.1.3.1. Study products should be segregated from non-study products; study products for different protocols should be segregated.

8.1.3.2. For blinded studies, the active study product must not be stored alongside the placebo agent, unless packaged together (e.g., kits); there must be a clear separation between the active and placebo study products.

8.1.3.3. Product that is designated for return or destruction must be segregated from active stock and placed in quarantine until final disposition.

8.2. Temperature and Environmental Control

8.2.1. Sites must address proper storage conditions such as temperature, light, moisture, ventilation, and sanitation during the protocol planning stages.

8.2.2. Temperature and environmental storage for study product(s) is protocol specific. Detailed instructions regarding appropriate conditions are described in the product package insert, the IB, the protocol, and/or MOP.

8.2.3. Temperature and environmental control must be maintained from the time of study product receipt until dispensation to the subject or is deemed no longer usable, unless otherwise specified in the protocol or by the manufacturer.

8.2.4. OSRO uses the temperature ranges in whole numbers as specified in the USP (see Glossary of Terms for *USP Storage Conditions Definitions*). As such, any temperature recording requiring the OSRO PM assessment should be rounded to the nearest whole number.

8.2.5. Temperature logs must be maintained for areas of study product storage (e.g., chart recorders). Continuous temperature monitoring and recording devices are required and must provide real-time and min/max temperature information for the designated study product storage area in which the system is installed. The device must monitor and record temperatures at frequent programmed time intervals for 24-hour temperature monitoring and should be set at a minimum of every 15 minutes. The temperature data from the device must be printed or, if electronic, downloaded and saved to a computer file, and reviewed at least weekly. Documentation of this review must be noted on the hard copy data printout (i.e., date and initial) or electronic computer file (i.e., electronic time-stamp and signature) and filed in the pharmacy files. Electronic temperature logs are strongly recommended.

8.2.6. In addition, a back-up temperature monitoring device (e.g., a minimum/maximum thermometer) is required for each study product storage area, serving as a back-up to the existing primary continuous temperature monitoring device.

8.2.7. In the event of a temperature excursion, for the purposes of the evaluation of appropriate temperature storage, the temperature readings from the primary continuous temperature monitoring device will be used to make the final determination. The manually documented temperature readings from the back-up device will only be used to determine temperature storage conditions if the primary continuous temperature monitoring device fails or if its data is unavailable.

8.2.8. All study product storage areas and equipment must have an alarm system to notify authorized personnel, 24 hours a day, 7 days a week, 365 days a year, of any temperature

deviation/excursion from the acceptable temperature range so that the lead research pharmacist may take immediate action to prevent loss of study product. Alarm settings within 0.5°C of the product storage temperature specifications are suggested to alert the lead research pharmacist of a potential excursion and to ensure that immediate corrective action can be taken prior to product exposure to temperatures outside of acceptable storage specifications.

8.2.9. Each site must have systems in place and SOPs defining responsibilities and procedures for the following:

8.2.9.1. To ensure proper storage conditions are continuously met.

8.2.9.2. To prevent or limit storage conditions from being compromised during emergency situations, such as a power failure or equipment malfunction (i.e. back-up power source and/or alternative storage arrangements).

8.2.9.3. To alert staff when temperature excursions have occurred and take corrective action. The PI and sponsor will be notified of a temperature excursion on the day it is discovered (or the next business day in the case of weekends, holidays or evenings).

8.2.10. Study product(s) must not be stored with food, specimens or any other products that may contaminate or compromise the quality of the study product.

8.2.11. If storage conditions have been compromised (i.e., temperature deviates from the allowable range) or if there is any suspicion that study product(s) has not been stored properly, the following actions must be taken:

8.2.11.1. Refer to the protocol and MOP for storage instructions and notifications.

8.2.11.2. Quarantine the study product(s) at the correct storage temperature (see *Section 8.4 Quarantine of Study Products*).

8.2.11.3. Immediately notify OSRO PM and PI and submit the OSRO Temperature Excursion Report Form, providing the protocol number, protocol name, study product description, lot number, date and time of discovery, temperature outside of the appropriate range at which study product was exposed, and cumulative duration of time out-of-range.

