1. PURPOSE

To define the minimum required practices for accountability for investigational drugs and biologics.

2. DRUG ACCOUNTABILITY

Treating physicians who oversee the expanded access use of investigational drugs are considered by the FDA to be *investigators*. Physicians who submit single-patient INDs and also treat the patient may be considered *sponsor-investigators*.

Requirements of investigators are detailed in 21 CFR 312.305(c)(4) and include, among other things, maintaining accurate drug disposition records. This process is typically referred to as "Drug Accountability." As with investigational drugs used in clinical trials, agents used in expanded access require the same degree of drug accountability.

For physicians at sites with an Investigational Drug Service (IDS) or Research Pharmacy (RP), agent management should be delegated to that unit, as it will have staff who are well versed in the handling of investigational products. *This is the best practice and should be followed whenever feasible.*

For physicians who do not have a Research Pharmacy available, drug accountability can be accomplished by a clinic or institutional pharmacy. The requirements are detailed below and assume that a site does not have an electronic drug accountability system. Manufacturers and institutions may have additional requirements; these are considered a minimum.

3. DRUG INFORMATION RESOURCES

3.1 The site should request an Investigator's Brochure (IB) and Pharmacy Manual from the manufacturer for each investigational agent. The IB will contain relevant clinical and pre-clinical safety and efficacy data about the drug. The Pharmacy Manual should describe storage, handling, preparation, and administration instructions.

4. REQUIRED DOCUMENTATION

4.1 Recordkeeping

4.1.1 The physician or pharmacy should create a dedicated physical binder to maintain drug accountability documents. The binder may be tabulated to help organize documents. "Shipment Receipts" and "Drug Accountability Logs" are essential tabs; other potentially relevant tabs may include, "Temperature Logs", "Pharmacy Manual", "Expiration Memos", "Training Logs", and "Correspondences".

4.2 Drug Accountability Record Forms (DARFs)

4.2.1 DARFs are logs used to record inventory transactions, including drug receipt, dispensing, and destruction. A dedicated DARF is required for each investigational agent; a DARF should not contain information for multiple drugs or INDs.

4.2.2 The header of the DARF should contain the following information and should appear on each page of the DARF:

4.2.2.1 Name of institution

4.2.2.2 The IND number and/or protocol name

4.2.2.3 The name of the sponsor or sponsor-investigator. If industry sponsored, included the name of the local primary investigator.

4.2.2.4 The agent name, strength, dosage form, and container size

4.2.3 DARFs should include a running inventory balance; the quantity of drug physically on-hand must match the balance indicated on the DARF. Any discrepancies should be immediately resolved.

4.2.4 Each entry on a DARF should be dated and signed or initialed by the recorder.

4.3 Receipt of Drug

4.3.1 When drug is received from the manufacturer, the physician (or designee) should confirm that the information on the invoice is accurate, and the correct product has been received.

4.3.2 The shipment may contain a temperature tracking device that requires inactivation upon shipment receipt. Follow the included instructions for stopping the device and reporting temperature information to the manufacturer or distributer.

4.3.3 Shipping receipts and temperature tacking information must be retained. File original versions in the binder.

4.3.4 When the shipment is received, promptly record receipt on the DARF. The following information should be recorded:

4.3.4.1 Date of receipt

4.3.4.2 The patient for whom the drug is to be used

4.3.4.3 Quantity received

4.3.4.4 Expiration or retest date(s)

4.3.4.5 Lot number(s) or batch number(s)

4.4 Dispensing

4.4.1 Drug should not be dispensed until informed consent is obtained.

4.4.2 Follow institutional, local, and federal standards for dispensing drugs. For example, a state board of pharmacy may require physicians to hold a special license in order to dispense to patients directly from a clinic. The board of pharmacy may also specify what information must be included on a prescription label.

4.4.3 Each time drug is dispensed or administered, the following information should be recorded on the DARF:

4.4.3.1 Date of dispense

4.4.3.2 Name of the investigator/physician overseeing treatment

4.4.3.3 The patient to whom it was dispensed

4.4.3.4 Prescribed dose

4.4.3.5 Lot/batch dispensed

4.4.3.6 Quantity dispensed

4.4.4 The dispensed product or container should have a label that states: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”

4.4.5 Patients should be asked to return any unused medication at their next visit.

4.5 Return

4.5.1 Any drug returned by a patient should also be recorded on the drug accountability log. This information should include:

4.5.1.1 Date of return

4.5.1.2 Quantity returned

4.6 Disposal

4.6.1 Excess product that the patient returns or remains available at the end of treatment should be disposed of per institutional requirements or returned to the manufacturer.

4.6.1.1 Consult the manufacturer and local institutional guidelines for appropriate disposal.

4.6.2 When product is destroyed or returned, the following information should be recorded on the DARF:

4.6.2.1 Date of destruction or return

4.6.2.2 Quantity destroyed or returned

4.6.2.3 Method of destruction or return

5. STORAGE

5.1 Investigational drugs and biologics should always be kept secure, in a locked room or cabinet, with access provided only to authorized individuals.

5.2 Investigational drugs and biologics should always be kept in climate controlled conditions. Consult the manufacturer for the necessary storage conditions. Temperature monitoring may be required.

5.3 Investigational drugs and biologics should always be kept separate from other drugs, including other investigational drugs under other protocols.

5.4 If a drug shipment experienced a temperature excursion during transit or a excursion was experienced during drug storage, immediately quarantine the drug and notify the manufacturer. Do not use the drug until authorized by the manufacturer.

6. REFERENCES

- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). Section 4.6: Investigational Product(s)
- Kay SC, Luke DG, Tamer HR. ASHP Guidelines for the Management of Investigational Drug Products. *Am J Health Syst Pharm* 2018;75:561-73. doi:10.2146/ajhp170812
- Smith AJF, Redic KA. Single-patient expanded access: A primer for pharmacists. *Am J Health Syst Pharm* 2022;79:2118-27. doi:10.1093/ajhp/zxac242

7. ADDITIONAL RESOURCES

7.1 National Cancer Institute Cancer Therapy Evaluation Program (NCI CTEP)

7.1.1 The NCI CTEP website provides DARF templates and instructional training videos. NCI templates and documentation standards are not necessary for expanded access but meet the requirements for drug accountability.

7.1.2 CTEP DARF Templates: https://ctep.cancer.gov/forms/

7.1.3 CTEP DARF Training Videos: https://ctep.cancer.gov/branches/pmb/drug_training_videos.htm