Pharmacy Guidelines and Instructions for DMID Clinical Trials

Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
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1. Introduction

1.1 Background

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

As a funding sponsor of clinical trials, DMID is responsible for ensuring compliance with domestic and international quality standards governing the receipt, use, storage, and disposition of study products in DMID-sponsored clinical trials. DMID must not only ensure that clinical sites are proceeding in accordance with International Conference on Harmonization (ICH) guidelines and all other applicable research standards, but, also, that all investigators establish and maintain records clearly documenting accountability of study product. Each clinical site/center participating in DMID-funded trials involving the use of study products must have appropriate pharmacy support, such as a pharmacist and a pharmacy (see definitions for *research pharmacist* and *research pharmacy*).

The investigator may enlist the aid of a pharmacist who is qualified in all aspects of study product management, keeping in mind that all aspects of the investigational trial, including conduct, management, and record maintenance, are ultimately the responsibility of the Investigator of Record (IoR). If a pharmacist is not utilized, the IoR must identify the qualified study staff member who is responsible for all pharmacy-related activities. For the purpose of this document, this individual is also referred to as the research pharmacist.

Responsibilities of the research pharmacist include, but are not limited to, study product ordering, receipt, storage, security, labeling, dispensing, disposition, and accountability. In addition, he/she is expected to develop and maintain an adequate study product management system to achieve DMID requirements. This individual may participate in the preparation of study products and special dosage forms, labeling and packaging of study products, monitoring adherence to study product treatment assignments, preparation of study product information sheets and development of research protocols.

1.2 Scope and Objectives

The purpose of this document is to provide DMID requirements related to the appropriate handling of study products and supplies in compliance with applicable federal and state regulations, international standards, and institutional policies and procedures. Since this document only provides general standards and requirements pertaining to study product handling, additional instructions may be found in the protocol, Manual of Procedures (MOP) and any other study specific standard operating procedures (SOPs). These requirements apply to all interventional trials funded by DMID, not limited to sites/centers within the United States regardless of funding mechanism or clinical site location.

The study product, as well as any drugs, devices, or study intervention supplies provided for a trial will be stored, dispensed, accounted for, and documented. Products that are not supplied specifically for an investigational trial do not need to be stored in the research pharmacy and do not need to adhere to the stringent storage and accountability requirements pertaining to study products. Some examples include drugs that are standard of care.

In circumstances where a site cannot comply with the general standards outlined in this document, the site must inform and obtain approval from DMID.

1.3 Resources

1.3.1 Contacts

Division of Microbiology and Infectious Diseases (DMID)

Office of Clinical Research Affairs (OCRA)

Address:	OCRA Help Office of Clinical Research Affairs DMID, NIAID 6610 Rockledge Dr. Bethesda, MD 20892 (express delivery zip code 20817)
Telephone:	301-496-7607
Fax:	301-480-0728
E-mail:	ocrahelp@niaid.nih.gov

1.3.2 Guidelines Applicable to Pharmacies

The following guidelines may be applicable to investigational pharmacies and may be accessed on the resource Web sites:

- International Conference on Harmonization Guidelines (ICH)
- Food and Drug Administration Guidance Documents (FDA)
- Regulatory File Document Guidelines (DMID)
- Source Documentation Standards Guidelines (DMID)

1.4 Pharmacy Standard Operating Procedures

DMID requires that sites have pharmacy standard operating procedures (SOPs) in place prior to the initiation of a clinical trial. The method of obtaining such SOPs is dependent on the study. The research pharmacist is responsible for establishing internal policies and procedures for the safe and proper use of study products and will perform the day-to-day dispensing and accountability activities.

1.5 Glossary of Terms

- **Clinical Research Site:** Discrete locations (eg, hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) where qualified professionals conduct clinical trial research in accordance with Good Clinical Practices (GCP).

- **Clinical Trial/Study:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological, pharmacodynamic and/or other effects of a study product(s), and/or to identify any adverse reactions to a study product(s), and/or to study absorption, distribution, metabolism, and excretions of a study product(s) with the object of ascertaining its safety and/or efficacy.

- **Form FDA 1572:** A federal form serving as a statement by the investigator that he will abide by the federal guidelines set forth in the Code of Federal Regulations for the use of drugs in an investigational setting.

- **Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

- **Institutional Review Board:** An independent body constituted of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

- **Investigator of Record:** Also known as the principal investigator (PI), this individual is responsible for the conduct of a clinical trial at a clinical research site. This person is the signatory for the Form FDA 1572 (Investigational New Drug [IND] studies) or the IoR Agreement (non-IND studies). Written delegation of authority for specific study responsibilities may be given to qualified individuals.

- **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, SOPs, GCP, and the applicable regulatory requirements.

- **Protocol:** A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial; the protocol usually provides the background and rationale for the trial, but these could also be provided in other protocol-referenced documents.