8.2.11.4. Document the incident, including a description of the circumstances surrounding the event with follow-up and/or corrective measures.

8.3. Storage Equipment

8.3.1. Appropriate storage equipment must be used, as applicable, in order to maintain the necessary environmental storage conditions for study products as required per the protocol or manufacturer's instructions. Examples of storage equipment that may be needed include:

- Refrigerators
- -20°C freezers

- -70°C freezers
- Temperature monitoring and recording devices
- Temperature alarming systems
- Air conditioning units
- Back-up power generators
- Back-up temperature systems to maintain specified environmental conditions

8.3.2. Storage equipment must be qualified, maintained and calibrated according to the manufacturer's specifications for optimal quality and use; maintenance and calibration must be documented.

8.3.3. OSRO does not recommend the use of household refrigerators and freezers since the temperature control may be variable.

8.3.4. OSRO does not recommend the use of self-defrosting freezers since the temperature may cycle on a routine basis.

8.3.5. If the site cannot maintain a consistent and reliable source of power, a back-up power generator should be used. Unless otherwise specified by manufacturer specifications, the back-up generator should be tested quarterly and should receive maintenance at least annually. Documentation of testing and maintenance should also be recorded and maintained. Back-up generators should be of a sufficient capacity to run continuously for 72 hours if necessary. In addition, plans should be made to ensure that an adequate supply of fuel is on hand. All equipment supporting pharmacy operations should be supported by a back-up power source.

8.3.6. The site should have an emergency plan in place for equipment failure or prolonged power failure. This plan should meet all storage, security, access, equipment and monitoring guidelines as stated in this manual.

8.4. Quarantine of Study Products

8.4.1. If the following situations occur, study products should be quarantined:

- Proper storage conditions have not been maintained
- There is evidence of product tampering or breakage
- Product is damaged, defected, recalled, or expired
- OSRO has requested that the product be quarantined

8.4.2. Quarantined product(s) must be:

- Physically segregated from study products that are still in use
- Maintained at the correct temperature unless OSRO has provided alternate instructions
- Clearly labeled that they are quarantined and must not be used

8.4.3. Quarantined products must not be used, destroyed, or returned until written permission is granted by OSRO PM.

9. Study Product Transport and Delivery

Study products must be maintained properly during transport from one location to another. This includes ensuring that control of the study product and environmental conditions have been maintained during transport. The protocol and/or MOP usually includes specific instructions for the handling and transport of products.

9.1. Control of Study Product during Transport

9.1.1. When study products are transported from one location to another whether within the institution or to a sub-site, an SOP addressing all steps in study product transport, including the method maintaining control of study product, should be in place.

9.1.2. Study products should remain in the custody of authorized personnel at all times during transport.

9.1.3. When study products are transported from one institution to other sites, the authorized personnel engaged in the transaction should be documented on the transport record, as applicable.

9.1.3.1. Transport of study products must remain in the receiving institution's immediate control. Unless permitted by OSRO PM, study products must not be re-shipped by mail or third-party delivery services to another institution, site, or study subject.

9.1.4. In general, the documentation for study product transport should include, but is not limited to the following:

- Protocol number
- Investigator's name
- Name and/or site number of the transferring site
- Name of courier or study staff who will transport study products
- Name and/or site number of recipient
- Name, lot number, individually labeled kit number (if applicable), and amount of contents being transported
- Date and time study product prepared (if applicable)
- Date and time study product dispensed
- Date and time study product received
- Subject name, medical record number, and/or subject identifier

9.1.5. Pneumatic tube systems must not be used.

9.2. Environmental Conditions during Transport

9.2.1. Requirements for maintaining environmental conditions should be identified prior to study product transport and included in the MOP or an SOP.

9.2.2. In addition to written site-specific processes and procedures, the site SOP should specify study product chain of custody at all times during transport, delivered directly to the off-site location,

and promptly unpacked and placed into appropriate storage units upon arrival. If transporting study product will require the use of a non-commercial vehicle, the passenger compartment must be used. Study product must not be placed in the trunk of the vehicle.

