# Study Product Guidelines and Considerations

 **Purpose:** The document is intended to guide research teams on important considerations and best practices regarding receipt, storage, use, and disposition of study product during a study to assure smooth study conduct, valid study product handling, and compliance with applicable regulations and guidelines. These best practices apply to all clinical research, whether or not the research falls under IND regulations or other regulatory regimes.

 **Audience/User:** NCCIH Clinical Investigators, site study coordinators, and clinical pharmacy staff

 **Details:**

* General considerations, applicable to all interventional clinical research studies, are presented in Section 1 of the document.
* Additional detailed suggestions and guidance are provided in Section 2 of the document.
* Further operational details will be covered during a site initiation visit.
* Note: Synonyms for “study product” may include any of the following: study intervention, investigational product, investigational medicinal product, investigational drug, investigational device, study drug, test article, or clinical trial material. Examples of study product include prescription and over-the-counter medications, investigational compounds, medical devices, toothpaste, fluoride varnish preparations, any combinations of the foregoing, and other such interventions.

## Tool Revision History

Version Number

Version Date

Summary of Revisions Made:

Version Number

Version Date

Summary of Revisions Made:

Version Number

Version Date

Summary of Revisions Made:

Version Number

Version Date

Summary of Revisions Made:

## 1. Considerations and Principles

### 1.1 Definition of study product

Study product is the general term for any of the following: study intervention, investigational product, investigational medicinal product, investigational drug, investigational device, study drug, or clinical trial material. Study product is that which is used in an interventional research project, whether or not the research is regulated, for example as a drug or device study, under FDA regulations.

### 1.2 Investigator responsibilities

For IND and non-IND studies alike and unless otherwise specified, the Investigator is responsible for managing and documenting all of the following: ordering, receiving, and tracking inventory; storing, dispensing, and returning study product properly; and, where necessary, labeling of study product prior to dispensing according to protocol guidelines and good manufacturing practices (GMPs) if applicable. In practice, a subset of these responsibilities is usually delegated to the research pharmacist. The Investigator is responsible for monitoring pharmacy activities to ensure all requirements are being met.

### 1.3 Accountability definition and principles

Study product accountability is the process of documenting all aspects of study product receipt, storage, use, and disposition so that a full accounting of each unit can be made. For IND-regulated studies, several regulations describe sponsor/Investigator obligations to manage study product appropriately. These can be found at 21 CFR Parts 312.57(a), 312.59, 312.61, and 312.62(a). Additional principles, for IND and non-IND studies alike, include the following:

* All study product supplied for a protocol must be accounted for and tracked in a manual or electronic accountability log for the study. Accountability of the study product must be documented from the time of initial receipt through dispensation and final disposal of leftover study product. The accountability log should indicate the date, amounts, batch numbers, and conditions at receipt for all materials received from the supplier.
* Each time study product is dispensed from the pharmacy to a participant, the occurrence should be thoroughly documented in the accountability log. The accountability log should be unique to a study and should indicate the date, batch number(s), expiration date, unique bottle or kit identifier (if applicable), and amounts dispensed to the participant and date, amounts, and condition of materials returned/destroyed/disposed by the participant. A balance of remaining study product should be maintained and documented in the study’s accountability log.
* At study completion, remaining study product should be returned or destroyed as dictated by the protocol, specific Investigator instructions, or other documented instructions. The balance returned or sent for destruction should be recorded in the study’s accountability log.

Quality assurance reviews/inspections of study product accountability documentation will be performed at intervals during a study by a clinical monitor. Similar document reviews may be conducted at any time by an auditor.

### 1.4 Placebos

For placebo-controlled studies, placebos should match the shape, color, burnish, smell, taste (if applicable), and any other defining characteristics of the active study product as much as possible. If the main supplier of study product does not have matching placebos on hand, an alternate manufacture strategy will be needed, with additional time set aside for planning and executing the manufacture; consult with Office of Clinical Trials Operations and Management (OCTOM) for additional specific advice.

Special packaging considerations may apply if the study calls for administering a mixture of active and placebo study product (e.g., to achieve multiple blinded dose levels). Packaging, including masking, should be conducted by dedicated packaging staff unaffiliated with the Investigator or any clinical staff involved in the conduct of the study. Randomization codes should be generated by an impartial statistician likewise uninvolved in the study, and these codes should be maintained in sealed, tamper-evident packages or in an equivalent locked electronic form if the codes are maintained electronically.

### 1.5 Initial planning and ordering of study product

It is important to communicate early with the study product supplier to ensure that study product is delivered in time for planned study start; delivery can sometimes occur months after a request is made. Sufficient quantities should be obtained to cover all possible study enrollment scenarios and should further allow for (a) laboratory procedures such as dilutions or unit-dose preparation that may involve loss of material as well as (b) accidental loss of, damage to, or destruction of finished material during the course of the study. If study product is not being donated, provisions should be made to ensure the budget can cover costs for this larger quantity of study product.

The frequency of study product shipments from the supplier should be calibrated with anticipated enrollment rates and the known stability of the drug. That is, products with short shelf lives should be ordered in frequent, small batches to ensure fresh material is always available for enrolled participants. Whenever possible, all shipments should come from the same manufacturing lot.

## 2. Operational Guidelines

### 2.1 Study product ordering and receipt

Study product may be ordered from the supplier, distributor, or manufacturer by the Investigator, study coordinator, or research pharmacist as designated by the Investigator.

