DMID Guidelines for Clinical Investigational Product Management

v2.0, 25Feb2026

Division of Microbiology and Infectious Diseases

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Table 1 Change Summary

Version Number	Date of Revision	Replaces
v2.0	25Feb2026	v1.0
Description of Revision/Retirement		
Removed DMID Signature Approvals for current DMID ORA Director and Pharmacists, page 2. Change Summary revised to Table 1 and populated with changes. Table of Contents, Updated. List of Tables, Updated. List of Abbreviations, Revised to Table 2. Glossary of Terms, Revised to Table 3 with no name or content changes. Revised, globally, “study” product to “investigational” product, except for instances regarding SPMP. United States Pharmacopeia/National Formulary (USP/NF) Storage Conditions Definitions updated to Table 4, Investigational Product Storage Conditions and Temperature Definitions, with current USP content and added a USP reference to General Chapter <659> PACKAGING AND STORAGE REQUIREMENTS. Section 1.1, Updated “DMID” to “the DMID” globally where applicable; made minor text clarifications. Section 1.2, Made minor text clarification. Section 1.3.1, Removed DMID PST phone number, updated CMS phone number, made minor text clarifications, moved to new section 1.4. Section 3.1, Made minor text clarifications. Section 3.2, Updated accountability and retention for used investigational product containers. Section 3.3, Updated expired product storage instructions and moved to section 3.3.2. Section 3.4, Updated Unused investigational product instructions; made minor text clarifications. Sections 4.1.1 and 4.1.2, Made minor text clarifications. Section 4.2, Clarified temperature range information. Section 4.3, Moved storage equipment to new section 4.8 and updated section 4.3 to Continuous Temperature Monitoring and Recording. Section 4.4, Moved Quarantine of Investigational Products to new section 4.11 and replaced with Daily Back-up Manual or Electronic Temperature Monitoring and Daily Temperature Log. Section 4.5, Added new section for Temperature Deviations/Excursions Notification or Alarm System. Section 4.6, Added new section for Temperature Deviations/Excursions Reporting and Quarantine.		

Section 4.7, Added new section Controlled Room Temperature Excursions.

Section 4.8, Moved Storage Equipment from section 4.3 and updated; moved Maintenance of Equipment to new section 4.9; moved Back-up Power Supply/Generator to new section 4.10.

Section 4.9, Moved Maintenance of Equipment from section 4.4 and updated.

Section 4.10, Added new section for Back-Up Power Supply/Generator.

Section 4.11, Moved Quarantine of Investigational Products from section 4.4.

Section 6.3, Updated labeling requirements information.

Section 8.2, Moved Record Retention to new section 8.3; Created new section 8.2 for Study Product Management Plan (SPMP) Documents.

Section 8.2.1, Created new section Study Product Management Plan (SPMP).

Section 8.2.2, Created new section Study Product Management Plan (SPMP) Modules.

Section 9, Deleted Quality Management section.

Section 10, Deleted Protocol Deviations section; Moved prior section 11 Additional Considerations/Responsibilities to section 9; section 10 is References.

Section 11, References, moved to section 10; added new references for 10.1 Code of Federal Regulations Title 21 Part 50; 10.14 CDC Vaccine Storage and Handling Toolkit, 10.15 DMID PST Temperature Excursion Reporting Form; and 10.16 FDA Guidance: Standardization of Data and Documentation Practices for Product Tracing Guidance for Industry; updated hyperlinks.

Section 12, Availability, moved to section 11.

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Table 2 List of Abbreviations

CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMS	Clinical Materials Services
CPM	Clinical Project Manager
DHHS	Department of Health and Human Services
DMID	Division of Microbiology of Infectious Diseases, NIAID, NIH, DHHS
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Documentation Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
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
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
PI	Principal Investigator
PPI	Product Package Insert
PST	Product Support Team
SOP	Standard Operating Procedures
SPMP	Study Product Management Plan
USP	United States Pharmacopeia

Table 3 Glossary of Terms

Alternate Pharmacist:	A licensed/registered pharmacist who performs the day-to-day pharmacy activities and investigational product management for the DMID-sponsored clinical trial(s) when the Research Pharmacist is absent.
Authorized Prescriber:	Responsible for ensuring that a prescription is written in accordance with all essential aspects and requirements of the protocol and local laws and regulations. The authorized prescriber is listed on the current FDA Form 1572 (IND studies) or authorized prescribers list (non-IND studies) for a given protocol at the participating site.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).
Chain of Custody:	A chronological documentation of an unbroken trail of accountability of authorized study personnel accepting and relinquishing possession of the investigational product.
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 Conference of Harmonization (ICH)/ Good Clinical Practice (GCP).
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.
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.
Cold Chain:	Cold chain refers to maintaining the required refrigerated or frozen conditions at or between a defined temperature range for investigational products according to the manufacturer's specifications.
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).
Institutional Review Board/Independent Ethics Committee (IRB/IEC):	An independent body consisting 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.
Investigational Product:	Any drug, biologic, device, or combination product that is provided for the study or identified in the protocol as an investigational product, including any diluents or placebos provided for use during the study. "Investigational product' and 'Study product' may be used interchangeably and are used in lieu of the following terms: Investigational drug (21 CFR Part 312); Investigational Device (21 CFR Part 812); Test article (21 CFR Part 50). Definition source: The NIAID/DMID
Investigator Agreement:	An agreement for an Investigational Device Exemption (IDE), which is signed by all investigators stating they will comply with investigator obligations per 21 CFR 812.43(c)(4).
Investigator of Record (IOR) Form:	An agreement signed by the principal investigator that he/she will abide by the regulations set forth in 45CFR46 and the requirements of the protocol. The form also lists sub-investigators, laboratories, and reviewing IRBs/IECs. It is used for non-IND/IDE studies in lieu of an FDA 1572 form.
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.
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 non-IND studies). Written delegation of authority for specific study responsibilities may be given to qualified individuals.
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.
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.

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.
Research:	According to 45 CFR 46, 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."
Research Pharmacist:	A licensed/registered pharmacist who is designated responsibility by the PI to perform the day-to-day research pharmacy activities and investigational product management at clinical research sites, including but not limited to the procurement, storage, preparation, dispensing, drug accountability, and final disposition of investigational products for the DMID-funded/sponsored clinical trial(s).
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 investigational products (e.g., hospital or institutional pharmacy, dispensary, drug storage unit).
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.
Research Pharmacy Equipment:	Apparatus (device or machinery) that is utilized to ensure the physical and scientific integrity of the investigational 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, 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, investigational product containers, fax machines, computers, or printers.
Unblinded Study Vaccine Administrator:	A study personnel member credentialed to administer vaccines and may also participate in dose preparation but will not be involved in study-related assessments or have subject contact for data collection following investigational vaccine administration.