- **Protocol Deviations:** Any nonadherence to that which is outlined in the protocol.

- **Quality Assurance (QA):** All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

- **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 Pharmacist:** An appropriate, qualified individual (ie, licensed/ registered, if appropriate) designated by the IoR to perform the day-to-day pharmacy activities and study product management including, but not limited to, the procurement, storage, preparation, dispensing, and final disposition of study products for DMID-sponsored or DMID-funded clinical research trial(s).

- **Research Pharmacy:** 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 (eg, dispensary, drug storage unit).

- **Study Product:** Any drug, biologic, vaccine, radiopharmaceutical, item, or device that is provided for the study or identified in the protocol as being a study product.

2 Inventory Control/Management

The IoR or designated individual (eg, research pharmacist) is responsible for ordering, receiving, inventory, labeling, dispensing, and returning study products properly.

2.1 Ordering and Receipt of Study Product

2.1.1 Study Product Ordering

- A proper communication plan must be developed between the product supplier and the study site to facilitate study product ordering and receipt. This plan includes contact individuals, phone numbers, fax numbers, and e-mail addresses, as appropriate;

- Ordering of study product(s) may be conducted by the IoR, study coordinator, or research pharmacist;

- If an individual other than the research pharmacist is responsible for ordering of study product(s), the pharmacy must notify the IoR and/or study coordinator of inventory levels which merit product reorder. This process will be established by the IoR and observed usage patterns;

- Study product(s) may be ordered manually or electronically from the product supplier with approval from DMID;

- If there is no contact from DMID or the supplier within 5 business days after requesting a shipment, DMID should be contacted promptly;

- Personnel responsible for ordering of study product(s) must establish a procedure to ensure that sufficient drug supply is available for the duration of the study if so required per a specific protocol.

2.1.2 Study Product Receipt

- Arrangements must be made between the product supplier and the study site to determine the most appropriate time and place for study product delivery. These arrangements will be agreed upon prior to delivering study product;

- Upon receipt of study product(s), the Investigator of Record or designated individual must ensure that the information on the packing slip matches with what has been sent to the site;

- At a minimum, the recipient should verify the following:

    - Product identification
    - Amount of product received
    - Lot numbers
    - Expiration dates
    - Physical product is in good condition
    - Storage conditions have been maintained

- The recipient must notify the supplier of the receipt and condition of the study products, according to the product supplier's specified instructions;

- If there are any discrepancies discovered upon receipt of the study products, the supplier and/or DMID will be promptly notified, and this notification must be dated and documented in the shipping records;

- If there is any evidence of breakage, compromised storage conditions (eg, refrigerated items that are not refrigerated upon receipt), or product tampering, the supplier and/or DMID will be notified promptly. Delivery issues must be documented in the shipping records. The study product must be quarantined and maintained under correct (manufacturer or protocol-specified) storage conditions until further instructions are given;

- Copies of shipping inventories and packing slips along with any correspondences with the supplier or DMID must be saved with other study records;

- Study products should not be dispensed until they are properly inventoried and the quality of the product is verified by authorized personnel.

2.2 Inventory and Accountability

- Although the IoR is ultimately responsible for ordering and accountability of all study products in his/her investigational trial, the research pharmacy shares this responsibility when it accepts/receives the study product;

- All study products supplied for a study-specific protocol, whether they are investigational or commercially available, must be accounted for in a manual or electronic accountability log. If an electronic accountability log is used, it must have an audit trail;

- Accountability of study product must be documented from the time of initial product receipt, dispensation, and final disposition of study product;

- Each time a study product is dispensed to a subject, received from the supplier or other source, and/or returned, destroyed, or transferred to another study, the occurrence must be documented on the accountability log. This log should indicate amounts received from the supplier, delivered/dispensed to the clinic or subject, returned to the supplier, disposed/destroyed, etc, as appropriate per protocol;

- Quality assurance and accountability may be performed through verification of inventory each time a drug is dispensed;

- Subject dispensing must also be compared with drug accountability logs for consistency to ensure that all subjects scheduled to receive a study product are enrolled in the study;

- Physical inventory of study products must be conducted at minimum of once quarterly to confirm that quantity on hand is consistent with the inventory balances on the accountability log. These procedures include a cross-check of drugs in stock with the amounts recorded on the drug accountability records, and a cross-check of expiration dates, preparation dates and lot numbers;

- Protocol specific inventories may be required for certain clinical trials. Such requirements should be verified in the protocol or study Manual of Procedures (MOP) prior to study enrollment;

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

- If the attempt to reconcile a discrepancy is unsuccessful, the actions attempted by the pharmacist must be documented on the accountability records and in a written report submitted to DMID.

