

ASHP Guidelines for the Management of Investigational Drug Products

Purpose

The purpose of these guidelines is to describe a standardized approach for the management of investigational drug products by the clinical research pharmacy, pharmaceutical industry, and cooperative and research network groups. The scope of these guidelines includes the receipt, accountability, storage, handling, preparation, dispensing, and final disposition of investigational drug products to ensure inspection readiness and compliance with regulations as provided in the Code of Federal Regulations (CFR), 21 CFR, Part 312,¹ as well as International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice² (GCP) (described in 21 CFR Part 312, section 120) and Good Manufacturing Practice³ (GMP) (described in 21 CFR Part 211), and the approved clinical study protocols. These guidelines will facilitate the adoption of best practices by new and established clinical research pharmacies (e.g., investigational drug service [IDS]) in collaboration with the pharmaceutical industry for the optimal management of investigational drug products. The ultimate goals of standardizing the management of investigational drug products are to improve patient safety, improve efficiency, and provide robust clinical data that allow new and innovative medications to reach the patients who need them.

Value of a Clinical Research Pharmacy

Since 1962, the Kefauver-Harris Amendments⁴ to the Federal Food, Drug and Cosmetic Act have required drug manufacturers to prove that new drugs are safe and effective. This requirement is the foundation for clinical studies as they are known today. The pharmaceutical industry spends billions of dollars each year to test investigational drug products for safety and efficacy, and it may take a decade or more for a drug product to obtain market approval.⁵ Thousands of subjects have been asked to consent and take part in the clinical research study process.

The current practice of the biopharmaceutical industry is to manufacture, distribute, and monitor investigational drug products for clinical research use while utilizing the expertise of healthcare providers, especially pharmacists, who manage the products at clinical study sites. It is imperative that pharmacists participating in these studies have the expertise to manage investigational drug products appropriately. The clinical research pharmacist is a critical member of the clinical study site team and has the expertise to understand the special handling requirements of investigational drug products.⁶ Clinical research pharmacists understand the importance of managing and properly documenting investigational product receipt, storage, dispensing, returns, and final disposition. Failure to accurately document investigational product accountability can undermine the validity of clinical study data, which could spur sponsors to halt a site's participation in current or future studies and result in a loss of local patients' access to clinical studies.

Clinical research pharmacy is a specialized area of pharmacy practice that has evolved to meet the needs of the clinical study sites, help ensure research participants' safety, and protect the integrity of clinical study data. Clinical research pharmacists possess an expert working knowledge of the clinical research study process, human subject protection, and national and local regulations governing drug research. They are responsible for providing information to the appropriate healthcare team members, including pharmacy staff, who may be unfamiliar with the investigational drug product, enabling them to correctly dispense it as described in the clinical protocol and ensure its safe use.

Clinical Research Pharmacy Models

A clinical research pharmacy may be as simple as a part-time pharmacist or as complex as a team of dedicated clinical research pharmacists, technicians, and coordinators. It most commonly is part of the larger pharmacy organization (e.g., the hospital pharmacy). In rare cases, it may be a freestanding entity. As the complexity and volume of clinical studies at an institution increases, the decision to create a dedicated clinical research pharmacy with highly trained and specialized personnel and management can be made.

When establishing a clinical research pharmacy, the appropriate institutional metrics (e.g., staffing-to-order volume ratios)^{6,7} should be used to determine the appropriate staffing, facility, and storage requirements needed to manage investigational drug products. A comprehensive approach will allow institutional leadership to fully support the creation of a clinical research pharmacy and should include a review of the types and therapeutic areas of studies that will be handled.

Each institution must also establish a funding model to support the clinical research pharmacy. This model may include (1) direct cost recovery from the sponsor-investigator, (2) indirect funding (e.g., based on institutional overhead such as grants to conduct research), (3) foundation underwriting of the research, or (4) institutions absorbing the cost of the clinical research. Clinical research pharmacy fees should be included at an early stage during the negotiation of each clinical study budget. Investigational drug products provided by sponsors at no cost to the clinical study site for use in clinical studies must not be charged to study participants.

Within the organization, pharmacy leadership, the clinical research pharmacist, institutional research leadership, and investigators should establish the locations where research participants will receive their care with the appropriate pharmacy support. A review of pharmacy activities and workflow for investigational drug product handling should be performed for the following locations, as appropriate: (1) inpatient units, (2) clinical research unit, (3) ambulatory care or outpatient clinic setting, and (4) a combination of inpatient and outpatient areas. The organization should develop a mechanism to handle participants being treated at multiple locations and facilities.

A dedicated team should be identified as the clinical research pharmacy staff. In institutions with a large volume of clinical studies, the clinical research pharmacy staff may form an IDS with the appropriate management structure depending on the practice environment. Members of the clinical research pharmacy staff must have knowledge and documented training on ICH GCP,² the Health Insurance Portability and Accountability Act,⁸ institutional review board (IRB) review and protection of human subjects,⁹ the *Belmont Report*,¹⁰ and all other competencies and policies required by the institution or the pharmacy.

