ACT 101

Drug Accountability
at the Investigative Site

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An FDA inspector once said that any individual should be able to perform drug reconciliation at an investigative site within 20 minutes. When drug accountability records are well designed and error-free, and appropriately reconcile from initial shipment to the site through final disposition, this statement should hold true. This article outlines the critical information needed for the study drug shipping manifest and the content of the dispensing and return and/or destruction documentation at the site. It discusses the importance of drug accountability records with respect to study data integrity and describes the role of study monitors in reviewing investigative site records and ensuring that they are complete and accurate. It also gives advice to auditors who assess drug accountability and discusses some of the findings from FDA inspections.

Here are some practical steps toward maintaining drug accountability records, which are crucial to data integrity and regulatory compliance.

Investigational drug shipment

An accurate investigational drug accounting process begins with the sponsor's shipping manifest. The regulations require control of investigational medications, and the safety reasons alone justify these restrictions. One must be able to confirm that investigational medication has not been dispensed to nonstudy subjects, and that subjects have not been exposed to doses in excess of protocol-defined regimens. Thus, all investigational medication documented as shipped to the site should reconcile with the documentation of used and unused supplies. Moreover, federal regulations restrict investigational drugs to research use. Marketing and commercialization are prohibited. Thus, chain of custody and strict accounting, as well as secure storage conditions at the site, must be in place for all investigational medications.

A well-designed manifest should identify the supplies enclosed, the quantity, the storage conditions, the name of the clinical investigator to whom the drug is being shipped, the date, and the subject or randomization kit numbers as applicable, and have an area for site personnel to note receipt of the supplies, their condition, and verify the inventory. The manifest should also preserve any blinding. Documentation at the site should reflect who received the shipment and when. The site should also have documentation, such as temperature and humidity monitoring logs, to reflect that the medication was stored under the conditions specified on the manifest for the period of drug storage. Site personnel should inspect the shipment, confirming the inventory against the information on the manifest. This information should be promptly reported back to the drug shipper, who should verify that the package was received.

Poorly prepared manifests are a common finding during clinical site audits. For example, some manifests do not clearly describe shipment contents. Some studies involve complicated packaging, where medication is contained in multiple subject dispensers. A one-month supply of study drug may be packaged as a "kit," where the kit comprises four subject dispensers, each containing seven doses of a tablet form of a medication. In this instance, the manifest for one subject might read, "One (1) subject kit, containing four (4) dispensers, with seven (7) tablets per dispenser." These details should be provided in the manifest even if the kits are supplied with tamper-evident seals.

Describing the contents strictly as "one kit" in this example would not allow the reviewer to ascertain the actual amount of medication in the shipment. Once the kit is assigned to a subject and opened, site personnel should again verify the quantity of medication against the manifest description. This also applies to other packaging types. The per- dose units should always be provided, whether the container is a bottle, blister pack, or dispenser containing vials of an injectable medication. Failure to provide full descriptions of shipment contents allows only gross reconciliation of supplies. This may meet regulatory require-

ABC Pharmaceuticals, Inc.
125 Somewhere Road
Springfield, IL 55502
(555) 555-1234

Protocol No.: ABC-2002-01 Shipment No.: 889913

Investigator: Charles Doctor, III, MD Site No.: 23
1300 Clinic Drive
Happyville, WY 81801
(555) 555-2525

Ship To: Jennifer Coordinator, RN
1300 Clinic Drive
Happyville, WY 81801
(555) 555-2525

Packed By: James Accurate
Date Shipped: January 10, 2002

Shipment Authorized By: _____ Date: _____

KIT NOS.	DESCRIPTION	LOT NO.	QUANTITY
555—559	curallamide hydrochloride (5 mg/mL single dose vials)	THX-1138	5 kits

Each kit contains four packers, each packer consisting of seven amber colored single dose vials.

STORAGE CONDITIONS

Store at 2—8° C. Protect from light.

ACKNOWLEDGMENT OF RECEIPT

Inspect and inventory the contents of this shipment upon receipt. Complete the sections below, and fax the signed manifest to James Accurate at (555) 555-2345. Retain this form for your records.

Quantity Received: _____ Lot No.: _____

Kit Numbers: _____

Received in acceptable condition? YES NO

If "No", comment: _____

_____

Received By: _____ Date: _____

A well-designed shipping manifest, one that provides full descriptions of shipment contents, can be a critical part of drug accountability.

ments, but it may be at the cost of subject dosing compliance information. Moreover, as will be discussed later, knowledge of the exact amount of medication shipped to the site is critical for verifying subject doses against randomization schemes in Phase 1 studies, and in studies with a crossover design (that is, studies in which each subject receives each of the study treatments).

Drug accountability at the investigative site

The drug accountability process continues at the investigative site, where the clinical investigator is responsible for maintaining adequate records of the disposition of the drug. The clinical investigator must also ensure proper security and storage of the investigational drug. Even when research pharmacists or intermediary home health pharmacies or vendors are involved, the clinical investigator retains this responsibility.