2.3 Product Expiration Review

- Systems must be in place to periodically monitor study product expiration dates;

- Quarterly monitoring is required at a minimum, but monthly monitoring is recommended;

- Expired products must be separated from active study products and placed in quarantine until they are destroyed on site or returned to the supplier;

- Disposal of expired products should be carried out on a quarterly basis or more frequently, as appropriate;

- Method of expired product disposition is at the discretion of DMID or the research sponsor (if other than DMID). Arrangements for product disposition may be outlined in a protocol, in a MOP, or conveyed in a written document.

2.4 Study Product Transport and Delivery

- An agreement outlining aspects of study product transport should be made between the research pharmacist and clinic in advance. This agreement may include the method of study product delivery, maintenance, and documentation of appropriate transport conditions and chain of custody. Documentation of this agreement may be kept in the pharmacy, as applicable;

- For research being conducted at locations other than the main site, a plan must be developed for the custody of study products prior to dispensing drugs at that location;

- Upon receiving study product(s) from areas outside of the research pharmacy, the research pharmacist must verify that the study product was maintained at appropriate storage conditions;

- Study products that have been supplied for a protocol must be packaged in containers designed to maintain the proper storage conditions during transport. Study products include additional pharmacy equipment to quantifiably document that storage conditions have been maintained;

- Chain-of-custody documentation must be maintained for all personnel involved in the transport and handling of study products, including the person delivering the product and the person receiving the product, as appropriate.

2.5 Study Product Disposition

- Study products may be returned or have an alternate means of disposal. For example, study products may also be destroyed on site, transferred to a different protocol, or released for clinical use;

- The means of study product disposal is at the discretion of DMID and/or the research sponsor (if other than DMID). The arrangements for disposal of a study product may be outlined in a protocol, in a MOP or conveyed in a written document;

- The pharmacist must provide written verification on the accountability records when study product supplies that have been supplied for a protocol are returned or destroyed, either before or at study completion (as applicable to the protocol);

- At study completion, study supplies must not remain at the site unless otherwise specified in the protocol or by DMID.

2.5.1 Study Product Return

- Reasons for which study products may be returned are as follows:

    - The clinical protocol has been completed or terminated at a site and undispensed study products may not be transferred to another DMID protocol;
    - The study product was damaged when received at the pharmacy/ clinical 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; and
    - The manufacturer has recalled the study product.

- A study product recall system must be in place for identifying, retrieving, and returning recalled study products. The pharmacist must respond immediately to recall notices and return study agent as indicated on the recall notice;

- 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 the product supplier.

2.5.2 On-site Destruction

- Reasons for which study products may be returned are also applicable to study product destruction;
- Written permission from DMID and/or the supplier is needed prior to on-site destruction;
- Sponsors, if other than DMID, may have additional requirements for notification or permission;
- Medical waste standards must be strictly adhered to. Usually, destruction includes the process of autoclaving;
- Destruction of study product must be documented in the accountability log. DMID and/or the supplier may request a copy of this documentation.

2.5.3 Study Product Transfer

- For some DMID-sponsored protocols, unused study products from a completed protocol may be transferred to an active protocol that requires the use of the same study product;
- Study product transfer, as outlined in this section, applies only to intra-institutional transfer of study products that were shipped for a specific DMID-sponsored protocol;
- Under no conditions should study products be transferred from one protocol to another protocol without prior authorization from DMID and/or the product supplier;
- The following conditions are required for intra-institutional study product transfers:
    - A transfer request that is approved by DMID and the supplier;
    - Study product is being transferred within the same site;
    - Study product is being transferred from a completed or discontinued protocol to an actively accruing protocol within the same site;
    - The protocol to which the study product is to be transferred is a DMID-sponsored protocol.

- Products that are expired or have not been properly stored must not be transferred;

- The transfer of the study product from one protocol to another must be recorded on the corresponding accountability records for both protocols and must include the date of occurrence.

3 Storage and Handling of Study Product

The pharmacy will provide proper storage conditions for study products, including segregation and controlled environmental conditions. Study products that are not stored in the pharmacy (eg, stored in the clinic) are not the responsibility of the research pharmacist and additional guidelines will be available for storage in such cases. However, once study products are received by the pharmacy from another location, the research pharmacist must verify the identification, quantity and the condition and quality of study product are adequate.

3.1 Security, Segregation, and Space

- Upon receipt, all study products supplied for a specific protocol must be stored in the research pharmacy;
- Study products and supplies must be kept under the custody of the research pharmacist;
- The storage area for study products and supplies must have limited access and be locked when not in use;
- Storage does not require a separate locked area within the pharmacy unless the medication has specific storage requirements defined within the protocol;
- Access is limited to essential and authorized research personnel, such as the designated research pharmacist or his/her designee;
- Systems must be in place for identifying and alerting staff when proper security conditions have been compromised;
- If security has been compromised, the IoR and DMID must be notified. This breach of security, along with additional correspondences, must be documented;
- Study products must be segregated from nonstudy products;
- Adequate space, equipment, and supplies for storage, preparation, packaging, and dispensing of study products must be assessed prior to study product delivery;

- Study products requiring special storage and/or handling must be identified and availability of space and equipment for storage will be determined by the research pharmacist before receipt of the study product.