9.2.3. Cold chain should be maintained during the transport. The number of times study product is handled and transported must be kept to a minimum. The appropriate temperature conditions must be maintained during transport, which may require the use of appropriate packaging materials, conditioned coolant packs, transport containers, and calibrated thermometers or temperature recording devices to document the temperature during transport.

9.2.4. Study product(s) should be packaged in containers with packaging materials designed to maintain the proper storage conditions during transport as per the protocol/MOP or SOP and to protect the study product from damage, leakage, contamination, and degradation.

9.2.5. If refrigerated study product requires transport or if frozen study product may be transported at refrigerated temperatures, OSRO recommends transport with the use of portable refrigerator units. Hard-sided insulated coolers with at least 2-inch walls or validated insulated shipping containers may be used if they can maintain the recommended temperature range (2°C and 8°C (36°F and 46°F)).

9.2.6. If frozen study product requires transport, OSRO recommends transport with portable freezer units.

9.2.7. Cold chain or other specified environmental conditions must be maintained at the recipient site.

9.2.8. If study product must be kept in a transport container at an off-site location, then

- The container must remain closed as much as possible,
- Only the required product should be removed for administration,
- The calibrated thermometer(s) (preferably with a biosafe glycol-encased thermometer probe) should be placed as close as possible to the study product,
- The temperature(s) inside the container(s) should be read and documented at least hourly,
- To minimize the exposure of the study product to external environmental conditions whenreading and documenting temperature(s) inside the container, the use of a digital thermometer with temperature display and external, detachable temperature probe is recommended.

9.2.9. For study products requiring room temperature storage, if transport of the product occurs within a temperature-controlled environment (such as within a building or temperature-controlled vehicle), temperature monitoring is not required. If transport of product occurs outside of a temperature-controlled environment, temperature monitoring is recommended. If environmental temperatures exceeding 40°C (104°F) are anticipated during transport, temperature monitoring and documentation are strongly recommended.

9.2.10. If the site cannot ensure that study products are transported under appropriate cold chain management or maintained under appropriate storage conditions upon arrival, then transport of study product must not occur.

10. Preparation, Dispensation and Administration

The lead research pharmacist is responsible for ensuring that the policies and regulations within their jurisdiction are followed when preparing and dispensing study product. This includes following requirements as they pertain to prescriptions, medication prescribing orders and labeling. In addition, instructions specific to a trial or about a study product must be followed. Therefore, it is important that the lead research pharmacist and PI have a system in place that ensures that the lead research pharmacist is provided the most updated essential information for preparation and dispensation of study product in a trial.

10.1. Prescriptions or Medication Prescribing Orders

For protocols that require a prescription or medication prescribing order prior to the dispensing of study product, the following requirements or elements must be included or considered:

10.1.1. By signing the Form FDA 1572 or IOR Form, the PI has certified that the study product will be administered only to subjects under his/her personal supervision or under the supervision of sub-investigators responsible to him/her.

10.1.2. The lead research pharmacist must receive a protocol-specific prescription, either a hand-written or an electronic order, signed by an authorized prescriber prior to dispensing study product. Verbal orders will not be considered valid.

10.1.3. Hand-written prescriptions must be handwritten with dark ink (blue or black indelible ink) ortyped.

10.1.4. Signatures on the prescriptions are to be handwritten or electronically signed. Signature stamps are not permitted.

10.1.5. Signing blank prescriptions or prescribing order forms is not permitted.

10.1.6. An unauthorized prescriber is not permitted to sign a prescription or prescribing order with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, study staff may not sign a physician's name to a prescription and then add her/his name to it if s/he is not an authorized prescriber.

10.1.7. Post-dated prescriptions or prescribing orders are not permitted. For example, it is not acceptable for a prescription written in January to have a February date.

10.1.8. An authorized prescriber must sign the prescription or prescribing order before sending it to the research pharmacy.

10.1.9. Study staff may prepare electronical or hand-written prescriptions in advance for an authorized prescriber to review and sign; however, study product will not be dispensed in advance of receiving a valid order by the research pharmacy.

10.1.10. The authorized prescriber is responsible for ensuring that the prescription or prescribing order is written in accordance with all essential aspects of the protocol and local laws and regulations.