Table 4 Investigational Product Storage Conditions and Temperature Definitions*

Cold:	Any temperature not exceeding 8° C (46°).
Controlled Room Temperature:	The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° C (68°–77° F). Mean Kinetic Temperature (MKT) may be used during an excursion provided: 1) MKT does not exceed 25° C (77° F); 2) excursion between 15° and 30° C (59° and 86° F); 3) transient excursions are not more than (NMT) 40° C (104° F); and 4) excursion time is NMT 24 hours. These limits (time and temperature) and the calculated MKT must be documented. Articles may be labeled for storage at "controlled room temperature" or at "20°–25° C", or other wording based on the same MKT. (See USP General Chapter <1079.2>.) 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. Storage time in controlled cold or cool place cannot be used to calculate excursion temperature outside of controlled room temperature ranges.
Cool:	Any temperature between 8° and 15° C (46° 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.]
Excessive Heat:	Any temperature above 40° C (104° F).
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 of the recommended storage condition.
Refrigerator:	A cold place in which the temperature is controlled between 2° C and 8° C (36° F and 46° F).
Room Temperature:	(Also referred to as Ambient temperature): The temperature prevailing in a working environment.
Warm:	Any temperature between 30° C and 40° C (86° F and 104° F).

***Source: USP– General Chapter <659> PACKAGING AND STORAGE REQUIREMENTS:**

https://doi.org/10.31003/USPNF_M2773_06_01

NOTE: Storage conditions are protocol-specific and are stated in the Protocol/Manual of Procedure (MOP).

Direct questions regarding the IP storage to the DMID Product Support Team (PST).

1. Introduction

1.1. The Product Support Team (PST)

The PST is a component of the Office of Regulatory Affairs (ORA), within the Division of Microbiology and Infectious Diseases (DMID) with specialized experience and expertise in pharmacy, investigational product quality control, and supply chain management.

1.2. DMID Background

The DMID is within the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

As a Sponsor of clinical trials, the DMID must ensure that clinical trials supported by the DMID are being conducted in compliance with U.S. federal regulations and any other applicable local regulations. The Principal Investigator is responsible for all activities, including day-to-day operations, performance, and compliance at the clinical research site level.

The Principal Investigator may delegate the day-to-day responsibilities of investigational product management to a licensed/registered pharmacist, but the ultimate responsibility lies with the Principal Investigator. This pharmacist is the Research Pharmacist. The Research Pharmacist is responsible for coordinating all research pharmacy operations and performing the day-to-day pharmacy activities related to the management of investigational product(s).

An additional licensed/registered pharmacist working at the site must be designated as the Alternate Pharmacist to assume the responsibilities of the Research Pharmacist, in the absence of the Research Pharmacist. For purposes of these guidelines, all references to Research Pharmacist also apply to the Alternate Pharmacist.

The information in these guidelines is meant to assist pharmacists in meeting the required standards of the DMID for the conduct of the DMID-sponsored and/or supported clinical trials. In addition to these guidelines, non-U.S. sites must also adhere to their local and in-country regulations governing the practice of pharmacy. If any differences exist between these guidelines and local and in-country regulations, the most stringent regulations must be followed. For any questions or clarifications, contact the PST at email: DMIDProductSupportTeam@niaid.nih.gov.

1.3. Scope and Objectives

The purpose of this document is to outline the DMID guidelines related to the appropriate management and handling of investigational products (see definition for investigational product) at the clinical research sites to comply with applicable regulations and international research standards. These guidelines apply to clinical trials supported by the DMID, 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 an investigational product, the investigational team should ensure instructions are included either in the protocol, MOP, Investigator's Brochure (IB)/package insert, and/or any other relevant investigational specific standard operating procedures (SOPs). In addition, certain protocols may include investigational products 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 an investigational-related intervention (e.g., rescue therapy, challenge investigational treatment management, toxicity management).

1.4. Contact Information

1.4.1. Contacts

- Division of Microbiology and Infectious Diseases (DMID) Office of Regulatory Affairs, Product Support Team

Product Support Team U.S. Postal Mail Address and Courier Services	DMID Product Support Team (PST) Office of Regulatory Affairs DMID, NIAID 5601 Fishers Lane Bethesda, Maryland 20892-9826 (Courier Zip Code: Rockville, Maryland 20852) U.S.A.
Email address:	DMIDProductSupportTeam@niaid.nih.gov

- Clinical Materials Services (CMS)

The CMS was established to support the DMID. As a contract of the DMID, the CMS's primary role is the storage and distribution of clinical investigational products and supplies.

CMS U.S. Postal Mail Address and Courier Service Address	Clinical Materials Services (CMS) Fisher BioServices 20439 Seneca Meadows Parkway Germantown, Maryland 20876 U.S.A.
Telephone Number:	+1-240-477-1350
Fax Number:	+1-240-477-1360
Email address:	DMID.CMS.@ThermoFisher.com

Hours of Operation

The CMS hours of operation are 8:30 AM - 5:00 PM, U.S. Eastern Standard Time (EST), Monday-Friday. The CMS is closed on weekends and all U.S. Federal holidays; therefore, shipments are not scheduled for delivery or to be picked up on these days.

Shipments

The CMS staff processes investigational product order requests for shipment after they are approved by the CPM/designee and then authorized by the PST.

For U.S. domestic sites, the CMS ships orders to arrive the next business day. Shipments from the CMS are sent out Monday-Wednesday. Thursday shipments sent for Friday delivery and Friday shipments sent for Monday delivery may be done but only with the PST approval. Same day shipments may be made where geographically possible with approval by the PST.

For non-U.S. sites, due to the time zone differences, it may take up two business days for the Research Pharmacist to receive an acknowledgement of receipt of the investigational product order request. The CMS coordinates shipments with a courier service and the Research Pharmacist to ensure that the investigational product orders arrive in the shortest period possible, on a day when pharmacy staff are present.

Order-It

Order-It is a web-based ordering application system used for the management of investigational products for the DMID-sponsored clinical trials. The system is used when investigational products and/or supplies are supplied through the CMS. Refer to the website at: www.order-it.org for instructional videos or contact the CMS for further details.

1.4.2. Documents Applicable to Research Pharmacies

Refer to section 10, for documents that may be applicable to research pharmacies.