3.2 Environmental Control

- Proper storage conditions should address issues such as temperature, light, moisture, ventilation, and sanitation, as applicable per the protocol;

- Study products must be stored away from food, specimens, or any other products that may contaminate or compromise the quality of the study product;

- Temperature storage for study products is protocol specific. Detailed instructions regarding appropriate temperature maintenance are described in the product package insert or the investigator's brochure.

- Temperature control must be maintained from the time of receipt of study 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 product supplier;

- Appropriate temperature conditions must be maintained during transport of study product to and from the pharmacy (eg, to the clinic, to investigational satellites). Requirements for special storage conditions will be identified prior to transport. This includes maintenance of the cold chain and temperature monitoring, if applicable;

- Ongoing temperature logs must be kept for areas of study product storage. Electronic temperature logs are strongly recommended. Electronic readings will be recorded every 15 minutes, at minimum. If temperature recordings are logged manually, then daily temperature readings will be maintained, at minimum;

- Drugs requiring room temperature maintenance conditions must be stored between 20°C and 25°C, unless otherwise indicated by the protocol;

- If storage conditions have been compromised (ie, temperature exceeds allowable range) or if there is any suspicion that study product(s) have not been stored properly, the following actions must be taken:

    - Quarantine study product(s) suspected of improper storage;

- Maintain product under correct storage conditions until further notice;

- Contact the supplier and/or DMID immediately (provide: protocol number, protocol name, amount of storage/temperature violation, and amount of storage violation time);
- Document the occurrence.

- Systems must be in place for identifying and alerting staff when proper temperature storage conditions have been compromised (ie, thermometer with alarm functions). Procedures outlining roles and responsibilities will be in place to ensure that storage issues have been addressed and rectified in an efficient manner.

3.3 Storage Equipment

- Refrigerators must be provided for study products requiring refrigeration. They must be maintained at temperatures between 2°C and 8°C and adequate space must be provided for storage of study products.

- If deemed necessary, appropriate freezer space must be provided, including:

    - Freezer space for study drugs requiring storage between -20°C and -10°C;
    - Freezer space for study drugs requiring storage in less than -70°C

- Storage equipment (eg, refrigerators, temperature monitors) must be maintained and calibrated according to the manufacturer's specifications for optimal quality and use;

- The site should have a plan that outlines the procedures and responsibilities in case of an emergency. For example, in the case of a power outage, an identified backup power source must be available to supplement the primary source, if needed. In the case of an equipment malfunction, the pharmacy must have arrangements for alternate storage to maintain study products within appropriate conditions.

4 Study Product Dispensing

This section discusses the minimal requirements prior to and during dispensing of study products. Dispensing of study product supply will be coordinated through the research pharmacy. Once a study product is dispensed, the IoR must ensure that study products responsible to him/her are administered in accordance with research standards and DMID requirements.

4.1 Authorized Prescribers

- Prescribers must be licensed clinicians allowed to prescribe in the site's jurisdiction;
- A mechanism must be established to ensure that study products are dispensed only upon the order of the IoR or a licensed clinician directly responsible to the IoR as stated on Form FDA 1572 (IND studies) or the IoR agreement (non-IND studies). Form FDA 1572 is a binding and legal document, whereby completing and signing the form, the IoR has certified that the study product will be administered only to subjects under his/her personal supervision or under the supervision of subinvestigators responsible to him/her;
- The investigator and research pharmacy must have a proper communication plan to notify the research pharmacist of authorized prescribers for an investigational trial;
- If the physician initiating an order for a study product is not listed as an authorized prescriber, the pharmacist must contact an authorized prescriber to verify that the ordering physician has the authority to prescribe the study medication;
- Prescriptions or orders written by anyone other than an authorized prescriber must not be filled.

4.2 Essential Information on Study Agents

4.2.1 IRB-approved Protocol

- The pharmacist is responsible for establishing a system to ensure that the current IRB-approved version of the protocol is on file for reference and is being followed when dispensing the protocol-specific drug;

- Any additional versions of the protocol should also be on file if there are subjects being followed on that version;

- The research pharmacist should receive and retain a copy of all bulletins, clarifications, or letters of amendment for each protocol.