Facilities, Security, and Limited Staff Access

According to GCP guidelines, the investigational drug product should be stored in a secure location as specified by the sponsor and in accordance with all applicable regulatory requirements.² Some institutions may have separate rooms for the storage of investigational drug products; others may have a separate storage area within the pharmacy department. In either case, the area should be secured (e.g., by key or electronic lock), with entry restricted to clinical research pharmacy or delegated staff.

Each institution must evaluate its ability to provide secure, limited access to investigational drug products. A clinical research pharmacy that does not have continuous (24-hour/365-day) support to provide access to investigational drug products may mitigate the need for access by utilizing regular pharmacy staff and considering on-call support by the clinical research pharmacists to supplement this staff.

Temperature Control and Monitoring

Control and monitoring of investigational drug product storage conditions are important for maintaining the integrity of the products and for the safety of the research participants. Documentation that proper storage conditions in the pharmacy have been maintained must be available. The sponsor shall determine and communicate acceptable storage temperatures, storage conditions (e.g., protection from light), and storage times for the products.¹¹ The clinical research pharmacist must be able to document the temperature storage conditions of the investigational drug products at all times while managed by the pharmacy. Each pharmacy location where investigational drug products are stored must be monitored to ensure that proper temperature storage conditions have been maintained.

Clinical research pharmacy and the pharmaceutical industry shall follow *United States Pharmacopeia* standards for controlled temperature storage.¹² Before the start of activities at the clinical study site, the sponsor should establish and communicate known allowable out-of-range temperatures and the maximum allowable deviation time (i.e., acceptable time out of range) for the investigational drug product. This information will enable the clinical research pharmacy to make independent decisions without quarantining the investigational drug product supply for acceptable excursions. An investigational drug product that does not meet the allowable excursion parameters must be quarantined under the proper storage conditions by the clinical research pharmacy, and the sponsor and principal investiga-

tor (PI) must be notified. Prompt direction from the sponsor regarding how to handle the quarantined product must be adequately documented and kept in the site study file.

If the investigational drug product is sensitive to humidity, the sponsor must work directly with the clinical research pharmacy regarding monitoring requirements for relative humidity.

All locations, including refrigerator, freezer, and room-temperature areas, storing the investigational drug product must have a temperature monitoring device or system. In addition, the temperature monitoring system should be calibrated at least annually to meet National Institute of Standards and Technology standards.¹³ Documentation of the calibration of each device must be maintained and available for inspection. If an electronic temperature monitoring system is not available, a calibrated manual thermometer with the ability to capture daily maximum and minimum temperatures should be used. A daily record of the maximum and minimum temperatures should be maintained.

Equipment used to store investigational drug product should be connected to a backup power supply in the event of power failure. All refrigerators and freezers shall have preventive maintenance completed annually. All calibration and maintenance records should be archived per institutional policy.

Site Qualification

The site qualification by the sponsor determines whether the site meets the potential protocol requirements.¹¹ A pharmacy assessment should be part of the sponsor's site qualification. Ideally, the sponsor's agent should review the site's policies and procedures and applicable sponsor site qualification requirements with the clinical research pharmacy staff. If the sponsor provides a written report of the site qualification to the site PI, a copy should also be forwarded to the clinical research pharmacy. This report serves as the minutes of the visit and agreement of the scope and services the clinical research pharmacy may provide. If a report is not provided, informal notes or minutes may be taken by clinical research pharmacy personnel and kept on file.

Clinical Research Pharmacy Staff Responsibilities

The clinical research pharmacy should be included in the pre-IRB review for new clinical protocols. During this pre-IRB review, the clinical research pharmacy should determine the safety and feasibility of conducting the clinical research study at the institution with respect to its policies, pharmacy services, and the fees that will be charged for the services provided. For this review, the clinical research pharmacist should compile the following documents and information from the clinical study site team and sponsor:

- Clinical trial protocol, including the following:
 - Research participant location (inpatient, outpatient, or both)
 - Number of research participants expected to be enrolled at the site and number of dispensing visits

- Duration of the study, including recruitment and treatment periods
- Randomization method (i.e., how participants are randomized in the clinical trial)
- Blinding (e.g., open label, single blind, double blind, third-party blinding by clinical research pharmacy)
- Investigator’s brochure (known investigational drug product information including safety data, any relevant animal and human data, and the doses previously studied; provided by sponsor)
- Investigational drug product handling manual (pharmacy manual), if available, which should include the following:
 - Interactive response technology (IRT) (e.g., interactive voice or Web response systems [IVRS/IWRS]) instructions, if applicable
 - Description of investigational drug product (e.g., dosage forms, strength, packaging)
 - Investigational drug product and ancillary supply sourcing (e.g., provided by sponsor, sourced locally by clinical research pharmacy)
 - Ancillary supplies required (e.g., filters, bags, tubing, bag covers)
 - Supply of concomitant medications required (e.g., adjunctive therapies, premedications)
 - A discussion should be raised during the study setup to determine which concomitant medications will be reimbursed and which will be considered standard of care
 - Investigational drug product storage conditions (e.g., temperature, humidity)
 - Special handling precautions (e.g., protect from light, hazardous handling precautions)
 - Investigational drug product preparation or dispensing information (e.g., diluents, stability of reconstituted vial and solution for administration, dispensing in original container or repackaging)
 - Handling of containers used in preparing dose
 - Handling of participant investigational drug product returns
- Administration of investigational drug product (e.g., flushing of infusion line, order of investigational drug product administration in relation to other drugs administered at the same visit, drug and food interactions)

