15 Accountability and Storage of Agents

The investigator is responsible for the proper and secure physical storage and record keeping of study agents received from CTEP. Specifically, the investigator must:

- Maintain a careful record of the receipt, use and final disposition of all study agents received from CTEP, using the NCI Investigational Agent Accountability Record Form (still referred to as the DARF), http://ctep.cancer.gov/forms/.
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy
- Maintain appropriate storage of study agents to ensure their stability and integrity
- Return unused study agents to PMB at study completion or upon notification that an agent is being withdrawn or has expired

The intent of the agent accountability procedures described in this section is to ensure that agents received from DCTD are used only for patients entered onto approved protocols. FDA regulation requires the record keeping described in this section. Investigators are ultimately responsible for the use of study agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator remains the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, http://ctep.cancer.gov/forms/index.html.

Investigators, clinical trials personnel and interested parties can find a training module that addresses the intricacies of study agent accountability on the CTEP web site, www.ctep.cancer.gov, in PMB's section under "Investigational Drug Handling Slide Show" (http://ctep.cancer.gov/branches/pmb/idh_slideshow.htm). This training module covers ordering, accounting for, and returning study agents. In addition, the PMB section of the web site also includes a "Frequently Asked Questions" section that can help sites deal with common problems.

15.1 Procedures for Agent Accountability and Storage

Investigators or their designees must maintain a NCI Investigational Agent Accountability Record Form (still referred to as the DARF) for every CTEP- supplied agent. A copy of this form may be found at http://ctep.cancer.gov/forms/index.html.

- Store each study agent separately by protocol. If an agent is used for more than one protocol, investigators or their designees should maintain separate physical storage for each protocol. Remember that CTEP provides and accounts for agents on a protocol-by-protocol basis.
- Maintain separate accountability records if
    - an agent is used for more than one protocol; maintain an accountability form for each protocol
    - CTEP supplies multiple agents for a protocol; maintain a an accountability form for each agent
    - A protocol employs different strengths or dosage forms of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different accountability form for the 1-mg vial than for the 5-mg vial); maintain a an accountability form for each strength or dosage form

    - Agents are stored in various places, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas; maintain a separate accountability form at each location
- Document other transactions (e.g., receipt of agent, returns to the NCI, broken vials, etc.) on the accountability form.
- Refer to individual protocols for ordering and storage information for CTEP-supplied agents. It is important to note that procedures for agent accountability may differ when PMB provides patient-specifically labeled supplies (e.g., the supplies for a double-blind randomized clinical trial). Please refer to the individual protocol or call PMB at 301-496-5725 if questions arise.
- DCTD-supplied study agents may be transferred, within an institution (intra-institutional transfer) from a completed DCTD protocol to another DCTD-approved protocol that employs the same agent, formulation and strength.
    - Complete and fax (301-402-0429) an NCI Investigational Agent Transfer form, http://ctep.cancer.gov/forms/index.html, to the Pharmaceutical Management Branch (PMB) for each agent transfer.
    - Submit transfer forms within 72 hours of the actual transfer.
    - Transfer of DCTD-supplied study agents from active protocols requires prior PMB approval (telephone 301-496-5725). (See PMB Policy and Guideline on the CTEP Home Page.)
- Inter-institutional transfer of DCTD study agents (transfer between institutions) is forbidden unless the PMB specifically pre-approves or authorizes such transfer.

PMB is seeing more subtle differences (yellow vs. brown tablets, micronized powder vs. soft gelatin capsule, investigational vs. commercial label) that might not be readily apparent to you (the site). A site could execute an after-hours emergency transfer without realizing that a subtle difference was a concern, and subsequently, PMB would be unable to approve the transfer. *PMB strongly recommends obtaining approval before transferring any agent.*

15.2 Study Agent Returns

Many investigators are not aware that unused study agents must be returned to the IND sponsor. DCTD, as the study agent sponsor, is responsible for study agent accountability, which includes receipt, distribution, and final disposition of all study agents. Investigators are required to return agents if:

- The study is completed or discontinued
- The agent is expired
- The agent is damaged or unfit for use (e.g., loss of refrigeration)

In situations where a DCTD agent is no longer required for a completed or discontinued protocol, DCTD procedures permit the transfer to another DCTD-sponsored protocol that is using the identical agent, formulation and strength through completion of the NCI Transfer Investigational Agent Form, NIH-2564-1, http://ctep.cancer.gov/forms/index.html, see Section 15.1.

In situations where there is excess inventory or agent that will expire before it can be used, and you have another DCTD protocol(s) using the identical agent, please contact the Pharmaceutical Management Branch (301-496-5725) for assistance in transferring the agent to another DCTD-sponsored study. Otherwise, return the agents as stated in the steps below.

To return study agents to DCTD:

- Package the agents securely to prevent breakage (enclose within a zip-lock bag)
- Complete the Return Drug List Form, NIH-986. Save a copy for your records.
- Send to the NCI Clinical Repository at the address indicated on the Return Drug Form within 90 days of the agent's expiration or closure of the study. Since agents are not re-used upon return, rush delivery and maintenance of labeled storage temperatures is unnecessary.

15.3 Verification of Compliance

Investigators are reminded that auditors will review compliance with procedures to ensure proper agent usage during site visits conducted under the monitoring program. Specifically, auditors will:

- check for appropriate maintenance of the agent accountability system
- spot-check agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol
- compare actual inventory with accountability form balances

15.4 Handling of Antineoplastic Agents

There has been considerable concern about the potential risk of chronic exposure to low-level concentrations of antineoplastic agents among health care workers routinely handling these agents. The potential mutagenic activity of antineoplastic agents has been examined *in vitro* and *in vivo*. Urinary alkylating and anthracycline agents have shown mutagenic activity in experimental systems, whereas this has not been demonstrated for most of the antimetabolites and vinca alkaloids. Reports indicate that workers who handle antineoplastic agents may absorb them. In addition, some compounds are carcinogenic in animals and are suspected of being so in humans, but only in patients receiving the agent at therapeutic levels.

No clear evidence indicates, however, that chronic exposure to low-level concentrations of antineoplastic agents has been carcinogenic in health-care workers. Nevertheless, it would seem prudent to consider the adoption of certain precautions in the procedures of workers handling these agents. Several professional organizations have reviewed the data on this subject in an attempt to develop guidelines for safe handling. While there are now several published sets of guidelines, they do not differ significantly.

We have reproduced the *Recommendations for Handling Cytotoxic Agents,* by the National Study Commission on Cytotoxic Exposure in Appendix VII. Please note that these are guidelines and do not have regulatory or legal force. They are included for your consideration and information.

Other pertinent references include:

- ASHP Guidelines on Handling Hazardous Drugs. Available at: http://www.ashp.org/DocLibrary/BestPractices/PrepGdlHazDrugs.aspx

- The CDC NIOSH has a very comprehensive list of recent articles at http://www.cdc.gov/niosh/topics/antineoplastic/pubs.html.