4.2.2 Investigator's Brochure/Product Package Insert

- A copy of the study-specific investigator brochure or most recent product package insert, containing current information as supplied by the manufacturer, is distributed to the appropriate sites/centers along with the latest version of a particular protocol;

- Such documents must be issued to the research pharmacist and maintained by the pharmacy for reference when dispensing;

- The information contained within the investigator brochure is proprietary and should not be reproduced or distributed to individuals outside of the research team (eg, pharmacists, investigators, other healthcare professionals involved in the specific study).

4.3 Prescriptions and Medication Orders

- Prescriptions are manually/hand-written with ink, typed, or generated by computer with an electronic signature;

- In general, medication orders should include:

    - Protocol number
    - Date
    - Subject identification number
    - Randomization number
    - Height and weight, if applicable
    - Medication prescribed (if study is blinded, study product will be labeled accordingly)
    - Quantity or instructions to indicate appropriate amount to be dispensed
    - Route of administration (if study is blinded, study product will be labeled accordingly)

- Prescriber's signature

- All prescriptions must be signed by a clinician who satisfies all the requirements for being an "authorized prescriber." By signing his/her name, this prescribing clinician is taking full responsibility for ensuring that the prescription conforms to the protocol and all applicable laws and regulations. In case the prescription does not conform to all essential aspects of the protocol, federal regulations, and DMID requirements, this prescribing clinician will be held responsible;

- The following items and actions are not permitted:

  - Signature stamps
  - Signing blank prescription forms
  - Postdated prescriptions

- An agent for the IoR or subinvestigator may prepare prescriptions in advance for the signature of a licensed practitioner;

- It is not permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add his/her own name in an effort to make it legal (eg, a nurse who is not an authorized prescriber may not sign a doctor's name to a prescription and then add his/her own name to it).

4.4 Investigational Study Summary Sheet

- Health care providers should be informed about the overall study objectives and procedures for a specific protocol;

- Nurses, pharmacists, physicians, and other healthcare practitioners involved in dispensation or administration of study products should have adequate written information about the study product;

- A study-specific pharmacy dispensing procedure or a study summary sheet outlining important pharmacy aspects in a clinical trial is recommended for prompt and accessible study product information. The following may be included in such a document:

  - Study identification (eg, study title, IRB number, protocol approval/renewal date and version number, IoR, authorized prescribers, protocol-assigned research pharmacist)
  - Background information

- Study design
- Treatment plan
- Drug description (eg, pharmacology, storage requirements, method of dose preparation and administration)
- Blinding/randomization procedures (if applicable)
- Compounding procedures
- Labeling information and samples
- Handling and disposition recommendations/requirements
- Authorized prescribers
- Documentation requirements (eg, randomization log, test article accountability log)

4.5 Study Product Preparation

- Study products that require any type of manipulation, such as mixing, formulating, counting, or compounding, should be handled by the pharmacist or pharmacy assistant;

- Appropriate space and equipment must be provided for study product preparation;

- Any personnel assisting in the preparation of study product(s) must be properly trained. If a pharmacy assistant or other pharmacy personnel aid in the preparation of a study product, his/her name should also be documented;

- The pharmacy assistant is directly responsible to the research pharmacist and therefore, all conduct, quality and accurate manipulation performed by the assistant will be reviewed by the research pharmacist;

- Preparation instructions for study products are outlined in the protocol and in additional accompanying documents, such as a MOP document;

- Supplies provided specifically for the preparation of study product(s) may be shipped directly to the research pharmacist;

- Final verification of all study products will be completed by the research pharmacist to ensure that correct preparation of the product was accomplished. This will be done prior to dispensing and/or delivery to the study site; and

- Preparation review and final verification by the pharmacist must be documented.

4.6 Labeling Requirements

- Study products must be labeled properly to ensure safe administration and use by the research staff and subjects;

- Prescriptions must be labeled in a format that adheres to all applicable labeling requirements per the protocol and regulations and still maintains subject confidentiality;

- It is the research pharmacist's responsibility to know the labeling requirements for his/her jurisdiction;

- Labels may include:

    - Name, address, and phone number of dispensing site
    - Protocol number
    - Subject identification number
    - Randomization number
    - Dispensing date
    - Directions for use/administration
    - Number of dosing units dispensed
    - Prescribing investigator's name
    - Name of study product or placebo, if appropriate (ie, unblinded study where confidentiality is not an issue)
    - Expiration date

- Expiration date should be one year from dispensing unless the manufacturer's expiration date for the drug expires before that time or the protocol states otherwise; and

- A copy of the study product label must be stored with other protocol-specific records, as applicable per the protocol.

5 Record Keeping Responsibilities

The records required for documentation of investigational trials will have limited accessibility. They will be filed separately from other pharmacy documents and records and will be available for inspection if needed. Such records will contain documents needed for protocol-specific dispensing, inventory control records, stability records, and compounding/labeling documents. They may take the form of file folders, one or more 3-ring binders, a filing system, or a combination of these organizational methods.