Pharmacist Listing on Statement of Investigator

The decision whether to list a pharmacist on the Statement of Investigator (Form FDA 1572) depends on the contribution the individual makes to the study.¹⁴ If the individual will make a direct and significant contribution to the data or is directly involved in the treatment or evaluation of participants, he or she should be listed. If the individual will provide ancillary or intermittent contributions, he or she should not be listed. A pharmacist who prepares investigational drug product doses and maintains drug accountability for multiple clinical studies that are conducted at an institution would not be making a direct and significant contribution to the data for a particular study; therefore, it would not be nec-

essary to list the pharmacist as a subinvestigator. However, the pharmacist should be listed in the investigator’s study records as an individual to whom specific responsibilities have been delegated.

Delegation of Authority to Technicians and Pharmacy Support Staff

Many sites utilize individuals who are not pharmacists to perform some of the functions of the clinical research pharmacy under the direction of a licensed pharmacist. Certified pharmacy technicians or pharmacy coordinators may be delegated tasks, according to institutional policy, that do not require a pharmacist license. The clinical research pharmacist is responsible for ensuring compliance with laws, rules, and regulations regarding technician responsibilities. In many states, a technician may only perform certain duties under the direct supervision of a pharmacist, and the pharmacist is ultimately responsible for the work performed by the technician; therefore, only the clinical research pharmacist should sign the sponsor’s Delegation of Authority log.

Clinical Research Pharmacy Staff Training

The clinical research pharmacist must be a participant in the sponsor’s site initiation visit or the internal site initiation meeting (for sponsor–investigator or cooperative group studies). The clinical research pharmacist must participate in the pharmacy-specific training session and have the opportunity to discuss the investigational drug product dispensing logistics with the sponsor and clinical site study team. The clinical research pharmacist should provide the sponsor with key policies and procedures and standard operating procedures (SOPs) for review and approval, if not provided at the site qualification visit. These may include but are not limited to SOPs on training and delegation of tasks assigned to pharmacy personnel regarding investigational drug product handling, temperature monitoring, onsite investigational drug product destruction, essential document retention, and monitoring visit guidelines. Occasionally, sponsors conduct the site initiation remotely via telephone or Internet conference. The clinical research pharmacist must be invited and should participate in the pharmacy-specific training session.

At the site initiation visit, the pharmacy responsibilities are determined and the Delegation of Authority form is completed and signed by the clinical research pharmacist and PI. Specific tasks need to be determined at study initiation by the clinical research pharmacy and the clinical study site team (e.g., which team member is accessing the IRT for randomization, kit/bottle assignment). The clinical research pharmacist should determine which qualified pharmacy staff member will perform the delegated roles. The clinical research pharmacist should also determine which pharmacy staff will require electronic signatures (user name and passwords) for protocol systems such as IRT and coordinate with the sponsor to obtain them.

All pharmacy staff who may dispense investigational drug products should be trained in the proper dispensing process and in GCP² as it relates to PI-delegated roles. Training should be completed upon hire, and the information should be reviewed periodically. Records of training must be

maintained and made available for inspection by regulatory agencies and sponsors.

Clinical research pharmacists and staff are required to follow all relevant pharmacy practice standards, institution policies and procedures, state and federal laws, and Joint Commission or other accreditation standards, as well as GCP guidance.² Clinical research pharmacy staff should maintain all certifications and competencies specified by the pharmacy department and the institution related to this requirement.

Formal sponsor training for every pharmacy staff member for each protocol and all protocol amendments is often not practical. Pharmacy staff should be trained to refer to the most recent version of the study-specific dispensing guidelines every time a delegated responsibility is performed. This practice ensures that the most recent procedures are used each time the investigational drug product is prepared and dispensed. Therefore, study-specific training by the sponsor is not indicated for all pharmacy staff. A pharmacy signature log with staff initials should be maintained and archived centrally by the pharmacy department for the purpose of verifying study-related records.

Sponsors frequently request the curriculum vitae (CV) of all pharmacy staff handling investigational drug product. However, since the institution maintains licensure and credentialing information, it is appropriate for clinical research pharmacy staff to only provide CVs to the sponsor if the pharmacist is listed on Form FDA 1571 (Investigational New Drug Application) or Form FDA 1572 (Statement of Investigator).¹

The clinical research pharmacist should determine whether interested parties can confirm pharmacist licensing information at the individual state licensing office and, if so, provide the sponsor with access information. It is not necessary to provide proof of pharmacy technician certification.

Clinical Research Pharmacy Study Setup

The process of opening a new clinical research study should include preparing dispensing guidelines, a model physician order (prescription template), and a template of the dispensing label. The process should also include creating a protocol-specific study drug entry and order set in the electronic medical record as well as setting up a clinical research pharmacy study file.

