15. Accountability and Storage of Investigational Agents

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received from CTEP. Specifically, the investigator must:
Maintain a careful record of the receipt, use and final disposition of all investigational agents received from CTEP, using the NCI Agent Accountability Record Form (DARF), http://ctep.cancer.gov/forms/index.html.

- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent
- Return any unused investigational agents to PMB at the completion of the study or upon notification that an agent is being withdrawn

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

15.1 Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that CTEP provides and accounts for agents on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Agent Accountability Record Form (DARF) for each protocol, http://ctep.cancer.gov/forms/index.html. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).
- The DARF has been designed for use at each location where agents are stored, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at http://ctep.cancer.gov/forms/index.html.
- DCTD-supplied investigational agents may be transferred, with an institutional (intra-institutional transfer) from a completed DCTD protocol to another DCTD-approved protocol that utilizes the same agent and formulation. An NCI Investigational Agent Transfer form must be completed and submitted by fax (301-402-0429) to the Pharmaceutical Management Branch (PMB) for each agent transfer. Transfer forms should be submitted within 72 hours of the actual transfer. Transfer of DCTD-supplied investigational agents from an active protocol requires prior PMB approval (telephone 301-496-5725). (See PMB Policy and Guideline on the CTEP Home Page.)
- Inter-institutional transfer of DCTD investigational agents is not permitted unless specifically pre-approved or authorized by the Pharmaceutical Management Branch.

15.2 Investigational Agent Returns

Many investigators are not aware that investigational agents must be returned to the IND sponsor. DCTD, as the investigational agent sponsor, is responsible for investigational agent accountability, which includes receipt, distribution, and final disposition of all investigational 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 and formulation 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 an obvious excess inventory, or the agent will not be used before the expiration date 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 investigational agents to DCTD:

1. Package the agents securely to prevent breakage (enclose within a zip-lock bag)
2. Complete the Return Drug List Form, NIH-986 (Appendix X). Save a copy for your records.
3. Send to the NCI Clinical Repository at the address indicated on the Return Drug Form. Since agents are not re-used upon return, rush delivery is not necessary.

15.3 Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the 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.

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. Recent reports indicate that antineoplastic agents may be absorbed by workers who are handling them. In addition, some of the compounds are carcinogenic in animals and are suspected of being so in humans, but only in patients receiving the agent at therapeutic levels.

There is, however, no clear evidence at this time 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 XIII. 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:

- Recommendations for the Safe Handling of Parenteral Antineoplastic Agents. NIH Publication #83-2621. Available from Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
- ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Agents. *Am J. Hosp. Pharm.* 1990: 47: 1033-1049.
- AMA Council Report: Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985: 253: 1590-1592.