Arrangements should be made between the product supplier and the study site to determine the most appropriate time and place for study product delivery, particularly for products requiring special storage conditions. Additional considerations apply for shipments made from locations outside the United States; consult staff from the OCTOM for drug importation guidance.

Upon receipt of study product, the Investigator or designee should ensure that the information on the packing slip matches the study product received. 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
* Maintenance of proper storage conditions

Evidence of breakage, compromised storage, or product tampering should be reported to the supplier immediately. The study product should be quarantined and maintained under the correct storage conditions until further instructions are given.

**Accountability**: Enter the amount received, lot numbers, expiration dates, and condition of the study product into the study’s accountability log. Keep copies of shipping inventories and packing slips with the accountability records.

Note: study products must not be dispensed to study participants until they are properly inventoried, the quality is verified and proper authorization has been received that the enrollment process can begin.

### 2.2 Study product storage

Study product should be stored in a limited-access location and according to instructions received from the supplier, distributor, or manufacturer. Proper storage conditions should address the temperature, light, moisture, ventilation, and sanitation needs of the study product. A log of key environmental conditions should be kept (e.g., a manual log or an automated recording of temperature and humidity) to document that required conditions were maintained during the entire storage timeframe.

Environmental controls (e.g., for temperature or light) may also be needed during transport between the pharmacy and the dispensing area. Meeting these handling requirements should also be documented.

Study products that are to be shipped offsite for a protocol must be packaged in containers that maintain the proper storage conditions during transport. Maintenance of proper storage conditions during transport should be documented if possible. Chain of custody documentation should also be maintained for the transport, handling, and receipt of study product.

If storage conditions have been compromised (e.g., temperature excursions from the allowable range), or if there is any suspicion that the study product has not been stored properly:

* Quarantine the study product.
* Maintain the study product under the correct storage conditions until further notice.
* Contact the Investigator immediately, providing the protocol number, the protocol name, description of the degree of temperature/storage violation, and the length of storage violation time.
* Document the occurrence and the action taken per Investigator input (e.g., return to general inventory, return to the manufacturer, onsite destruction).

### 2.3 Study product requisition and dispensation

Study product should be maintained under the control of pharmacy staff at all times until a request is made by an authorized Investigator for release to an authorized trial staff person for administering to a specific enrolled trial participant. A mechanism must be established to ensure that the study product is dispensed only upon the order of the Investigator or the licensed clinician directly responsible to the Investigator, as stated on Form FDA 1572 (IND studies) or the Investigator agreement (non-IND studies). Form FDA 1572 is a binding and legal document, whereby in completing and signing the form the IoR has certified that the study product will be administered only to participants under his/her personal supervision or under the supervision of sub-investigators responsible to him/her. Prescribers (investigators) must be licensed clinicians allowed to prescribe in the site jurisdiction.

For intramural studies, study product delivery to the designated trial staff person is authorized by means of a study product order (e.g., a prescription) issued by the Investigator. For extramural studies, a similar process should be in place to document a request for study product from the Investigator for dispensing to a specific trial participant. Study product orders are an important part of the accountability documentation chain for all study products, prescription or not.

In general, study product orders should include the following:

* Protocol number
* Date of the order
* Participant identification number
* Randomization number, if available
* Participant height and weight, if applicable
* Study product prescribed (if study is blinded, the study product will be labeled accordingly)
* Quantity or instructions to indicate appropriate amount to be dispensed
* Route of administration
* Prescriber’s signature

The pharmacist should ensure that there is a current IRB-approved version of the protocol, Investigator’s Brochure, and/or a product package insert on file for reference, and that the protocol is followed when dispensing the protocol-specific drug. Additionally, the research pharmacist should receive and have on file all protocol amendments, study-specific manuals of procedures (SOPs), and study-related correspondence, as applicable.

If the study product is custom-compounded at the pharmacy for use in the study, specific procedures should be established (and verified/validated as appropriate) before study conduct gets underway. Such procedures may be defined in the protocol or in specific study product preparation instructions. All preparation procedures must be fully documented, including details on specific equipment used, lot numbers for all ingredients, and initials of the person performing or reviewing each step.

Specific procedures should be established to ensure appropriate allocation of active vs. placebo study product in the case of a blinded study.

Study product delivered by the pharmacy for use in a study must be labeled with the following information at minimum:

* Protocol number
* Participant number or identifier
* Amount dispensed
* Dosing and storage instructions
* Date of dispensing

**Accountability:** Pharmacy staff should record in the study’s accountability log the date of dispensing, participant number, amount, and lot number(s) of the study product dispensed.

### 2.4 Study product use and return

The date/time and amount of study product administration to an identified study participant should be documented in the case report form (CRF) for that participant. If the participant is sent home with a supply of study product for use over a period of time, the amount given to the participant and the day/time that the study product was given to the participant should likewise be recorded in the CRF.

Any study product returned by a study participant should be returned to the pharmacy and may also be recorded on the CRF if it is so designed.

**Accountability:** Pharmacy staff should record study product returned from a study participant in the study’s accountability log.

### 2.5 Study product disposition

At the end of a study, the Investigator or designee should ensure that leftover study product is either destroyed with appropriate documentation thereof, donated as agreed to with the manufacturer (for marketed products only), or returned properly to the supplier, distributor, or manufacturer from where it came. Study product should be stored and shipped to the appropriate individual under conditions suitable to the product.

**Accountability:** Pharmacy staff should record in the study’s accountability log the amount destroyed/donated/returned, lot numbers, expiration dates, and condition of product.