Dispensing guidelines should be prepared by the clinical research pharmacist using the clinical protocol and any other relevant information provided to the clinical research pharmacy by the sponsor (e.g., investigational drug product handling manual, site initiation visit materials, investigator's brochure). It is the responsibility of the PI to ensure that the research pharmacy has the most up-to-date versions of all study documents. Dispensing guidelines describe the protocol-specific functions that the clinical research pharmacy staff must perform in order to adhere to the protocol and complete all responsibilities delegated to the pharmacy by the PI.¹⁴ The dispensing guidelines are intended to operationalize the management of investigational drug products for a specific protocol within the institution and are used as a training tool by the pharmacy staff involved in the preparation and dispensing of the investigational drug product. A sample of dispensing guidelines has been previously published.¹⁵ A draft version of the dispensing guidelines should be prepared before the site initiation visit to allow the clinical

research pharmacist to identify the information that needs to be obtained at the meeting and to ensure that the clinical site will have all of the information needed before enrolling the first participant into the study.

Dispensing guidelines should be revised as appropriate after IRB approval of protocol amendments or other changes to study procedures. The clinical research pharmacist should maintain a system to document version control. Dispensing guidelines should be available (in print or electronic formats) to any pharmacy staff responsible for participant care.

The physician order template for the investigational drug product should be prepared by the clinical research pharmacist using the clinical protocol and other relevant information provided by the sponsor.⁵ In institutions that use computerized provider order entry, the clinical research pharmacist should ensure that an order set is available in the system.

The investigational drug product should be entered into the pharmacy computer dispensing systems, if available. A dispensing label template should be created to ensure that information required by the clinical protocol is included on the label and that the administration instructions are consistent with the clinical protocol.

The dispensing label for the investigational drug product must comply with all state and federal rules and regulations as well as protocol requirements. The information on the label should be consistent with the information and instructions on the physician's order as well as the original drug container. The institution's contact information should be included on the label to aid in coordination of the participant's care by an outside institution. Special instructions should be included on the dispensing label or provided as auxiliary labels (e.g., food intake recommendations, storage conditions).

If the clinical research pharmacy repackages the investigational drug product, the Federal Investigational Drug Caution Statement—"Caution: New Drug—Limited by Federal (or United States) law to investigational use"—should be on the clinical site pharmacy label.¹⁶ All labeling must also comply with applicable local and state regulations. In addition, the clinical research pharmacist should ensure that any required medication counseling (e.g., for psychiatric or teratogenic medications) is to be provided by the clinical research pharmacist or an appropriate member of the clinical site study team.

Considerations for Blinded Studies

When preparing dispensing guidelines for blinded studies in which the clinical research pharmacy staff are unblinded, the clinical research pharmacist should be cognizant that there are clinical site personnel with direct patient care responsibilities who are blinded to the research participant's treatment assignment, and the dispensing guidelines should be designed accordingly. Ideally, unblinded clinical site personnel should not be involved in direct patient care for study participants. Interactions between blinded and unblinded personnel should be minimized, and care should be taken to avoid communication that could inadvertently reveal a participant's treatment assignment. Any pharmacy staff member who is unblinded must use extreme care when communicating with blinded staff regarding any patient care

information in order to avoid revealing the participant's blinded treatment assignment.

Active and placebo investigational drug products must be identical in appearance, labeling, preparation time, expiration date and time, and supplies used. Considerations when preparing blinded investigational drug products include

- Ensuring that the preparation times for the active drug and the placebo dose are the same,
- Providing the identical information on the active drug and placebo labels, including the expiration date and time; if the active drug and placebo products have different expiration dates and times, the shorter of the 2 times should be used,
- Making the port on intravenous bags look the same (i.e., if a commercial bag of diluent is used as the placebo, insert a needle into the port using aseptic technique to give the appearance that a drug has been added; if additive port covers are used, ensure matching covers), and
- Using the same type of needle and tubing for administration of the active drug and the placebo dose.

An unblinding process must be established that allows the blinded treatment assignment to be determined. Examples of events that require unblinding include a research participant experiencing a severe adverse reaction and an unauthorized person ingesting or being administered the investigational drug product. An unblinding process that allows for immediate determination of the participant's treatment assignment or access to the sponsor's medical monitor should be developed. In order to allow continuous access to the unblinding process in the event of an emergent need to determine a participant's treatment assignment, a clinical site-specific plan should be developed that is not dependent solely on the PI.

When labeling a blinded study medication, the clinical research pharmacy must label it such that the blinding is protected and that clinical site study staff are not able to determine the actual contents of the container. The product should be labeled as "drug name or placebo." The protocol acronym should not be used solely in place of the product name; if a research participant presents at an emergency department, the treating physician should be able to identify the potential contents of the container so that treatment is not delayed.