5.1 Protocol-specific Documents

- The current IRB-approved version for each protocol must be available for reference;
- An investigator's brochure or most recent product package insert must be available for reference;
- A MOP or other additional information to assist in outlining the correct process of an investigational trial must be available for reference;
- Depending on the responsibilities previously defined in the protocol, a treatment assignment list may be developed and maintained by the pharmacist. Access to this information must be limited to only appropriate personnel, especially if blinding is a concern in the trial;
- A study summary sheet outlining important aspects of a clinical trial, such as appropriate dispensing, abbreviated compounding instructions, or labeling requirements, is recommended;
- A study product sample label may be saved to document compliance with labeling regulations and requirements, as appropriate;
- The names of the investigator, coordinator, and product supplier, along with an authorized prescriber signature list, must be maintained for each protocol, as applicable. This list should be updated whenever individuals are added or deleted, but at a minimum of once yearly;
- Any relevant correspondence between the pharmacy and the investigator, DMID, or any other involved authorities that are important to a study must be saved. Some examples of important correspondence include

monitoring reports, audit reports, and information regarding final disposition.

5.2 Inventory Control Records

- The pharmacy must retain copies of all drug inventory records for accountability of study products and supplies;
- Record keeping must be in accordance with the requirements of DMID and regulatory agencies having authority over dispensing and custody of research drugs and supplies;
- A continuous inventory system may include, but is not limited to, the following:

5.2.1 Shipping Documents for Drug Delivery

- Shipping documents include copies of all drug records including order forms, packing slips, and/or invoices and receipts upon delivery from the product supplier;
- The condition of the study product upon arrival should be noted and documented in the shipping records;
- Any correspondence between the research site/pharmacy and the product supplier concerning compromised storage conditions upon delivery to the pharmacy must be documented along with other shipping records.

5.2.2 Storage, Temperature, and Stability Logs

- If, for any reason, security has been compromised, the occurrence, reason(s) explaining the breach of security along with correspondences with the investigator and/or DMID must be retained;
- Temperature logs must be maintained for areas where study products are stored, including the pharmacy or pharmacy satellite;
- Electronic temperature logs are strongly recommended for refrigerators and freezers. Electronic readings will be recorded every 15 minutes, at minimum. If temperature recordings are logged manually, then daily temperature readings must be maintained, at minimum; and

- If, for any reason, temperature conditions have not been preserved, the occurrence must be documented as well.

5.2.3 Chain-of-custody Documentation

- Study products must be tracked and accounted for, even during transport and delivery (eg, to investigational satellites, pharmacy satellites, clinic, study site);

- When study products are transported from one secure area to another, personnel engaged in the transaction should be logged into a chain-of-custody record, as applicable;

- In general, the following information should be documented:

    - Protocol number
    - Investigator and/or site number
    - Name of carrier
    - Name of recipient
    - Name and amount of contents

5.2.4 Preparation and Compounding Logs

- All study products that need to be compounded or prepared specifically for a protocol will be recorded. A separate compounding form may be used to document other products that have been added and amount added during preparation;

- Products or agents that are added during the process of compounding, may also be tracked for completeness of records;

- Names of any personnel, including the research pharmacist and/or pharmacy assistant, aiding in the preparation of a study product must be noted on the compounding forms;

- Final verification by the research pharmacist will be documented with the pharmacist's signature.

5.2.5 Study Product Accountability/Dispensing Logs

- All drugs dispensed in a research protocol will be accounted for in an ongoing inventory system;

- The study product accountability log or dispensing log may take the form of a continuous computerized record or a paper document. If a computerized log is used, it must have an audit trail;

- Information may include:

    - Name, dosage form, strength of the study product
    - Manufacturer or other source
    - Date of receipt of the study product
    - Quantity received
    - Expiration, retest, or repass date (memo from DMID or noted on the protocol indicating that the expiration is centrally managed is acceptable)
    - Control, lot number, or other identification number
    - Investigator of Record
    - Protocol number
    - Subject identification number
    - Quantity dispensed
    - Balance of drug currently available

5.2.6 Return, Transfer, and Destruction Documents

- Any time a study product is returned to the product supplier, destroyed on site, or is transferred from one protocol to another, this occurrence must be documented in the accountability log(s);

- The following information may be included for record keeping:

    - Name and address of IoR
    - Information specific to the drug including but not limited to the drug name, strength, dosage form, quantity of drug per container, number of containers, lot/control number, etc.
    - Date of return/destruction/transfer
    - Name and signature of personnel responsible for destruction.