10.1.11. Refills are not allowed. Each dispensation of study product requires an original prescription or prescribing order.

10.1.12. Prescriptions or prescribing orders should include, but are not limited to the following:

- Subject name (or initials)
- Protocol number
- Subject identifier
- Randomization number or treatment assignment (for blinded studies, blinding must be maintained)
- Study Product prescribed - name, dose, strength, formulation, route, or for blinded studies a protocol specific randomization code (if applicable)
- Quantity or instructions to indicate amount to be dispensed
- Body Surface Area (BSA) calculation or height and weight of subject (if applicable or required per protocol)
- Directions for use
- Authorized Prescriber's signature
- Date prescription is signed by an authorized prescriber
- Any special instructions (i.e., dose reduction, dose escalation)

10.2. Study Product Preparation

10.2.1. Space and Equipment for Preparation

10.2.1.1. Appropriate space and equipment must be provided and used for study product preparation as per section 8.1.

10.2.1.2. The lead research pharmacist must ensure that there is sufficient stock of ancillary supplies for preparing and dispensing study products.

10.2.1.3. Certain study products may require preparation using aseptic technique, using a biological safety cabinet (BSC), aseptic isolator, or laminar air flow hood. Specific requirements will be included in the protocol or MOPs and must be reviewed for site equipment needs or training prior to receipt of study product.

10.2.1.4. Every laminar air flow hood, BSC, and isolator must be maintained and evaluated for proper performance, in accordance with the manufacturer's instructions.

10.2.2. Personnel Involved in Preparation

10.2.2.1. OSRO requires that compounding of study product must be performed by or under the direct personal supervision of a licensed pharmacist (i.e., lead research pharmacist) and must be dispensed by a licensed pharmacist.

- Compounding is defined as the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription or medication order.
- Examples of compounding include, but are not limited to, reformulation of a drug, preparation of an intravenous admixture, manipulation of commercial products that may require the addition of one or more ingredients, or making a preparation that requires special calculations or procedures (such as calibration of dosage unit mold cavities) to determine quantities of components per preparation or per individualized dosage units.

10.2.2.2. In certain instances, due to site-specific logistics or study product-specific characteristics (e.g., limited stability of product relative to distance of clinic), other authorized health care practitioners may be called upon for dose preparation of study product immediately prior to administration to a subject.

10.2.2.2.1. In these limited cases, the lead research pharmacist/designee must prepare, label, and dispense the study product, so that the prescribed dose may be obtained and administered by the authorized healthcare practitioner in accordance with the protocol or MOP.

10.2.2.2.2. It is the responsibility of the PI to ensure all local jurisdiction and state laws or regulations comply with the procedures performed at the clinical site.

10.2.2.2.3. The lead research pharmacist/designee must provide detailed instructions and training for the dose preparation to the authorized healthcare practitioner and documentation of this training should be maintained in the site pharmacy files. In addition, SOPs to address site-specific processes, procedures, and preparation documentation must be developed.

10.2.2.3. For CCR sponsored protocols, where a study product requires only a single level or one step of non-compounding manipulation (e.g., simple reconstitution of lyophilized vaccine, thawing of frozen product for immediate administration), an authorized health care practitioner may be called upon to prepare study product immediately prior to administration to a subject.

10.2.2.3.1. In these instances, the lead research pharmacist/designee must first label and dispense the study product to the authorized health care practitioner. The study product may then be prepared by the authorized healthcare practitioner in accordance with the protocol or MOP.

10.2.2.3.2. It is the responsibility of the PI to ensure all local jurisdiction and state laws or regulations comply with the procedures performed at the clinical site.

10.2.2.3.3. The lead research pharmacist/designee must provide detailed instructions and training for study product preparation to the authorized health care practitioner and documentation of this training should be maintained in the site pharmacy files. In addition, SOPs to address site-specific processes, procedures, and preparation documentation must be developed. These may take the form of Drug Fact Sheets, SWU or Helper Pages. Order sets shall be prepared by lead research pharmacist or designee.

10.2.2.4. Names of any personnel or authorized health care practitioners aiding in the preparation of a study product must be documented.