Documentation. At minimum, the site should document drug receipt, subject dispensing and return, returns of used and unused supplies to the sponsor (or on-site destruction), and should maintain a current accounting of all supplies in inventory—that is, a balance-on-hand log. The balance-on-hand, or dispensing, log should contain the protocol number, the investigative site(s), the drug name, and the medication units—such as tablets, capsules, or vial).

The site should document receipt of each drug shipment in the balance-on-hand log, noting the date, amount, and lot, batch, or ID numbers. When dispensing drug to a subject, site personnel should record the date, subject number, and amount dispensed. When a subject returns a drug, the amount used and unused should be documented, as should an explanation for any inadvertent loss or destruction of supplies. A well-maintained balance-on-hand log allows the study monitor to efficiently assess drug accountability during routine site visits, and at the final drug reconciliation.

When sponsors use a per-subject dispensing and return log, it is difficult for sites to readily determine the current amount of unused drug supplies in inventory, the quantity dispensed to subjects, and the amount separated for return or destruction. This is particularly true for large studies. Some study coordinators have expressed frustration about using systems that lack a running inventory log. They say they need to count the supplies to determine whether they have study drug on hand for the next subject or next subject visit. Such a system, in which records are in many individual files, also requires that site personnel initiate a drug accountability log prior to the supplies being assigned to a subject. Often such a log is not prepared. However, this documentation is necessary for the site to be able to account for final disposition of the supplies, specifically in the event that the kit is not dispensed to a subject.

In a case where the supplies are not dispensed, and no per-subject drug accountability form is initiated, the site is left with a manifest for the supplies documenting shipment, but no record of final disposition. If a separate form is used for return to the sponsor or for drug destruction, this issue is avoided. However, site personnel still must review several forms to determine whether supplies are present in inventory (or count the actual supplies). Ultimately, drug accountability documentation should be simple and useful.

Audits of investigative sites often reveal inadequate drug dispensing logs. The units of the drug or the actual balance on-hand may not be present or accurate. This is particularly troublesome when the site personnel write in the units themselves and are inconsistent in the units. One trial, for example, involved sealed dispensers that contained several individual doses. In

some cases, site personnel documented the subject dispensation in terms of a dispenser, and in others, in terms of the individual dose units. This made reconciliation difficult and troublesome.

Occasionally, the drug dispensing logs are completed retrospectively from information in the source documents or from CRF entries. This practice is inappropriate. Rather, the log should be initiated based on the current state of affairs, and a note to file should be written explaining that the log was not maintained in an ongoing manner.

The clinical investigator is responsible for drug accountability and proper security and storage of investigational drug at the study site.

Ensuring compliance and reconciliation. Site personnel should assess dosing regimen compliance and drug reconciliation in an ongoing manner. At each subject visit, subject compliance should be evaluated and documented, including calculating the expected amount of consumed drug given the regimen and amount of time between visits. This figure should be compared with the amount dispensed minus the amount the subject returned. Site personnel should question the subject regarding any discrepancies in these amounts and document the explanation.

If subject diaries are used, site personnel should verify that the amount of drug used corresponds with the diary. Any questionable diary entries should be reviewed with the subject, and the discussion documented. Quite often these types of assessments are not performed, resulting in inadequate documentation that the subject took the drug per protocol. It also presents safety concerns, as the subject might be under- or overdosing. Documented explanations are critical to support compliance.

Poor subject compliance accountability documentation obviously brings into question the validity of study data. In the event subject compliance is poor, the data will reflect an artificially low drug effect—and likely a better-than-expected safety profile. If subjects are using more drug than the protocol-defined regimen, a greater-than-actual efficacy effect might be observed, and perhaps a worse safety profile. In either case, these data will be undesirable to the holder of the marketing application. Thus, any subject misdosings or instances of poor compliance should be documented and explained.

Drug accountability and reconciliation is critical in studies involving a complete crossover and in studies including pharmacokinetic (PK) sample collection. If it is not possible to identify the subject(s) who received the incorrect dose, an error of one dose can bring into question the usability of the data for an investigative site, and even the entire study.

Consider the scenario of a single-dose, two-period crossover study involving a comparator drug and the investigational drug, in which one study objective is to show that the novel drug is superior to the comparator. The study is completed and drug accountability is being performed. Five subjects participated in the study, and each received one dose of each of two treatments. Ten tablets of each product were supplied, and the site staff documented confirmation of the inventory upon drug receipt. The site ran the study and documented that each subject received one dose of each product. However, at the time of reconciliation, the monitor notes that four tablets of comparator drug and five tablets of novel drug remain in inventory. Though there may be several explanations for this discrepancy, the possibility exists that a subject received an extra dose of comparator. Given such an error, how can a statistician interpret the superiority effect of the novel drug? If a subject did indeed receive an extra dose, the data likely would reflect a greater effect for the comparator, and/or lessen any observed difference between the novel drug and the comparator. Any PK samples from this study would also be affected adversely. Specimen assay levels would likely reveal any dosing errors.

In other studies, dosing errors are also readily apparent. Incorrect drugs may show up in a specimen or, in placebo-controlled trials, drug levels might be found in samples for a subject who was to receive a placebo. Obviously, drug accountability records are paramount in such studies.