5.3 Record Retention

- Record maintenance for study products (eg, drugs, biologics, devices, therapeutics) by the research pharmacy must comply with federal and state regulations as well as requirements outlined by DMID;

- For investigational trials where a New Drug Application (NDA) is not being filed, or the study product is not being studied under an IND, records must be retained for a period of at least 2 years following the date the study has been completed, terminated, or discontinued;

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

    - A period of at least 2 years following the date that an NDA is approved for the indication for which it is being investigated
    - A period of 2 years following the date that an IND is withdrawn (if the NDA is not approved for the investigated indication)

- If local policies are stricter than the federal regulations, records should be maintained according to the stricter policy;

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

6 Monitoring and Quality Assurance

The research pharmacist at each DMID-sponsored site is the primary individual who is expected to develop and maintain a quality assurance system assessing technical procedures for study product ordering, control, dispensing, and accountability for a specific protocol. The following section highlights such aspects of research pharmacy conduct that are subject to review for quality assurance.

6.1 Internal Pharmacy Audits

- A systematic process for quality assurance monitoring and problem solving activities should be implemented to internally review and evaluate the quality and appropriateness of the research pharmacy service;
- At a minimum, the research pharmacist should conduct an audit quarterly to ensure compliance with regulations, policies and standards;
- Aspects of study product review 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; and
- In addition to periodically monitoring for quality assurance in the research pharmacy, the pharmacist should also audit and review for quality assurance in the clinic, if applicable.

6.2 External Monitoring/Auditing Visits

- The investigator and research pharmacist msut make arrangements for monitoring/auditing visit(s) in advance, including availability of personnel who will meet the monitor/auditor and accommodations for the monitor/auditor;
- Appropriate space must be provided for the monitor/auditor to conduct his/her activities;
- The focus of the monitoring visits should be on the site operations of the pharmacy or on the conduct of a specific protocol(s), or both;

- All protocol records must be available for inspection and copying by an authorized employee or representative of the FDA or DMID upon request; and

- Pharmacies are usually visited twice a year, but at a minimum of once yearly. Frequency of visits may be increased for more complicated protocols, if problems are identified or upon discretion of DMID.

7 Study Blinding and Randomization

In many DMID-sponsored trials, the pharmacist is unblinded to a subject's treatment assignment and participates in the randomization process to assign a consented subject to a randomized treatment. It is crucial that the pharmacist ensure the scientific integrity of clinical trials by managing access to treatment assignment records in blinded studies and by ensuring that the correct drug is dispensed. For this reason, randomization assignments must be stored in a location with limited access to only appropriate personnel.

7.1 Randomization Assignments

- The process by which a subject is assigned a subject identification number varies according to the site and the protocol;
- The pharmacist should make every attempt to maintain blinding in a study to ensure statistical validity and confidence in data;
- The treatment assignment information must be maintained in a secure location and available only to unblinded study personnel, such as the research pharmacist.

7.2 Unblinding Procedures

- Unblinding is very rare and should not be exercised except in extreme cases;
- A valid reason to unblind might be the need for a treatment decision that can be made only with knowledge of drug assignment;
- In the rare case that the pharmacist receives a request to unblind, he/she must use his/her professional judgment. If there is any way to resolve the situation without breaking the treatment assignment code and without exposing the subject to unreasonable harm, such as simply stopping treatment, this must be exercised first;
- The pharmacist, investigator, DMID, and/or sponsor (if other than DMID) must agree on a procedure for unblinding the treatment assignment in an emergency;
- In general, the IRB should be notified when unblinding has occurred;

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

- The pharmacist must notify the IoR and/or clinical coordinator if the blinded treatment assignment code is broken, if they are not already aware;

- The research pharmacist must report any and all unblinding to DMID as soon afterwards as feasible. This report will include, but is not limited to, the following:

    - The protocol name and number
    - The subject identification number
    - Date and time that unblinding occurred
    - Names of all individuals who were unblinded
    - Reasons for unblinding

8 Protocol Deviations

Protocol deviations may include any action or inaction that is noncompliant with the protocol, protocol summary, GCP, the protocol-specific MOP, or any other information relating to a clinical trial. It is the responsibility of the IoR and research pharmacist to use continuous vigilance to identify and report deviations.

8.1 Pharmacy-related Deviations

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

8.1.1 Storage, Handling and Accountability Deviations

- Improper storage of study products including significant excursions in temperature, moisture, light, etc.
- Incorrect compounding procedure
- Unresolved or unreconciled accountability discrepancies

8.1.2 Dispensing Errors

- Failure to comply with any dispensing or dosing requirements (eg, failure to comply with dose adjustments per the protocol)
- Dispensation of incorrect study medication
- Use of an expired product
- Use of commercial inventory instead of study inventory

8.2 Deviation Reporting

- The IoR and/or study coordinator must be promptly notified of protocol deviations;

- Protocol deviations must be reported within 5 working days of deviation identification or within 5 working days of the scheduled protocol required activity;