10.2.3. Preparation Procedures

10.2.3.1. Products requiring reconstitution, dilution, or mixing under conditions defined in the protocol or MOP should be prepared in compliance with local and state requirements, and institutional procedures.

10.2.3.2. Preparation instructions for study products are outlined in the protocol and in additional accompanying documents, such as a MOP document and F01-501-S07 CCR/OSRO Sponsor Investigational Product Preparation Form.

10.2.3.3. The lead research pharmacist/designee must document that study products were prepared correctly. This includes documenting all products used or added during preparation, amounts that are added or removed from the final product, temperature ranges and critical time points maintained, as applicable.

10.2.3.4. If applicable, a separate compounding form may be used to document the preparation procedure.

10.2.3.5. Preparation review and verification by the lead research pharmacist/designee must be documented with the lead research pharmacist's initials prior to dispensation.

10.2.3.6. Any issues or errors with product preparation, including improper mixing, treatment assignment errors, etc. should be immediately reported to the PI and OSRO PM, as directed by the protocol or MOP. If an issue or error occurs in a blinded study, the lead research pharmacist must maintain blinding during discussions with the investigator or other individuals who may be blinded to treatment assignment (see *Section 11 Maintenance of Study Blind*).

10.3. Labeling Requirements

10.3.1. Labeling must comply with local regulations and requirements.

10.3.2. If the drug is further manipulated (e.g., use of mixing vials or drawn into syringes), the protocol or MOP must be followed for additional labeling instructions.

10.3.3. If applicable, study products should be labeled in a manner that maintains the study blind.

10.3.4. Additional label requirement: The IND or IDE caution statement on the label of the product should be in a language understood by any staff preparing or dispensing study product.

10.4. Study Product Administration

10.4.1. Study product(s) must be administered by qualified individuals based on experience, training, education and licensure/registration/certification (as applicable).

10.4.2. At a minimum, the following should be verified before the study product(s) is administered:

- Subject identification and enrollment into the study
- Subject signed informed consent for the current version of the protocol
- Study product identification (including name and/or unique code number assigned, if applicable) is correct based on treatment assignment
- Dose of study product
- Volume of study product
- Route of administration
- Product appears to be in good condition based on physical inspection (for example, there is no visible particulate matter or discoloration)
- Proper storage conditions
- Expiration date if provided

10.4.3. Unused study product returned by a trial subject must never be redispensed to another subject. Receipt of the returned study product must be documented on the appropriate accountability log and stored in quarantine separate from active study product inventory. Disposition shall follow instructions in the protocol or directions from sponsor.

11. Maintenance of Study Blind

Blinded trials require special provisions to be made in order to maintain blinding of subjects and study personnel, as applicable. Such provisions may include but are not limited to masking the product, specialized labeling of the study product and careful custody of blinded materials, such as treatment assignment codes. There are some studies where blinding is required but because of preparation appearance or administration, some staff must be unblinded. When unblinded study personnel are used, a plan or SOP should be in place that articulates the steps to be followed to prevent possible unblinding to others.

11.1. Blinding and Masking Considerations

11.1.1. Study products provided to and handled by blinded personnel must be labeled in a manner that does not reveal the treatment assignment.

11.1.2. Unblinded personnel must:

11.1.2.1. Prevent inadvertent unblinding when communicating with blinded members of the study team.

11.1.2.2. Not be engaged in blinded study activities, such as protocol-related assessments.

11.1.2.3. Maintain assignment lists in a secure location and unavailable to blinded study personnel.

11.2. Unblinding Procedures

11.2.1. The need for unblinding is very rare and should not be exercised except in extreme cases.

11.2.2. A procedure for unblinding the treatment assignment in an emergency, should be agreed upon by OSRO and the PI, and be described in either the protocol, MOP or a separate SOP.

11.2.3. The PI is responsible for documenting any approved or unapproved unblinding in the study file. OSRO must be notified by the PI that unblinding occurred, but OSRO should still remain blinded. The report should not include the study treatment assignment; however, the following should be included:

- The protocol name and number
- The subject identification number
- Date and time that unblinding occurred
- Names of study personnel who were unblinded
- Reason(s) for unblinding

11.2.4. In general, the IRB should be notified when unblinding has occurred.

11.2.5. If unblinding occurs, every effort should be made to minimize the number of persons at the site who are informed of the treatment assignment.