Blinded, crossover design studies using tablet dosing preparations pose a unique situation in terms of reconciliation. That is, once a drug is removed from bulk stock for dosing, it should not be returned to bulk stock if it is not dispensed to a subject. The monitor should be able to verify—by the amount of remaining medication—that the randomization was followed exactly. If a dose is returned to bulk stock, the monitor cannot perform ths verification, and cannot confirm that the dose returned is not masking another dosing error.

Consider the previous example, in which the site received two bottles, each containing 10 tablets (Bottles A and B for treatments A and B, respectively). For blinding purposes, the sponsor encapsulated the tablets in identical capsules. Five one-tablet doses from Bottle A and five from Bottle B were removed from bulk stock. One dose of treatment B was not administered and was subsequently returned to bulk stock. However, the study coordinator states she inadvertently returned the tablet to the incorrect bottle, Bottle A. At the time of reconciliation, the monitor discovers this error and notes that six doses remained in Bottle A, though the randomization and the source documentation reflect that five doses from Bottle A were dispensed. Five tablets were present in Bottle B, and the documentation supported the dispensation of five Treatment B doses as per the randomization.

At first the issue appears reconcilable, as the tablets could be analyzed and one could identify the Bottle B tablet in the Bottle A remaining supply. However, it cannot be concluded with any certainty as to when the Bottle B tablet was placed into the Bottle A supply. That is, it is equally possible that the error occurred sometime during preparation, and not upon return of the tablet, even in light of the study coordinator's recollection. And in this scenario, the trust that your subjects were dosed correctly would be founded on the study coordinator's word alone. This likely would be disconcerting to an

FDA reviewer examining your PK data.

Corrections. Problems also stem from hastily made, unverified corrections to drug records—for example, changes to study dispensing logs to match the remaining inventory at the site, without correcting the progress notes and/or CRFs. Reconciliation should be based on actual documented subject returns, not the remaining inventory on-site at study completion. In some cases, drug returns are documented in multiple locations, without a clearly identifiable source document. These multiple sources increase the chance for discrepancies.

Drug accountability documentation should be simple and useful.

During one audit, it was noted that some entries on a drug accountability log had been corrected and changed based on amounts of used medication counted during the monitor's drug reconciliation. In this particular case, the changes resulted in entries that were illogical. The dose regimen was one vial to be injected daily for four weeks. Subject visits were once per week, and seven vials were dispensed at each visit. One subject chart reflected that the subject was dispensed seven vials at Week 1 and returned seven used vials at Week 2. The study coordinator placed the used vials in a bag labeled with the date of the Week 2 visit. The subject chart then reflected that the subject was dispensed another seven vials at Week 2 and returned seven used vials at Week 3. Upon return, the study coordinator placed these used vials in the Week 2 bag as well. During drug reconciliation two months later, the monitor noted the 14 vials in the Week 2 bag. Based on this count, the monitor requested that the site change the entry for the Week 2 returns on the drug accountability log from 7 to 14. This change was not supported by the entries in the subject chart and was not logical, as the subject would have returned more vials than he or she had been dispensed. These types of observations are surprisingly common, though not always as blatant as the example provided. Nonetheless, this illustrates that drug accountability documentation should not be reconciled based on returned supplies in inventory.

Monitors. The study monitor is key to ensuring accurate drug accountability. During routine visits, monitors should assess the site's drug preparation and dispensing procedures, as well as subject compliance, and ensure proper drug storage and log maintenance. The monitor should also verify that the clinical investigator or an authorized representative is dispensing the supplies. Further, monitors should confirm that all supplies are accounted for and returned or destroyed, report and investigate any discrepancies, and resolve all items before site closure.

By periodically reviewing drug accountability documentation throughout the study, monitors can identify inappropriate practices as they occur and retrain site staff as needed. Problems detected early are more easily resolved. Proper review of drug records could uncover poor subject compliance with drug administration, incorrect supplies at the site, errant drug preparation, incorrect randomization, and potential unblinding of subjects who were dispensed coded labels. Upon noting problems, monitors should immediately implement corrective action plans to prevent future occurrences.

Drug return or destruction

The final step in the drug accountability process is drug return or destruction. Throughout the study, drug returns and destruction should be properly documented, including protocol and drug identifiers, units, and lot numbers. If applicable, the returned supplies should be attributed to specific subjects. In addition, the records should distinguish between unopened (not dispensed) and unused (by the subject) supplies, identify broken or lost supplies, and show that 95–100% of supplies are accounted for. Any larger discrepancies must be investigated and explained.

Drug return logs should be orderly and clear, though often this is not the case. Common findings include medication amounts or lot numbers that do not reconcile with receipt documents or dispensing logs. Incomplete listings of returned supplies or replication of returned supplies (returns of the same supplies on different dates) are also common. Such errors result in drug supply amounts that do not reconcile. Sometimes the return form does not distinguish between used and unused supplies, complicating both compliance assessments and matching of the amounts and specific supplies the subject used.

What auditors should observe

An investigative site audit tests the drug accountability process and can help gauge the readiness of the records for an FDA inspection. