Guidance for an FDA Inspection: Handling of Investigational Agents

This is the second of a three-part series designed to help sites prepare for a possible FDA inspection. Part Two addresses the handling and accountability of investigational agents.

This document includes guidelines to ensure proper distribution, storage, dispensing and disposition of investigational agents. Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for study-supplied agents.

Investigational Agent Distribution

Investigational agents for use in NCI-sponsored or funded clinical trials are provided to eligible investigators with an active CTEP investigator registration status. Investigational agents for studies where the NCI holds the IND are distributed by the Pharmaceutical Management Branch (PMB), CTEP and by industry suppliers when SWOG holds the IND.

- Investigational agents are shipped to the investigator's designated shipping address only. Investigators can have only one designated shipping address.
- Investigational agents must NOT be re-shipped by mail or overnight delivery services to another institution, site, or study subject.
- Investigational agents must NOT be transferred to another institution or site without prior approval.
- Investigational agents may be received by a Control Dispensing Area/Pharmacy and then transported to a Satellite Dispensing Area/Pharmacy given the following:
    - Control Dispensing Areas/Pharmacies support Satellite Dispensing Areas/Pharmacies either within a single institution, within a medical center complex consisting of two or more institutions, or to local community-based investigators.
    - Agents must be transported to Satellite Dispensing Area/Pharmacy via staff or institutional courier using appropriate temperature controls and hazardous/infectious transportation procedures according to written institutional policies.
    - Control Dispensing Areas/Pharmacies are responsible for overall inventory control and must provide copies of both control and satellite accountability records during audits.
- When a number of investigators are participating on the same clinical study at the same institution, one investigator should be designated the ordering investigator under whom all investigational agents for that protocol are ordered.
- In accordance with the FDA Guidelines on Good Clinical Practice and The Joint Commission, whenever possible, the pharmacy department should be responsible for agent receipt, storage, accountability, and preparation.

Control Dispensing Area/Pharmacy

The Control Dispensing Area for each investigator is identified as the shipping address receiving the study-supplied agent from the supplier. The Control Dispensing Area is responsible for:

- Direct receipt of study-supplied agent from the supplier
- Appropriate storage, accountability and security of study-supplied agents
- Dispensing study-supplied agent to patients as prescribed by authorized physician investigators with an active investigator registration status with CTEP
- Overall agent accountability and inventory control
- Provision of agent to satellite dispensing areas, oversight of satellite dispensing areas, and dissemination of agent stock recovery information

- Timely final disposition of non-dispensed study-supplied agents (e.g., returns, authorized transfers or local destructions)
- Destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures

Satellite Dispensing Area/Pharmacy

The Satellite Dispensing Area receives study-supplied agents from a Control Dispensing Area. The Satellite Dispensing Area is under the direct responsibility and oversight of the Control Dispensing Area and is responsible for:

- Receiving study-supplied agent from the Control Dispensing Area
- Appropriate storage, accountability and security of study-supplied agent
- Dispensing study-supplied agent to patients as prescribed by authorized physician investigators with an active investigator registration status
- Timely return of non-dispensed study-supplied agent to the Control Dispensing Area for further or final disposition
- Destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures

Accountability and Storage of Investigational Agents

FDA regulations require investigators to establish a record of the receipt, use, and disposition of all investigational agents. Investigators may delegate responsibility for agent ordering, storage, accountability and preparation to his/her designee(s). However, the investigator is ultimately responsible for all agents shipped in his/her name. The intent of agent accountability is to assure that investigational agents are administered only to patients enrolled on approved NCI trials and to track complete disposition of the agent.

- Agent disposition (receipt, dispensing, transfer, return or authorized local destruction of un-dispensed agent) must be documented on the NCI Investigational Agent (Drug) Accountability Record Form (DARF) or the NCI Investigational Agent Accountability Record for Oral Agents (Oral DARF) as appropriate. Electronic accountability systems may be used. Paper printouts of electronic DARFs must be identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy.
- Control NCI DARFs must be maintained at the location that directly receives agent from the NCI.
- Satellite NCI DARFs must be maintained at each location that receives investigational agent from a Control Dispensing Area/Pharmacy and stores an agent for more than one day (overnight or longer).
- Store investigational agents in a secure location which is only accessible to authorized personnel.
- Store each agent separately by protocol, strength, and formulation.
- Store agents under proper environmental conditions with documentation of temperature monitoring.
- Maintain separate NCI DARFs for each protocol, agent, strength, and formulation.
- Maintain separate NCI DARFs for each study participant on patient-specific supply studies as dictated by the protocol.

Investigational Agent Transfers

PMB supplied investigational agents may be transferred from an NCI sponsored protocol to another NCI sponsored protocol (intra-institutional transfer) in the following situations if the protocol utilizes the same agent, strength and formulation supplied by PMB:

- An NCI Investigational Agent Transfer Form must be submitted to obtain prior approval for each agent transfer. Transfer forms for urgent medical need should be submitted within 72 hours of the actual transfer.
  - Transfers must be documented on the Control DARF and written documentation of NCI authorization must be retained as part of the accountability records.
  - Only whole containers can be transferred.

- Transfer of PMB supplied investigational agents between protocols:
  - Example situations: notification of protocol status change (e.g., closed to accrual and treatment complete), excessive inventory for a protocol, investigational agent has short dating, or urgent medical need.
- Transfer of PMB supplied agents when the Control Pharmacy/Dispensing Area relocates requires prior approval.

Transfer of industry-supplied agents from the same distributor may be allowed with prior approval. Contact Quality Assurance at qamail@swog.org.

Investigational Agent Returns

Investigators/Designees must return un-dispensed PMB supplied investigational agent to the NCI Clinical Repository.

- PMB requires that all PMB supplied investigational agents be returned to PMB for accountability and final disposition.
- Return only PMB supplied agents to the NCI Clinical Repository. Do NOT return agents received from other sources.

PMB supplied agents should be returned when:

- The agent is no longer required for the study and the agent cannot be transferred to another NCI sponsored protocol.
  - Whenever possible, PMB supplied investigational agents should be transferred to another NCI sponsored protocol that utilizes the same agent, strength, and formulation.
- The agent is unsuitable for clinical use.
  - Investigators/designees should contact the PMB prior to returning investigational agents because of stability concerns due to temperature excursions.
  - Do NOT return broken containers, empty vials or partial patient returned bottles. These containers should be destroyed at the clinical site per institutional procedures.
- Investigators/designees have received written stock recovery notification from PMB.
- Un-dispensed patient specific agent should be returned at the time the patient completes therapy.

In general, un-dispensed industry-supplied agents should not be returned to the distributor but should be destroyed as outlined below. For additional information, see the Drug Information section of the protocol.

Investigational Agent Local Destruction

Investigators/Designees must request local destruction of un-dispensed PMB-supplied agents when special circumstances prohibit the return of agent to the NCI Clinical Repository.

Industry-supplied agents (un-dispensed drug, broken containers, empty vials or partial patient returned bottles) should be destroyed according to institutional policy and applicable regulations. For additional information, see the Drug Information section of the protocol.

Additional Resources

The Quality Assurance and Audits page of the SWOG website has links to the following:

- PMB FAQs
- PMB Investigational Drug Accountability Training Videos
- SWOG Investigational Agents Handling Video
- Chapter 6 of the ORP Manual with instructions on completing the DARF
- NCI-CTMB Guidelines for Monitoring of Clinical Trials