11.2.6. The lead research pharmacist/designee must confirm that the PI and/or study coordinator are aware that the blinded treatment assignment code is broken.

12. Record Keeping Responsibilities

Documents, logs and records pertaining to study product(s) should remain in the research pharmacy. These documents may be protocol-specific or general to research pharmacy operations. Refer to ICH E6(R2) GCP section 4.6.3 (Reference 16.6) for additional information.

12.1. Study Product Documentation

12.1.1. Study product records should include, but are not limited to, the following:

- Shipping and receipt
- Study product accountability/dispensation
- Storage temperature logs
- Study product transport
- Preparation and compounding
- Expiration/ Retest date (when applicable)
- Study product disposition
- Randomization/treatment assignment

- IB (current and earlier versions) for non-marketed products or package insert for marketed products
- Training documentation
- Pharmacy SOPs
- Orders for study product and/or adjunct products
- Signature log/delegation of duties roster
- Device Manuals

12.2. Record Retention

12.2.1. Record maintenance for study products (e.g., drugs, biologics, devices, therapeutics) by the research pharmacy must comply with U.S. federal and local regulations and institutional policies as well as any protocol-specific requirements. The strictest requirement applies.

12.2.2. For investigational trials requiring an IND/IDE or for those investigational studies that are conducted with FDA-regulated products, records will be retained as such:

12.2.2.1. A period of at least 2 years following the date that a marketing application is approved for the indication for which it is being investigated.

12.2.2.2. A period of 2 years following the date that the investigation is discontinued and the FDA notified, if a pre-market approval or a marketing application (licensure) is not being filed.

12.2.3. Records must not be destroyed until approval by OSRO has been granted.

13. Quality Management and Monitoring

Quality management and monitoring are two methods in which sites and OSRO may verify that appropriate management of the study product has been maintained.

13.1. Quality Management

Quality management is a collective term that includes quality control and quality assurance. These principles can be applied to review and verify that aspects of study product management are correct and complete.

- A systematic process for quality management and problem solving activities should be implemented to internally review and evaluate the quality and appropriateness of the research pharmacy service.
- Aspects reviewed may include study product storage, control, accountability, dispensing, and disposal.
- When problems are identified, the actions that are taken to resolve the problems should be appropriately documented and reported.

13.1.1. Quality Control

Quality control encompasses real-time observations and documentation to ensure correctness and completeness.

13.1.1.1. The lead research pharmacist/designee must ensure that the day-to-day activities of study product management are conducted correctly and accurately; and

13.1.1.2. Quality control should be exercised upon preparation and dispensation.

13.1.2. Quality Assurance

Quality assurance describes a more periodic and systematic examination to verify correctness and completeness.

13.1.2.1. At a minimum, the lead research pharmacist should conduct an audit quarterly to ensure compliance with regulations, policies and standards.

13.1.2.2. In addition to periodically monitoring for quality assurance in the research pharmacy, the lead research pharmacist should also audit and review for quality assurance activities in the clinic, if applicable.

13.1.2.3. Notify OSRO PM and PI of any missing study products, incorrect dosing, incorrect storage, or any other issues that could impact the study or safety.

13.2. Clinical Monitoring/Auditing Visits

13.2.1. The Principal Investigator or lead research pharmacist must make arrangements for clinical site monitoring/auditing visit(s) in advance, including availability of personnel who will meet the clinical site monitor/auditor and accommodations for the clinical site monitor/auditor.

13.2.2. Appropriate space must be provided for the clinical monitor/auditor to conduct his/her activities.

13.2.3. The number of clinical site monitoring visits to the research pharmacy are at the discretion of OSRO.

13.2.4. Clinical site monitoring visits may focus on the site operations of the research pharmacy, the conduct of a specific protocol, to observe storage conditions, or review pharmacy records such as temperature logs or accountability records.

13.2.5. All protocol records must be available for inspection and copied by an authorized employee or representative of the sponsor upon request.