1.5. Research Pharmacy Standard Operating Procedures (SOPs)

Sites are expected to have research pharmacy SOPs in place prior to the initiation of a clinical trial. The Research Pharmacist is responsible for having detailed, written instructions governing pharmacy operations and investigational product management, for conducting the DMID-sponsored and/or supported clinical trials and to assure compliance with all applicable laws and regulations. At minimum, the research pharmacy should have written SOPs that govern the receipt, storage, preparation, dispensing, chain of custody, final disposition of investigational product(s), accountability, inventory process, labeling, and quarantine of investigational products.

For some protocols, the Research Pharmacist may be required to generate protocol-specific SOPs, as indicated, based on the requirements in the protocol or investigational- specific MOP.

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

- Accountability of Investigational Product
- Chain of Custody of Investigational Product
- Cold Chain Management of Investigational Product
- Communication between Pharmacy and the Clinic

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

2. Essential Information Required for Investigational Products

- The PI is responsible for providing any investigation-related documents with essential information on investigational products to the Research Pharmacist.
- Documents with essential information on investigational products should include but are not limited to the following:
    - IRB/IEC-approved Protocol (most recent and current version)
    - Manual of Procedures
    - Pharmacy Manual (if applicable)
    - Product Package Insert (PPI) or Investigator's Brochure (IB)
- The Research Pharmacist must have detailed knowledge of and must adhere to the requirements as outlined in the above documents. The Research Pharmacist must maintain all essential information, pertaining to investigational products being used in the DMID-sponsored clinical trials, in the pharmacy files.

- The PI and Research Pharmacist 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.
- The PST should be contacted for any investigational product related questions. If there are any questions regarding the content or instructions contained in any other investigational product related documents, the DMID Clinical Project Manager (CPM) should be contacted for clarification.
- If the investigation is blinded, a treatment assignment list may be used by the 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.
- The names of the investigator(s), investigational coordinator, and product supplier, along with an authorized prescriber signature list, should be maintained for each protocol, as applicable. This list should be kept current with updates whenever individuals are added or deleted.
- The information contained within the investigation-related documents may be proprietary and should not be reproduced or distributed to individuals outside of the clinical research site team.

3. Accountability and Inventory Control

The PI is responsible for maintaining investigational product accountability. The PI may designate or delegate this task to a Research Pharmacist who will maintain accountability, documentation and control of the investigational product inventory used from the time the investigational product is first received at the site until final disposition. Refer to section 3.2 for additional information.

3.1. Ordering and Receipt of Investigational Product

For most of the DMID studies conducted under the DMID-held INDs, investigational products will be supplied CMS. Less frequently, products are 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.

3.1.1. Investigational Product Ordering

- The DMID must be provided with the following documents before investigational product can be shipped to a clinical research site:
  - IRB approval
  - Form FDA 1572/ Investigator Agreement or Investigator of Record (IOR) Form
  - PI curriculum vitae (CV)
- The DMID or its designee will issue a site activation memorandum, if applicable, once all the documentation and internal approvals are in place.

- An appropriate communication plan must be developed between the product supplier and the clinical site to facilitate investigational 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.
- Personnel responsible for ordering investigational products 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 investigation per specific protocol, to include estimates for any product loss due to suspected waste or compromise.
- The Research Pharmacist (or designee, as determined by the PI) is responsible for ordering of investigational product(s). If the PI (or designee, as determined by the PI) must be notified of inventory levels, the Research Pharmacist (or designee) must do so without breaking the blind. This process will be established by the PI and Research Pharmacist (or designee) based on current and forecasted usage patterns and storage capacity.

3.1.2. Investigational Product Receipt

- Arrangements, as needed, must be made between the product supplier and the investigational site to determine the most appropriate time, place, and individual to receive investigational product at the site. These arrangements will be agreed upon prior to shipment or delivery of investigational product
- Upon receipt of investigational product(s), the Research Pharmacist must ensure that the information on the packing slip matches what has been sent to the site and that investigational product(s) sent are appropriate for the trial as described in the protocol and MOP
- At a minimum, the Research Pharmacist should verify the following:
    - Product identification
    - Date of shipment and date of receipt
    - Quantity of products received
    - Lot number(s)
    - Unique code numbers assigned, if applicable
    - Expiration dates or re-test dates, if available
    - Physical products are in good condition
    - Storage conditions, especially temperature control, have been maintained
- The Research Pharmacist must notify the supplier of the receipt and condition of the investigational 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)

- The investigational product(s) can be placed in active inventory if they do not appear damaged or if there are no discrepancies or temperature deviations/excursions
- When any discrepancies are discovered upon receipt of the investigational product(s), the supplier will be promptly notified, and this notification must be dated and documented by the Research Pharmacist in the shipping records
- When 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, the PST should be notified promptly, and details of the incident must be documented in the shipping records. The investigational product must be quarantined (see section 4.11) and maintained under the correct storage conditions until further instructions are given
- When there are any discrepancies with the investigational product(s), the affected investigational product may not be placed into active inventory or dispensed, until notification is received in writing from the DMID, by email, or fax, that the investigational product(s) may be safely used
- 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 print outs, if applicable
- The date/time and condition of the investigational product upon arrival and before being placed into active inventory should be noted and documented in the shipping records
- Investigational products must not be dispensed until they are properly inventoried, and the quality of the product is verified by authorized personnel

3.2. Investigational Product Accountability

- Although the PI is responsible for ordering and accountability of all investigational products in his/her clinical trial, the Research Pharmacist can be delegated this responsibility when he or she accepts/receives the investigational product.

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

  Each time an investigational product is received from the CMS or other source, dispensed to a participant, and/or returned to the CMS or other source or destroyed, it must be documented on the Investigational Product Accountability Log.

All entries on the Investigational Product Accountability Log must match the dispensing activity. The investigational product accountability log may take the form of a continuous electronic record or a paper document.

- When a paper document is used, all entries must be made in dark indelible ink. Never use a 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. Entries/corrections should be made consistent with 10.13. 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 on the reverse of the paper document, clearly defining which entry the comment refers to or addresses. In addition, the original entry should not be obscured.
  When 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

  Information in the investigational product accountability log should include, but is not limited to the following:

  - DMID protocol number
  - Name, dosage form, strength of the investigational product
  - Manufacturer or other source
  - Control, lot number, or other identification number
  - Expiration and/or retest date
  - Date of receipt of the investigational product
  - Quantity received from supplier
  - Subject identification number
  - Quantity dispensed as amount or dose per subject
  - Balance of investigational products currently available
  - Disposition of drug if not dispensed to an investigational subject (e.g. disposed/destroyed or returned to supplier as per protocol or MOP or as directed by the DMID)

  The investigational product accountability log should be accessible only to the Research Pharmacist, PI, study coordinator, the DMID monitors, the DMID representatives, and regulatory agency representatives. If the study is blinded, blinding must be maintained.

- Accountability may be performed through verification of inventory per section 3.3 and during monitoring.

- The DMID does not require used containers of investigational product to be maintained at the research pharmacy until the clinical monitors have confirmed the disposition of all investigational products
- Retention of used containers of investigational product for monitoring is only required when the local institution's SOP/policy mandates it. If local SOPs allow/require destruction of used containers of investigational product, the used containers can be destroyed by the site's SOPs with a second staff member's observation and signed verification (two signatures) that the used containers were destroyed

3.3. Systematic Reviews

3.3.1. Product Inventory Review

- A physical review of investigational product inventory should be conducted monthly, at a minimum, to support accountability records and to confirm that physical quantity on hand is consistent with the inventory balances on the accountability log. These procedures should include a cross-check of quantity on hand with the amounts recorded on the drug accountability records, dispensing or preparation dates, expiration dates, and lot numbers. The inventory balance documented on the accountability log should always match the actual physical inventory, on hand
  - More frequent reviews may be indicated (e.g., running balance) at a frequency concurrent with dispensing and storage indications.

The Research Pharmacist must attempt to reconcile any discrepancies between the accountability records and the physical quantity on hand. The attempt to reconcile discrepancies must be documented.

The Research Pharmacist must immediately notify the DMID CPM when an attempt to reconcile a discrepancy is unsuccessful, and the actions attempted must be documented on the accountability records. If the study is blinded, blinding must be maintained.

3.3.2. Product Expiration Review

- The Research Pharmacist should establish written procedures for the process of investigational product expiration date review, including when non-routine reviews may be required
- Expiration dates should be made clear in the available documentation
- A routine review of investigational product expiration/retest dates should be conducted.
- Expiration review must be conducted quarterly
  - Expired products must be segregated from active investigational products and placed in quarantine (see section 4.11) until they are monitored and upon receipt of written authorization destroyed on site or returned to the supplier. If local SOPs require destruction of expired investigational product containers instead of returning to sponsor or manufacturer/supplier, the site must first obtain approval in writing from the DMID. The

expired vials can then be destroyed with a second staff member's observation and signed verification (two signatures) that the used vials were destroyed

- Instructions regarding storage of expired investigational products, such as whether storage conditions need to be maintained, must be provided by the DMID. If there are any questions, the PST should be contacted via email
- The Research Pharmacist must review the expiration/retest date information provided for the investigational product before dispensing of investigational product. If applicable, the Research Pharmacist must also ensure that the investigational product dispensed will not reach the expiration date before the subject's next required supply of investigational product

3.4. Investigational Product Disposition

- Unused investigational products (e.g., expired investigational product, unexpired investigational product upon completion of the study) will be destroyed or returned to the product supplier, unless otherwise specified in the protocol or MOP and after written notice from the DMID.
  - Investigational product designated for destruction or return must be segregated from active investigational products and placed in quarantine (see section 4.11) until they are monitored and/or accounted. Once DMID written authorization of final disposition is provided, the products may be destroyed on site or returned to the manufacturer/supplier
  - If local SOPs require destruction of Unused investigational product containers instead of return, the site will require written approval from the DMID. Unused containers can then be destroyed per the site's SOPs with a second staff member's observation and signed verification (two signatures) that the used vials were discarded
- The method and timing of investigational product disposition is at the discretion of the DMID. The arrangements may be outlined in a protocol, in a MOP, or conveyed in a written document from the DMID
- Accountability records will be monitored before authorization of final disposition
- The Research Pharmacist must provide written documentation of investigational product disposition on the accountability records, either before or at study completion (as applicable to the protocol)
- After study completion, investigational product must not remain at the site unless authorized by the DMID
- The following information should be included for record keeping:
  - Name of PI and contact information
  - Number of units
  - 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, lot/control number, etc.

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

3.4.1. Investigational Product Return

- Reasons for which investigational products may be returned include, but are not limited to, the following:
  - The clinical protocol has been completed or terminated at a site
  - The investigational product was damaged when received at the pharmacy/ clinical research site
  - The investigational product has been stored improperly and can no longer be used safely
  - The investigational product has expired
  - Return of the investigational product has been requested by the supplier
  - The manufacturer or sponsor has recalled the investigational product
- An investigational product recall system must be in place for the identification, retrieval, quarantine, and return of recalled investigational products. The Research Pharmacist must respond immediately to recall notices and return investigational product as directed by the DMID
- When there are additional instructions regarding return of investigational product, those instructions must be specified in a protocol-specific document(s) or be conveyed by the DMID

3.4.2. On-site Destruction

- The DMID will provide written authorization for the destruction of investigational products. The investigational products to be destroyed must be quarantined in a separate area from the active stock
- 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 and local, state, and federal regulations for destruction of investigational product. Strictly adhere to any applicable medical waste standards
- Destruction of investigational product must be documented in the accountability log. The DMID and/or the supplier may request a copy of this documentation

4. Storage of Investigational Product

The PI or designated Research Pharmacist is responsible for the storage of investigational product(s) in the research pharmacy, ensures that the proper storage conditions are maintained, and that documentation is adequate. Investigational 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.

See also section 10.6 (ICH E6, GCP section 4.6.4).

Investigational products for the DMID studies must be stored in safe, secure, and appropriate locations and at correct storage conditions based on the requirements of the manufacturer and the investigational protocol. For the purposes of this document, this location will be referred to as the research pharmacy. For further details, see the definition for research pharmacy.

For most of the DMID studies conducted under DMID-held INDs/IDEs, investigational products will be supplied through the DMID Clinical Materials Services (CMS). Less frequently, products are supplied directly from the manufacturer, purchased commercially through a wholesaler, or obtained through the hospital/institutional pharmacy.

4.1. Space, Security, and Segregation

4.1.1. Space

- Upon receipt, all investigational products supplied for a specific protocol must be stored in the research pharmacy (see definition for *research pharmacy*).
- Adequate pharmacy space, facilities, equipment, and supplies for storage, preparation, packaging, and dispensing of investigational products must be assessed prior to receiving investigational product(s) at the site to guarantee appropriate storage, ensuring protection from vermin, extreme temperature, and humidity
    - The research pharmacy facilities must follow all local, state, and federal regulations and be of adequate size, organization, and ample lighting. Hand washing and cleaning facilities must be available for cleaning purposes and workspaces should be adequate for the preparation of investigational products, investigational product accountability, and record management
    - Investigational product(s) requiring special storage, handling, or preparation (for example, hazardous drugs, non-standard temperature requirements, protection from light, sterile or aseptic conditions, etc.) should be identified and availability of space and equipment for storage should be determined by the Research Pharmacist prior to receiving investigational product(s) at the site

4.1.2. Security

- Investigational products and supplies must be kept in custody of the Research Pharmacist or his/her designee until dispensed for the subject or upon final disposition
- The storage area for investigational products and supplies must have limited and secure access and must be locked when not in use
- Access to investigational product is limited to essential and authorized personnel only with approved access to the research pharmacy, such as the designated Research Pharmacist or his/her designee
- Systems must be in place to prevent unauthorized entry and unauthorized access to investigational products and to identify and alert staff when proper security conditions have been compromised

- When investigational product security has been compromised, the PI and the DMID must be notified. This breach of security, along with additional correspondence, must be documented

4.1.3. Segregation

- Investigational products should be segregated from non-investigational products; investigational products for different protocols should be segregated
- Investigational products **must not** be stored with food, specimens, or any other products that may contaminate or compromise the quality of the investigational product
- For blinded studies, the active investigational 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 investigational products
- Product that is designated for return or destruction must be segregated from active stock and placed in quarantine until final disposition

4.2. Temperature and Environmental Control

- All pharmacy investigational product storage areas and pharmacy refrigerators and freezers must have TWO INDEPENDENT temperature monitoring devices
- Sites must address proper storage conditions in the protocol planning stages such as temperature, light, moisture, ventilation, and sanitation
- Temperature and environmental storage for investigational product(s) is protocol specific. The research pharmacy must be maintained at the appropriate temperature setting to preserve the integrity, stability, and effectiveness of investigational products for each protocol. Detailed instructions regarding appropriate conditions are described in the product package insert, the IB, or the protocol/MOP
- Temperature and environmental control must be maintained from the time of receipt of investigational product until the product has been used by the subject or is deemed no longer usable, unless otherwise specified in the protocol or by the manufacturer
- The DMID 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 PST assessment will be rounded to the nearest whole number (e.g. for Controlled Room Temperature storage, temperatures between 19.50˚C and 19.99˚C round up to 20˚C and temperatures between 25.10˚C and 25.49˚C round down to 25˚C)

4.3. Continuous Temperature Monitoring and Recording

Research pharmacies must have equipment that can record the temperature 24 hours a day, 7 days a week, and 365 days a year. Continuous temperature monitoring and recording devices are required and must provide real-time and min/max temperature information for the designated investigational product storage area in which the system is installed. The device must monitor and record temperatures at programmed time intervals and should be set, ideally, every 15 minutes with more frequent recording

desirable, but no more than 30 minutes. Electronic data must be stored on a system that is backed up on a regular, recurrent basis. Data storage capacity must either meet the need of providing temperature data reports for years of investigational product storage conditions, or if there is limited data storage capacity of the electronic temperature data logger, then interval data reports should be created and stored either electronically or printed and saved.

4.4. Daily Back-up Manual or Electronic Temperature Monitoring and Daily Temperature Log

A back-up temperature monitoring device (e.g., a minimum/maximum thermometer); see also USP <1079> Good Storage and Shipping Practices) is required for each investigational product storage area, serving as a back-up to the existing primary continuous temperature monitoring device. The temperature readings from the back-up monitoring device must be manually documented on a temperature log once daily each workday (preferably in the morning) or electronically documented to verify that the temperature is within range. The daily temperature verification is also used to verify that the alarm systems are functioning properly, alerting the Research Pharmacist if the temperature was out of acceptable temperature range. The temperature monitoring log is to be reviewed at least monthly to observe trends that may indicate that equipment requires adjustment or service. When the back-up temperature monitoring device is electronically documented, a separate alarm notification must be in place to alert the Research Pharmacist if the temperature was out of acceptable temperature range. This electronic monitoring log is to be reviewed at least monthly to observe trends that may indicate that equipment requires adjustment or service.

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 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.

4.5. Temperature Deviations/Excursions Notification or Alarm System

Every research pharmacy refrigerator, freezer, and room temperature area 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 Research Pharmacist may take immediate action, to prevent loss of investigational product. Alarm settings within ±0.5°C of the product storage temperature specifications are suggested to alert the 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

- Each site must have systems in place and SOPs defining responsibilities and procedures to:
    - Ensure proper storage conditions are continuously met
    - Prevent or limit storage conditions from being compromised during emergency situations, such as a power failure or equipment malfunction (e.g. back-up power source and/or alternative storage arrangements)

- Alert staff when temperature excursions have occurred and take corrective action

4.6. Temperature Deviations/Excursions Reporting and Quarantine

The Research Pharmacist is responsible for ensuring that the investigational product is maintained at the protocol-specified, long-term temperature storage range to preserve the integrity, stability, and effectiveness of the investigational product(s) for each protocol (See Storage and Temperature Monitoring Section). A temperature deviation/excursion indicates a temperature reading that is outside of the specified long term temperature storage range.

The continuous temperature monitoring device is designated as the primary device to determine whether a temperature excursion has occurred. If during review of the manual temperatures, an excursion is noted, the data from the primary device prevails. If the primary device does not indicate an excursion, temperature excursion does not need to be reported to the PST. The Research Pharmacist should make every effort to investigate why there may be a discrepancy (e.g., check for recalibration and maintenance of device, power source, placement of probe, etc.).

In the event, a non-permitted temperature excursion occurs (e.g., temperature deviates from the allowable range) or if there is any suspicion that investigational product(s) have not been stored properly. The investigational product should be immediately quarantined at the appropriate storage temperature, and the occurrence reported directly to the PST, using the *DMID PST Temperature Excursion Reporting Form*. The PST will review the reported temperature excursion and communicate investigational product suitability to the Research Pharmacist. The Research Pharmacist should await final disposition instructions from the Clinical Project Manager (CPM). Refer to the protocol and MOP for storage instructions and notifications.

4.7. Controlled Room Temperature Permitted and Non-Permitted Excursions

If the investigational protocol states “store between 20°C and 25°C, with excursions permitted within 15°C and 30°C (59°F and 86°F)”, temperature excursions occurring **below** 15°C or **above** 30°C must be reported to the PST as non-permitted excursions.

If the investigational protocol states store “at 25°C, with excursions permitted within 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]” or similar language referencing USP Controlled Room Temperature, the investigational product may be stored between 20°C and 25°C, with excursions permitted within15°C and 30°C (59°F and 86°F). Temperature excursions occurring **below** 15°C or **above** 30°C must be reported to the PST as non-permitted excursions.