Barcoding of Investigational Drug Products

Improved patient safety with barcoding has been well documented.¹⁷ Although barcoding is desirable, the lack of a standard system limits its ability to be implemented with investigational drug products. Development of a standardized barcode lexicon that will facilitate the implementation of a global barcoding system is necessary. ASHP has urged the Food and Drug Administration (FDA) and other regulatory agencies, standard-setting bodies, contracting entities, health systems, and pharmaceutical manufacturers to develop and implement a universal symbology (e.g., barcodes, radio frequency identifiers) that are readily deciphered by commonly used scanning equipment to code for the National Drug Code, lot number, and expiration date on all unit dose, unit-of-use, and injectable drug packaging.¹⁸

Investigational Drug Product Accountability and Documentation

Detailed records, required to be kept by the sponsor, must identify the investigator to whom the investigational drug product is shipped as well as the date, quantity, and batch or code mark of such shipment.¹⁹ The clinical site is required to maintain records detailing the participant to whom the investigational drug product was dispensed, the date, the quantity, and the batch or code mark dispensed. Incomplete or inaccurate drug accountability is a deficiency frequently cited in Form FDA 483 Inspectional Observations notices.²⁰ U.S. law does not require the use of an expiration date, use-by date, or retest date on product labels. In many cases, the date may be found on the packing slip; however, the clinical research pharmacy may reach out to the sponsor to request documentation of the retest or expiration date.

Routine inventory counts (e.g., monthly) should be performed for each investigational drug product in order to ensure that the physical quantity on hand corresponds to the quantities recorded on the drug accountability record form (DARF) and to manage investigational drug product with limited use dates. Any discrepancy should be reviewed and resolved for each investigational drug product.

According to the CFR and GCP guidelines,^{1,2} investigational drug product receipt, dispensing, participant returns, and disposition are required transactions that must be documented. Sponsors may provide investigational drug product accountability records, or individual clinical research pharmacies may have their own accountability records. Frequently, sponsor-provided DARFs do not contain sections to document all of the required transactions. For clinical research pharmacies with multiple ongoing clinical studies, DARFs from different sponsors requiring inconsistent information can cause confusion. Use of standardized DARFs containing sections for the required transactions would ensure consistency and compliance with applicable regulations. Figure 1 displays a template for a DARF, which can be customized for different clinical protocols and sites but maintains a standard appearance that will allow clinical research pharmacy personnel to complete the forms correctly and provide sponsors with the required documentation. The form allows the site to document the receipt and dispensing of individual bottles, vials, or kits, and the header of the form can be customized for the specific needs of the protocol. If a hard copy of the DARF is required by sponsors and an electronic dispensing/accountability system is used, it must have the capability of printing a hard copy of the DARF that shows the required transactions. At a minimum, the items on the form should be adhered to, ensuring site and sponsor compliance with regulatory agencies. The clinical research pharmacy DARF may be customized to include additional information requested by sponsors, such as the time of dose preparation or investigational drug product container numbers.

When the investigational drug product is transferred from the clinical research pharmacy to a satellite pharmacy or dispensing location, a separate DARF must be maintained with the investigational drug product. The DARF in the clinical research pharmacy should reflect the transfer of investigational drug product to the satellite location, and the satellite location's DARF should reflect receipt of the investigational drug product from the clinical research pharmacy.

Figure 1. Template of a drug accountability record form. PI = principal investigator, CRA = clinical research associate.

(site name) Clinical Research Pharmacy Drug Accountability Record Form (DARF)															
Protocol Title:												Internal Protocol #:			
PI:				Source:				Lot:							
Study Drug Name:				Synonym:				Drug Location:				Kit:			
Strength:				Drug Storage:				Exp/Retest:							
Dosage Form:				Units Per Container:				Room Temp ___ Refrig # ___ Other ___							
Receipt Or Dispense Date dd/mm/yyyy	Rx# or Pt Care Unit	Patient Initials FML or E-L	Patient Study #	Dose/ Frequency	Quantity Received or Dispensed	Balance	Staff Init	CRA Verify Init	Patient Returns			Disposition			CRA Verify Init
									# Returned	Date Returned	Staff Init	Return to Sponsor or Destroy	Date	Staff Init	
Comments: _____												Page ___ of ___			

The satellite location's DARF should reflect all dispensing activity at that location. Any remaining investigational drug product must be returned to the clinical research pharmacy and documented in both DARFs accordingly.

The DARF is an official record, and, as such, any corrections that are made must be performed by making a line through the original entry, accompanied by the recorder's initials and date. The original entry may not be obscured.²¹

Investigational Drug Product Receipt

The clinical protocol or investigational drug product handling manual will indicate how to obtain the investigational drug product once a study site is approved to receive the product from the sponsor. The study site may need to enroll the first research participant before the product is shipped, or a study site may be allowed to have the investigational drug product onsite in anticipation of participant enrollment. When the product is shipped, the sponsor must ensure it is appropriately labeled so that it is easily identified as an investigational drug product for a specific clinical protocol. The immediate packaging container for the investigational drug product is required to bear the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."¹⁶

In addition, it is strongly recommended that the sponsor's investigational drug product label contain the following information²²:

- Investigational drug product name
- Investigational drug product name may be the generic name, company molecule name, or compound name but must match the name used in the clinical protocol; the sole use of protocol acronyms should be avoided.
- If the investigational drug product used in the clinical research study is blinded and placebo controlled, the label must indicate "[Investigational Drug Product Name] or Placebo."²¹
- Investigational drug product strength or concentration unless this aspect of the trial is blinded
- Investigational drug product quantity (e.g., number of tablets, volume)
- Investigational drug product lot number and/or container or kit number
 - Lot number(s) should be referenced in the packing slip or receipt document, and terminology should be consistent with the clinical research study-related documentation (i.e., if the lot number is labeled as "Lot Number" on the package, it should not be referred to as "Batch Number" in supporting documentation).
 - Investigational drug products may also contain a unique container or kit number that will be used to identify the contents or to assign specific container or kit to a participant; in that case, the container or kit number may appear in place of the lot number, but the container or kit number must be cross-referenced with the packing slip.
- Expiration or retest date (period of use) of the investigational drug product

- While it is preferred to be on the investigational drug product label, this information may be provided on the packing slip or via a memo included with the shipment to the clinical study site.
- Sponsor or manufacturer name and address
- Clinical research protocol number
 - When a sponsor is working on clinical studies using the same investigational drug product in parallel protocols for different indications, it may be difficult for a clinical site to determine which protocol the product belongs to unless this information is provided on the container.
 - The sponsor may provide pooled supplies of investigational drug products to be used for multiple clinical research studies at the same clinical study site. The investigational drug product may be labeled with multiple clinical research protocol numbers, or the clinical research pharmacy may be required to assign each individual unit to a specific clinical research study at the time of dispensing. The assignment process must be clearly explained in the investigational drug product handling manual or the clinical protocol and be communicated clearly to the clinical research pharmacies.
- Oral medication intended to be dispensed to a participant for self-administration at home must comply with the Federal Poison Prevention Packaging Act²³ and be packaged in a child-resistant container. If the disease indicated in the clinical protocol is not conducive to this type of packaging, a statement must be included in the consent form alerting the potential participant that there is a risk to children in the home due to the lack of child-resistant packaging.

The investigational drug product shipment must be accompanied by a packing slip. Clinical research pharmacy staff are responsible for verifying the contents against the packing slip and assessing the condition of the package. Proof of receipt should be provided to the sponsor or supplier; this should be clearly outlined in the protocol or investigational drug product handling manual or on the packing slip. Any discrepancies (e.g., broken vials, missing product, temperature excursions) must be reported immediately, and the resolution of discrepancies must be appropriately documented. Sponsors may request that the product be quarantined in the interim; quarantined product must be maintained under the specified storage conditions. Sponsors should be prompt in responding to discrepancies or temperature excursions. The packing slip, shipment temperature records, and any other documents received with the investigational product shipment shall be stored in the pharmacy study-specific file. All investigational drug products received must be documented on a DARF.

Investigational Drug Product Dose Preparation and Dispensing

When preparing and dispensing an investigational drug product, the clinical research pharmacy should utilize site-developed, study-specific dispensing guidelines to ensure the investigational drug product handling requirements in

the protocol are met. The clinical research pharmacy may store partial or empty vials of nonhazardous investigational drug product in a limited-access, secure area until returned or destroyed per the sponsor's direction. Sponsors should be diligent in the reconciliation and disposition of the used materials. Used and partial vials of hazardous investigational drug product should be destroyed according to the institutional policies and procedures immediately after dose preparation.

Remote Site or Clinic Dispensing

Remote site or clinic dispensing within a health system may be considered when clinical research pharmacy involvement may present a hardship for research participants or adversely affect the conduct of the clinical research study, especially in situations where timely access to the investigational drug product may be a challenge.

The clinical research pharmacy should review studies that may require remote site or clinic dispensing before IRB review to assist in determining how the investigational drug product should be managed at the remote site or clinic and in determining the best dispensing option. In situations in which pharmacist dispensing is not practical, physician dispensing may be an option. State laws and regulations should be reviewed to determine whether physician dispensing is permitted. If physician dispensing is allowed, all applicable state and federal laws and regulations with respect to handling investigational drug products (e.g., secure storage conditions, labeling requirements for outpatient use) as well as those regulating accountability and dispensing must be followed. The clinical research pharmacy should provide guidance on the applicable state laws and regulations that apply.

In such cases, the PI must maintain appropriate study-specific accountability records. These records should document the investigational drug product received and dispensed to participants enrolled in the clinical research study. Investigational drug product returned from participants and final disposition of investigational drug product must also be recorded.

The clinical research pharmacy should also perform periodic audits and inspections of storage facilities and drug accountability procedures that are managed by the PI.²⁴

Investigational Drug Product Returned from Participants

Per GCP, the PI is responsible for ensuring and assessing clinical research protocol adherence.² This may include receiving, counting, and documenting investigational drug product returned from participants in the case report form or the electronic medication administration record, if required, in the protocol. This function may be delegated by the PI to the clinical research pharmacy; in such cases, the unused supply and empty investigational drug product containers should be returned to the clinical research pharmacy for documentation of the unused investigational drug product returns from participants and its final disposition. The clinical research pharmacy should record on the DARF the date and the quantity of investigational drug product returned, as directed in the investigational drug product handling manual. On occasion, the date of the investigational drug product

count may differ from the actual date of participant return because the clinical research pharmacy may not be able to process the return immediately. Returned investigational drug product should be deemed not usable and should be stored in an area separate from the investigational drug product that is available for dispensing to research participants.

Used or partially used nonhazardous investigational drug product returns should be stored by the clinical research pharmacy in a limited-access, secure area until directed by the sponsor to return or destroy the product. The clinical research pharmacy should determine storage space availability and notify the sponsors in advance of any space limitations. The sponsor should visit the clinical research pharmacy at appropriate intervals based on study activity to return or destroy used investigational drug product. If such visits do not occur, the clinical research pharmacy should contact the sponsor to obtain permission to destroy or return the product.

Hazardous investigational drug product returns and returns of investigational drug product supplied by the National Cancer Institute should not be stored onsite. These products should be destroyed under the appropriate institutional hazardous drug disposal procedures immediately after counting and documentation on the DARF; exceptions should require approval by the clinical research pharmacist and the PI and should be stated in the dispensing guidelines. Each site should refer to its specific institutional policies regarding the destruction of hazardous drug products.

Investigational Drug Product Final Disposition

For investigational drug product returned to the sponsor or destroyed onsite, the return or destruction must be documented on the DARF by the clinical research pharmacy. If required by the sponsor, a separate return or destruction form may be used to document return or destruction of the investigational drug product. If the return of unused investigational drug product to the sponsor is required per the clinical research protocol, instructions on the return procedure should be provided to the clinical research pharmacy staff by the sponsor. If destruction of investigational drug product by the clinical research pharmacy is approved by the sponsor, the product should be destroyed per institutional policy. If the sponsor requests return of a hazardous investigational drug product, the shipper must comply with U.S. Department of Transportation regulations for shipping hazardous material.²⁵ Investigational drug products that are controlled substances should be returned to the sponsor for final disposition or destroyed per institutional policy; returns of such drug products must adhere to Drug Enforcement Administration regulations for shipping controlled substances.²⁶

Clinical Research Pharmacy Study File

The clinical research pharmacy should create a study-specific pharmacy file using selected essential documents that are deemed necessary by the clinical research pharmacist for the routine management of investigational drug products. Original documents (e.g., DARFs, investigational drug

product physician orders, packing slips) that are part of the clinical research study-specific pharmacy file are considered source documentation. These essential clinical research pharmacy documents will be retained throughout the study and must be readily available for inspection by the sponsor (or designee), PI (or designee), and regulatory agencies (e.g., FDA). Copies of temperature monitoring logs and policies do not need to be filed in individual clinical research-specific files but should be available on request.

Documents in the pharmacy file may be stored in hard copy or electronic format and should include sponsor-provided and site-prepared documents. Sponsor-provided documents should include the following:

- IRB-approved clinical research protocol and associated amendments,
- Investigator's brochure and associated amendments,
- Investigational drug product handling manual (version controlled) and associated amendments,
- Investigational drug product ordering instructions and forms,
- IRT (IVRS/IWRS) manuals (instructions and forms),
- Investigational drug product shipment documentation (e.g., packing slips, other drug receipt documents),
- Supporting investigational drug product information (e.g., package insert, safety data sheet, certificate of analysis, as applicable),
- Expiration and retest correspondence (period of use),
- Temperature excursion forms (if required),
- Correspondence (e.g., communication sheet, letters, e-mails),
- Investigational drug product disposition information and forms, and
- Miscellaneous documents (e.g., worksheets, sponsor-specific forms).

Site-prepared documents should include the following:

- IRB approval letter,
- Access to IRB-approved consent (to establish documentation of research participant-specific medication training disclosure),
- Pharmacy-prepared dispensing guidelines,
- Pharmacy fee sheet with billing information,
- Pharmacy computer system entry information,
- Investigational drug product physician order or prescription template(s),
- List of authorized prescribers for the clinical trial,
- Research participant list and treatment assignment (if applicable),
- Clinical research pharmacy and pharmacy satellite DARFs (if applicable),
- Monitoring visit and audit forms, and
- Notes to file.

If an investigational drug product is not dispensed from the clinical research pharmacy, a satellite-specific file should be created that includes a research participant list, dispensing guidelines, DARFs, and other study-specific documents (e.g., investigational drug product dose calculation worksheets); the file should be kept in the satellite pharmacy where the investigational drug product is being dispensed.

Monitoring Visits or Audits of the Clinical Research Pharmacy

It is the responsibility of the sponsor to monitor the progress of the clinical research study to ensure data integrity and participant safety.¹ If the clinical research study is an investigator-initiated protocol (sponsor–investigator), it is the responsibility of the local PI to meet all of the requirements of the sponsor, including monitoring and safety-reporting regulations.

The sponsor may delegate the monitoring and auditing responsibilities to a contract research organization. Clinical research associates who are employees of the sponsor or their agents from a contract research organization will be sent to monitor the clinical site. Sponsor audits at clinical sites may be conducted by representatives of the sponsor or independent auditors as well as inspectors from regulatory authorities. Communication regarding clinical site monitoring expectations will occur during the site initiation visit.