14. Protocol Non-Adherence

Protocol non-adherence is defined as any noncompliance with the clinical trial protocol, GCP, or protocol-specific procedural requirements or MOP on the part of the participant, the PI, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial. It is the responsibility of the PI and lead research pharmacist to use continuous vigilance to identify and report protocol non-adherence related to study product.

14.1. Research Pharmacy-Related Non-Adherence

The following is a list of examples of protocol deviations that may be related to the research pharmacy. This list is intended as a guide and is not all-inclusive.

14.1.1. Storage, Handling and Accountability Non-Adherence

- Improper storage of study products including excursions in temperature, moisture, light, etc.
- Incorrect compounding procedure
- Unauthorized use or access to study product
- Unresolved or non-reconciled accountability discrepancies

14.1.2. Dispensing Errors

- Failure to comply with any dispensing or dosing requirements (e.g., failure to comply with dose adjustments per the protocol)
- Dispensation of incorrect, improperly stored, or expired study product
- Use of commercial inventory instead of study inventory
- Study product dispensed or administered to incorrect subject
- Study product preparation or dosing errors

14.2. Protocol Deviation Reporting

14.2.1. Refer to the protocol, MOP and/or OSRO SOP Clinical Protocol Non-Adherence System (Reference 16.14) for specific instructions regarding reporting of protocol deviations and non-adherence.

14.2.2. Protocol deviations must be reported to the local IRB per their guidelines.

14.2.3. Reports of protocol deviations and non-adherence must be maintained in the site regulatory file and in the subject research record/source documentation record.

15. Additional Considerations/Responsibilities

15.1. Lead Research Pharmacist Coverage

15.1.1. Lead pharmacist or designee should be available at all times for study product preparation and dispensing.

15.1.2. If the primary lead research pharmacist for a trial is absent, an alternate pharmacist must be available who can perform the functions related to study product management for that trial (see definition for *alternate pharmacist*).

15.1.3. The alternate pharmacist must be trained in the requirements of clinical trials by the lead research pharmacist to perform activities including, but not limited to, the following: study product receipt and inventory, storage, preparation, dispensing, accountability, and record keeping. The training must be documented.

16. References

16.1. CFR Title 21 Part 312: Investigational New Drug Application

16.2. CFR Title 21 Chapter 9 Subchapter V Part A Section 353a: Pharmacy compounding

16.3. CFR Title 21 Part 812: Investigational Device Exemptions

16.4. CFR Title 45 Part 46: Protection of Human Subjects

16.5. CFR Title 21 Part 50: Protection of Human Subjects

16.6. International Council for Harmonization (ICH) Efficacy Guidelines

16.7. ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry (FDA), March 2018

16.8. USP-NF General Chapter <659> Packaging and Storage Requirements

16.9. USP-NF General Chapter <795> Pharmaceutical Compounding-Non-sterile Preparations

16.10. USP-NF General Chapter <797> Pharmaceutical Compounding-Sterile Preparations

16.11. USP-NF General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings

16.12. USP-NF General Chapter <1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products

16.13. Centers for Disease Control and Prevention (CDC): Vaccine Storage and Handling Toolkit (September 2021)

16.14. 104-S02 Clinical Protocol Non-Adherence System (OSRO SOP)

16.15. F01-104-S02 Site Protocol Non-Adherence Log (OSRO Form)

17. Change Summary

Revision Number	Effective Date	Description of Change
1	09NOV2020	New Document
2	25MAR2022	General updates to grammar Section 3. Abbreviations – Added DAR Drug Accountability Record. Step 4.8. Added Drug Accountability Record (DAR) definition. Step 4.27. Added Sponsor Investigational Product Preparation Form. Step 7.2.3. Added Step 7.2.5 and 7.2.9. Added DAR Step 10.2.3.2. Added “and the Sponsor Investigational Product Preparation Form” Section 16. Updated references and hyperlinks

Revision Number	Effective Date	Description of Change
3	10MAY2023	General updates to grammar and process Step 7.4.2. Added site destruction SOP must be approved prior to destroying study product Step 8.2.11.3. Added the Temperature Excursion Report Form Steps 9.1.3 and 9.1.4. Added guidance on transport of study product Step 10.1.11. Added guidance on study product refills