Any controlled room temperature excursion that occurs within the investigational protocol-specified, permitted temperature excursion window of 15°C and 30°C (59°F and 86°F), must be reported as a permitted excursion to the PST using the *DMID PST Temperature Excursion Reporting Form*, however, the investigational product may remain in active inventory and dispensed to participants. Reporting of these permitted excursions must occur upon identification.

Note: Protocol-specified, permitted controlled room temperature excursions facilitate continued use of investigational products; however, they are still excursions outside of the long-term storage temperature range and must be reported to the Sponsor.

4.8. Storage Equipment

- Appropriate storage equipment must meet all storage, security, access, and monitoring guidelines as stated in this manual and must be used, as applicable, to maintain the necessary environmental storage conditions for investigational products as required per the protocol or manufacturer's instructions. Examples of storage equipment that may be needed include:
    - **Refrigerators** (The DMID does not recommend the use of household refrigerators and freezers since the temperature control may be variable. Instead, scientific grade refrigerators are recommended)
    - **Freezers** (The DMID does not recommend the use of self-defrosting or auto defrosting freezers since the temperature may cycle on a routine basis. Instead, scientific grade freezers are recommended)
    - **Temperature monitoring and recording devices**
    - **Temperature alarm systems**
    - **Heating and air conditioning units**
    - **Back-up power supply or generator**
    - **Back-up temperature systems to maintain specified environmental conditions**

4.9. Maintenance of Equipment

Storage equipment must be maintained in a clean and sanitary condition, in good working order and capable of maintaining the appropriate temperatures. Each storage equipment must be calibrated, according to the manufacturer's specifications for optimal quality and use; maintenance and calibration must be documented. Maintenance and calibration records for all pharmacy equipment should be retained in the pharmacy and/or immediately available upon request.

4.10. Back-Up Power Supply/Generator

All equipment supporting pharmacy operations must be supported by a back-up power source (e.g., back-up battery power source or generator). Unless otherwise specified by manufacturer specifications or per individual institution policy, the back-up power supply should be tested quarterly and should receive maintenance at least annually. Documentation of testing and maintenance should also be recorded and maintained. Ideally, back generators should have sufficient capability to run continuously for the duration of the longest possible blackout.

4.11. Quarantine of Investigational Products

- Investigational products should be quarantined when:
    - Proper storage conditions have not been maintained

- There is evidence of product tampering or breakage
- The DMID has requested that the product be quarantined

NOTE: Excursions between 15-30°C (59°F to 86°F), the product can continue to be used (no quarantine) but the site needs to complete the DMID Investigational Product Support Team Temperature Excursion Reporting Form and submit to PST. Based on USP guidelines (General Chapter <659> Packaging and Storage Requirements, see section 10.7), excursions between 15°C and 30°C are allowed and will not be considered deviations

- Quarantined product(s) must be:
  - Physically segregated from investigational products that are still in use
  - Maintained at the correct temperature unless the DMID has provided alternate instructions
  - Clearly labeled that they are quarantined and should not be used
- Quarantined products must not be used, destroyed, or returned until written permission is granted by the DMID

5. Investigational Product Transport and Delivery

Investigational products must be maintained properly during transport from one location to another (e.g. satellite pharmacy or clinical location). This includes ensuring that control of the investigational product and environmental conditions have been maintained during transport. The protocol and/or MOP usually include specific instructions for the handling and transport of products.

5.1. Control of Investigational Product during Transport

- When investigational products are transported from one location to another, an SOP addressing all steps in investigational product transport, including the method maintaining control of investigational product, should be in place
- Investigational products should always remain in custody of authorized personnel during transport.
- When investigational products are transported from the institution to other sites, the authorized personnel engaged in the transaction should be documented on an investigational product transport record, as applicable
- In general, the documentation for investigational product transport should include, but are not limited to the following:
  - Protocol number
  - Investigator and/or site number
  - Name of courier
  - Name of recipient

- Name and number of contents being transported (for example, if vials are individually labeled, those label sequences should be recorded)
- Date and time investigational product prepared (if applicable)
- Date and time investigational product dispensed
- Date and time investigational product received at final transport destination

- Pneumatic tube systems must not be used.

5.2. Environmental Conditions during Transport

- Requirements for maintaining environmental conditions should be identified prior to investigational product transport and included in the MOP and a local SOP
- In addition to written site-specific processes and procedures, the site SOP should specify that investigational products always be in custody during transport, delivered directly to the off- site location, and promptly unpacked and placed into appropriate storage units upon arrival. If transporting investigational product will require the use of a non-commercial vehicle, the passenger compartment must be used. Investigational product must not be placed in the trunk of the vehicle
- Cold chain should be maintained during transport. The number of times investigational products are 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
- Investigational 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 local SOP and to protect the investigational product from damage, leakage, contamination, and degradation
- When refrigerated investigational product requires transport or if frozen investigational product may be transported at refrigerated temperatures, the DMID 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 it can maintain the recommended temperature range (2˚C and 8˚C [between 35.6˚F and 46.4˚F])
- When frozen investigational products require transport, the DMID recommends transport with portable freezer units
- Cold chain or other specified environmental conditions must also be maintained at the recipient site
- When investigational product must be kept in a transport container at an off-site location:
  - Keep the container closed as much as possible.
  - Remove only the required product for administration.

- Place the calibrated thermometer(s) (preferably with a biosafe glycol-encased thermometer probe) as close as possible to the investigational product
- Read and document the temperature(s) inside the container(s) at least hourly
- Use a digital thermometer with temperature display and external, detachable temperature probe to minimize the exposure of the investigational product to external environmental conditions and to read and document temperature(s) inside the container

- For investigational 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 products 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 is strongly recommended
- Transport of investigational products must not occur when the site cannot ensure that investigational products are transported under appropriate cold chain management or maintained under appropriate storage conditions upon arrival

6. Preparation, Dispensation and Administration

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

6.1. Prescriptions or Medication Prescribing Orders

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

- By signing the Form FDA 1572 or IOR Form, the PI has certified that the investigational product will be administered only to subjects under his/her personal supervision or under the supervision of sub-investigators responsible to him/her
- The Research Pharmacist must receive a prescription or medication prescribing order signed by an authorized prescriber (see definition for authorized prescriber) prior to dispensing investigational product
- Prescriptions or prescribing orders must be handwritten with dark ink, typed, or computer generated
- Signatures on the prescriptions or prescribing orders are to be handwritten or electronically signed. Signature stamps are not permitted
- Signing blank prescriptions or prescribing order forms is not permitted