The clinical research associate (monitor) will visit the clinical study site to review the records and verify the accuracy of the documentation with the source documents onsite. Source documents include any original documents, data, and records, including (but not limited to) patient medical records, visit notes, protocol data collection forms, laboratory notes, participant drug administration diaries, and the clinical research pharmacy DARFs and associated records. The monitor must have access to the source documents; in some cases, this may require access to electronic medical records. Access to these systems should be provided in accordance with institutional policies.

The monitor should communicate with the clinical study site to determine a mutually agreeable time to meet with study staff and reserve a space to work. The clinical site should accommodate these visits whenever possible. The clinical study site should have a dedicated space in the same area as the protocol records where the monitor can work. The PI must be available for questions and discussion at some time during the visit. Some research protocols will allow remote monitoring activities in lieu of a visit to the site, and monitors may send queries to the clinical site for clarification. Depending on the time required by the clinical research pharmacy staff to respond to information requests, an additional charge may be imposed to accommodate these remote visits.

The monitor will need to visit the clinical research pharmacy to review pharmacy documentation. If the clinical research protocol is a blinded study and the clinical research pharmacist is unblinded, there should be a separate unblinded monitor specifically for clinical research pharmacy review. The unblinded contact(s) should be clearly stated in the pharmacy records. All others should be considered blinded and communications handled accordingly. An appointment should be made for each clinical research pharmacy visit to allow the staff to adequately prepare.²⁷ The clinical research pharmacy staff should meet with the monitor and provide access to pharmacy source documents for review. The monitor should confirm drug accountability and storage conditions and review a participant's returned investigational drug product. The monitor may return investigational drug product to the sponsor or authorize its destruction. All personal health information of the participants should be removed from investigational

product labels and forms before being returned to the sponsor or should be destroyed.

Monitoring Visit Logs

The clinical research pharmacy staff should document monitoring visits and the reason for the meeting. Information documenting the identity of the monitor, company affiliation, study reviewed, and the duration of the visit to the clinical research pharmacy is useful to the sponsor and the pharmacy department. Figure 2 provides an IDS monitor/visitor log template to capture such information.

At the end of a monitoring visit, the clinical research pharmacy staff or the sponsor should document any outstanding requests or issues that need to be completed before the next visit. A template of a study monitor exit summary report that can be used to capture issues for follow-up appears in Figure 3. Both the clinical research pharmacist and the monitor should sign the form to document their understanding of requests.

Study Close and Archiving of the Clinical Research Pharmacy Study Files

A site is required to retain all records for at least 2 years after the marketing application is approved for the indication being investigated. If the drug is not approved or if no application is filed, then records must be retained for 2 years after the investigation is discontinued.²⁶ Many institutions have retention policies that exceed these requirements. Trials taking place in other countries may also be subject to longer retention periods. Sponsors should indicate when this is the case and follow retention requirements where applicable. It is the responsibility of the sponsor to notify the clinical site and the clinical research pharmacy of these requirements. Each site must be familiar with state, local, and institutional policies and regulations regarding record retention. The clinical research pharmacy should provide written notice to the sponsor of impending document destruction.

Upon termination of a study, the clinical research pharmacy should work with the PI to determine who will maintain the following pharmacy-related documents:

- Drug accountability records and documentation of investigational drug product destruction
 - Investigational drug product shipment documentation
 - Proof of receipt and/or packing list
 - Certificates of analysis
 - Safety data sheets
 - Participant enrollment log
 - Participant identification code list
 - Participant-specific preparation records (batch control records for compounded items) and worksheets
 - Certain pharmacy documents, such as filled prescriptions or medication orders, must remain with the clinical research pharmacy in accordance with state board of pharmacy rules and regulations.
 - IRT-related documents

ologist who performs diagnostic imaging that is part of the research). In these cases, the IRB should not consider this a conflict of interest with regard to reviewing an IRB submission, provided the member's role in the study is limited to the provision of a service to the PI and he or she is not otherwise engaged in the study. Under these circumstances, the clinical research pharmacist serving on an IRB should not be listed on the Statement of Investigator (Form FDA 1572).

Summary

Clinical study sites that handle a significant volume of clinical studies should establish a formal IDS pharmacy utilizing these best practices as a foundation. Standardizing the processes for managing investigational drug products used by clinical research pharmacies will improve patient safety and protect study data integrity while maintaining regulatory compliance. Standardization will also provide guidance for clinical study sites that are new to handling investigational drug products. Adopting these best practices will enable clinical research pharmacies to enhance their collaboration with sponsors and the biopharmaceutical industry by aligning processes and systems to improve clinical study execution. Ultimately, these best practices will support the development of new and innovative medications for the patients who need them most.

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Stephen C. Kay, B.S.Pharm., Clinical Research Pharmacy, Pfizer, Andover, MA.

Darlette G. Luke, B.S.Pharm., Investigational Drug Service, Fairview Health Services, University of Minnesota Medical Center, Minneapolis, MN.

Helen R. Tamer, Pharm.D., Research Pharmacy, Michigan Medicine (University of Michigan), Ann Arbor, MI.

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