- A DMID Protocol Deviation Form must be completed for each protocol deviation. The completed form must be sent to DMID and the IND

sponsor, if other than DMID, or as specified by the protocol or Manual of Procedures. The submission may be via fax or Web based, as applicable to the site and protocol;

- Study-specific requirements for protocol deviation reporting is addressed in the protocol;

- Protocol deviations should be reported to the IRB according to the IRB-specific guidelines;

- All protocol deviations must be addressed in the study-specific source documents;

- The report may include the following:

    - Name of site
    - Name of IoR
    - Dates (including date of deviation, date of report, etc.)
    - Protocol number
    - Subject identification number, if applicable
    - Description of incident or problem
    - Reason(s) for the incident
    - Effects of protocol deviation
    - Description of steps taken to resolve, reconcile and/or prevent future recurrence of the deviation

9 Additional Considerations/Responsibilities

9.1 Pharmacist Coverage

- The research pharmacist should be available at all times for study product dispensing;
- If the research pharmacist is absent, an equally qualified individual, a backup pharmacist, must be available who can perform the functions of the research pharmacist;
- The backup pharmacist must be trained in the conduct of clinical trials by the research pharmacist to perform activities including, but not limited to, the following: study product dispensing, receipt and inventory, storage, accountability, and record keeping;
- The backup pharmacist should be knowledgeable about specific aspects of the protocol(s) that they are covering.

9.2 International Site Considerations

- Studies performed in international sites may pose additional challenges in implementation and logistics. Investigators and research pharmacists in international sites must be aware of such challenges prior to starting an investigational study. All potential issues must be addressed and alternate plans reviewed;
- The research pharmacist must be aware of and plan for potential difficulties associated with international sites, such as problems importing study product(s) into and out of a country;
- The research pharmacist must be aware of and plan for complications in the event of a delay in study product delivery. For example, some complications in procurement of study products and supplies into a country may decrease the shelf life of the study product, expose the study product to extreme temperature excursions, or even delay the clinical trial;
- Concerns regarding the storage of study products, especially security, temperature, and moisture must be rigorously addressed. Some issues include differences in ambient temperature, humidity, sanitation, and security of storage units;

- Shipping documentation required for international sites includes commercial invoices and import permits (if applicable), in addition to receipts and records required for domestic sites.

Appendix A Guidelines and Instructions for Division of Microbiology and Infectious Diseases (DMID) Clinical Trials

"STORAGE AND HANDLING FOR AREAS OUTSIDE OF THE PHARMACY"

1 Storage of Study Product

1.1 Security, Segregation and Space

- Investigational products that are not stored in the pharmacy under the custody of the research pharmacist must be stored under the direct supervision of the investigator;
- Security and space requirements for storage in the pharmacy also apply to study products stored outside of the pharmacy. For example, the storage area in the clinic must be clean and locked, with an alarm system to notify if there is a breach of security;
- Access to the storage area must be limited to only appropriate and authorized research personnel;
- Study products must have appropriate storage space to allow for appropriate segregation from nonstudy products;
- Availability of adequate space must be assessed prior to study product delivery to the storage area;
- Security for storage areas of study product must be logged and documented;
- Storage and security used by the investigator may be subject to auditing by the research pharmacist to ensure that the methods used are in compliance with federal and state regulations, institutional policies, and DMID requirements;

1.2 Environmental Control

- Proper storage conditions, including protection from light and moisture, temperature, ventilation, and sanitation must be maintained for the study product within the storage area;

- Study products must not be stored with food, specimens, or any other products that can contaminate or compromise the quality of the study product;

- Temperature monitors and alarm systems must be active for temperature excursions;

- Storage temperature must be documented with ongoing temperature logs;

- If storage conditions have been compromised (eg, temperature exceeds allowable range) or if there is any suspicion that study product(s) have not been stored properly, the following actions must be taken:

    - Quarantine study product(s) suspected of improper storage
    - Maintain product under correct storage conditions until further notice
    - Contact the supplier and/or DMID immediately (provide the following information: protocol number, protocol name, amount of storage/temperature violation, and amount of storage violation time)
    - Document the occurrence

- Roles and responsibilities must be prospectively outlined in the case of emergency storage and temperature malfunctions.

1.3 Storage Equipment

- If deemed necessary, appropriate refrigerator and/or freezer space must be supplied for storage of cold-chain study products;

- Availability of storage equipment (eg, refrigerators, freezers) must be assessed prior to study product delivery to the study site;

- The temperature within the storage equipment must be monitored continuously;

- Storage equipment must be maintained and calibrated according to the manufacturer's specifications for optimal quality and use.

2 Pharmacy Returns

- Correct storage conditions must be maintained during transport back to the research pharmacy;

- Conditions at which study products were stored, including temperature, must be easily assessed by the research pharmacist during receipt of study products; and

- If needed, temperature monitors must be used to clearly display storage conditions during transport.