- It is not permitted for an individual who is not an authorized prescriber to sign a prescription or prescribing order with an authorized prescriber's name and then add her/his own name 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
- 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
- An authorized prescriber must sign the prescription or prescribing order before sending it to the research pharmacy
- Study staff may prepare electronically or hand-written prescriptions in advance for an authorized prescriber to review and sign; however, no investigational product should be dispensed until after the Research Pharmacist receives the signed prescription
- 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
- 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)
    - Investigational 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 (e.g., dose reduction, dose escalation)

6.2. Investigational Product Preparation

6.2.1. Space and Equipment for Preparation

- Appropriate space and equipment must be provided and used for investigational product preparation as per section 4.1
- The Research Pharmacist must ensure that there is sufficient stock of ancillary supplies for preparing and dispensing investigational products

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

6.2.2. Personnel Involved in Preparation

- The DMID requires that compounding of investigational product must be performed by or under the direct personal supervision of a licensed pharmacist (e.g., 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, intravenous admixture preparation, 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
- In certain instances, due to site-specific logistics or investigational 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 investigational product immediately prior to administration to a subject. A Site Research Pharmacist may be delegated the responsibility of investigational product preparation and dispensation. The Research Pharmacist must be a licensed, registered pharmacist and is the preferred healthcare practitioner to be delegated to perform this activity. If the Research Pharmacist is not available, a physician, nurse practitioner, physician assistant, registered nurse, or other authorized healthcare practitioner, who is a member of the clinical study staff, may be delegated to prepare and dispense the investigational product. These personnel must be licensed, trained, and qualified to prepare investigational product and must be authorized to dispense the investigational product under state and local rules and regulations
- In these limited cases, the Research Pharmacist must prepare, label, and dispense the investigational product, so that the prescribed dose may be obtained and administered by the authorized healthcare practitioner in accordance with the protocol or MOP
- It is the responsibility of the PI to ensure all local jurisdiction and state rules or regulations comply with the procedures performed at the clinical site
- The Research Pharmacist 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 also be developed

- For the DMID protocols, where an investigational 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 investigational product immediately prior to administration to a subject
    - In these instances, the Research Pharmacist must first label and dispense the investigational product to the authorized health care practitioner. The investigational product may then be prepared by the authorized healthcare practitioner in accordance with the protocol or MOP
    - It is the responsibility of the PI to ensure all local jurisdiction and state rules or regulations comply with the procedures performed at the clinical site
    - The Research Pharmacist must provide detailed instructions and training for investigational 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 also be developed
- Names of any personnel or authorized health care practitioners aiding in the preparation of an investigational product must be documented

6.2.3. Preparation Procedures

- 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
- Preparation instructions for investigational products are outlined in the protocol and in additional accompanying documents, such as a MOP document
- The Research Pharmacist must document that investigational 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
- If applicable, a separate compounding form may be used to document the preparation procedure
- Preparation review and verification by the Research Pharmacist must be documented with the Research Pharmacist's initials prior to dispensation
- Any issues or errors with product preparation, including improper mixing, treatment assignment errors, etc. should be immediately reported to the PI, the DMID, as directed by the protocol or MOP, and the PST. If an issue or error occurs in a blinded study, the Research Pharmacist must maintain blinding during discussions with the investigator or other individuals who may be blinded to treatment assignment (see section 7)

6.3. Labeling Requirements

- The Research Pharmacist must label all prepared investigational product doses (e.g., use of mixing vials or drawn into syringes) appropriately to ensure safe administration by a clinician or use by study participants. Labeling must comply with all local, state and in-country regulations and requirements
- If the Unused investigational product is further manipulated (e.g., use of mixing vials or drawn into syringes), the protocol or MOP must be followed for additional labeling instructions (reference the DMID Investigational Product Label Requirements for labeling of immediate package of an investigational new drug):
- DMID Investigational Product Label Requirements
- For blinded studies, labels must be prepared in a manner that maintains the blinding of the investigational product.

6.4. Investigational Product Dispensing and Administration

- Double-check Process Requirement Description:

  Upon dispensing of investigational product by the site Research Pharmacist to the clinic or location where investigational product administration will occur and prior to investigational product administration, a "double-check" of the dispensed investigational product must be performed. The 'double-check' required is performed by an individual licensed to administer drugs before the investigational product is administered. This individual must also be appropriately qualified by training, licensure and registration to perform this function

  This 'double-check' is exemplified as follows:

  - In instances where no further manipulations or dose preparation after dispensing is required, after receipt of the dispensed investigational product, the individual licensed to administrator investigational product verifies that the investigational product corresponds with the protocol-assigned treatment (e.g., treatment assignment, product name (if unblinded), strength/concentration, dose, route, and frequency)
  - In instances where, after dispensing by the site Research Pharmacist, the investigational product requires additional manipulation or dose preparation prior to administration (e.g., withdrawal of a single-dose from a multi-dose vial or single-step dilution of a vaccine for immediate administration), the individual performing the additional manipulation verifies investigational product corresponds with the protocol-assigned treatment (e.g., treatment assignment, product name (if unblinded), strength/concentration, dose, route, and frequency). A "double-check" by a second individual (again, licensed to administer drugs) must also occur during and/or after manipulation or dose preparation and prior to administration of the product

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

  - Subject identification and enrollment into the study

- Subject provided written informed consent for the current version of the protocol
- Investigational product identification (including name and/or unique code number assigned, if applicable) is correct based on treatment assignment
- Dose of investigational product
- Volume/quantity of investigational 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

- Investigational product(s) must be administered by qualified individuals based on experience, training, education and licensure/registration/certification (as applicable)
- Unused investigational products returned by trial subject must never be re-dispensed to another subject. The returned investigational product must be documented on the appropriate accountability log and stored in quarantine separate from active investigational product inventory

7. Maintenance of Study Blind

Many trials sponsored by the DMID are randomized, blinded interventional trials. Blinded trials require special provisions to be made 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 investigational 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 local plan or SOP should be in place that articulates the steps to be followed to prevent possible unblinding to others.

7.1. Blinding and Masking Considerations

- Investigational products that will be provided to and handled by blinded personnel must be labeled in a manner that does not reveal the treatment assignment.
- Unblinded personnel must:
  - Prevent inadvertent unblinding when communicating with blinded members of the study team
  - Not be engaged in blinded study activities, such as protocol-related assessments
  - Maintain assignment lists in a secure location and unavailable to blinded study personnel

7.2. Unblinding Procedures

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

- A procedure for unblinding the treatment assignment in an emergency should be agreed upon by the DMID and the PI and described in either the protocol, MOP or a separate SOP.
- The PI is responsible for documenting any approved or unapproved unblinding in the study file. The DMID must be notified that unblinding occurred, but the DMID should 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
    - Reasons for unblinding
- In general, the IRB/IEC should be notified when unblinding occurs.
- If unblinding occurs, every effort should be made to minimize the number of people at the site who are informed of the treatment assignment
- The Research Pharmacist must confirm that the PI and/or study coordinator are aware that the blinded treatment assignment code is broken

8. Record Keeping Responsibilities

Documents, logs and records pertaining to investigational product(s) should remain in the research pharmacy. These documents may be protocol-specific or general to research pharmacy operations.

See section 10.6 (ICH E6 (R2) GCP section 4.6.3).

8.1. Investigational Product Documentation

- Investigational product records should include, but are not limited to, the following:
- Shipping and receipt
- Investigational product accountability/dispensation
- Storage temperature logs
- Investigational product transport
- Preparation and compounding
- Expiration/ Retest date (when applicable)
- Investigational 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 investigational product and/or adjunct products
- Signature log/delegation of duties roster

8.2. Study Product Management Plan (SPMP) Document

8.2.1. Study Product Management Plan (SPMP)

The Site Research Pharmacist (or designee with review by the Site Research Pharmacist) must complete a Study Product Management Plan (SPMP) for each pharmacy that participates in a DMID-funded Clinical Research Site. The SPMP documents that the pharmacy has the required personnel, facilities and equipment necessary for studies requiring controlled room temperature. The SPMP must be submitted directly to the PST for review and acceptance at DMIDProductSupportTeam@niaid.nih.gov

with a copy to the Contracting Officer Representative (COR) or Project Officer (PO) for the clinical research site, or by non-VTEU sites to their network Project Manager (or designee) for initial review, and then to the PST for subsequent review and acceptance.

An SPMP must be submitted if one of the following conditions occurs:

- A new research pharmacy is being established
- The beginning of a new funding cycle
- The pharmacy is moving to a new location
- There is significant change in the procedures outlined in the previously approved SPMP
- Upon the PST request

Once the SPMP is received, processed, and accepted by the PST, the PST acceptance email must be printed and filed with the accepted SPMP.

8.2.2. SPMP Modules

The Site Research Pharmacist (or designee with review by the Site Research Pharmacist) must complete the SPMP modules below, if applicable to the CRS pharmacy. The SPMP modules must be submitted directly to the PST at DMIDProductSupportTeam@niaid.nih.gov with a copy to the Contracting Officer Representative (COR) or Project Officer (PO) for the clinical research site, or by non-VTEU sites to their network Project Manager (or designee) for initial review, and then to the PST for subsequent review and acceptance if one of the following conditions exists:

- Refrigerated Storage Module: This module must be submitted for review and acceptance to the PST before the CRS is able to participate in any protocol requiring investigational product(s) storage under refrigerated storage conditions (2°C – 8°C).

- -20°C Freezer Storage Module: This module must be submitted for review and acceptance to the PST before the CRS is able to participate in any protocol requiring investigational product(s) storage under -20°C freezer storage conditions.

- -70°C Freezer Storage Module This module must be submitted for review and acceptance to the PST before the CRS is able to participate in any protocol requiring investigational product(s) storage under -70°C (<-65°C) freezer storage conditions.

- Biosafety Cabinet/Isolator Module: This module must be submitted for review and acceptance to the PST before the CRS is able to participate in any protocol requiring investigational product(s) preparation within a Biosafety Cabinet/Isolator.

- Transportation/Chain of Custody Module: This module must be submitted for review and acceptance to the PST if any unused investigational product, or pharmacist-prepared participant-specific investigational products are transported and/or stored in a different physical location other than the pharmacy (e.g., from the pharmacy to a BSC in another room outside of the pharmacy or to another pharmacy or clinic).

8.3. Record Retention

Record retention applies to clinical research records that are generated, stored and retained, as required by U.S. regulations, laws, and policies. All study documents for investigational products retained by the DMID sponsored CRS must be maintained by the CRS as per federal and local regulations.

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:

- 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
- 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.
- Records must not be destroyed until approval by the DMID has been granted.

9. Additional Considerations/Responsibilities

9.1. Research Pharmacist Coverage

- A qualified Research Pharmacist should always be available for investigational product preparation and dispensing
- If the primary Research Pharmacist for a trial is absent, an Alternate Pharmacist must be available who can perform the functions related to investigational product management for that trial (see definition for Alternate Pharmacist)
- The Alternate Pharmacist must be trained in the requirements of clinical trials by the Research Pharmacist to perform activities including, but not limited to, the following: investigational product receipt and inventory, storage, preparation, dispensing, accountability, and record keeping; the training must be documented

9.2. International Site Considerations

Studies performed at international sites may pose additional challenges in implementation and logistics. PIs and Research Pharmacists at international sites must be aware of such challenges prior to starting an investigational study. All potential issues must be addressed. If the research site cannot comply with the guidelines as outlined in this manual, please contact the PST to determine how to best proceed.

- The study site must ensure that all documents for import, export and in-country use are in place

- Shipping documentation required for international sites includes, but is not limited to, commercial invoices and import permits (if applicable), in addition to receipts and records required for domestic sites

- The Research Pharmacist must be aware of and plan for potential challenges associated with international sites, such as import/export issues and related documentation
- Customs agents are usually engaged by the DMID to help facilitate entry
- The site is responsible for having a receiving party and proper transport from the point of entry to the site
- The Research Pharmacist must be aware of and plan for complications in the event of a delay in receiving investigational product at a site. For example, some complications in procurement of investigational products and supplies into a country may decrease the shelf life of the investigational product, expose the investigational product to extreme temperature excursions, or even delay the clinical trial
- Concerns regarding the storage of investigational products, especially security, temperature, and moisture, must be rigorously addressed. Some issues include differences in ambient temperature, humidity, sanitation, and security of storage units

10. References

10.1. Code of Federal Regulations Title 21 Part 50

10.2. Code of Federal Regulations Title 21 Part 312

10.3. Code of Federal Regulations Title 21 Part 812

10.4. Code of Federal Regulation Title 45 Part 46

10.5. Code of Federal Regulations Title 21 Part A Section 353a

10.6. International Conference on Harmonization E6: Good Clinical Practices

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

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

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

10.10. USP-NF General Chapter <800> Hazardous Drugs – Handling in

Healthcare Settings

10.11. CDC Vaccine Storage and Handling Toolkit

10.12. DMID PST Temperature Excursion Reporting Form

10.13. FDA Guidance: Standardization of Data and Documentation Practices for Product Tracing Guidance for Industry

11. Availability

This document is posted externally to the DMID-CROMS WebLibrary at:

https://www.dmidcroms.com/CRS/StudyProducts

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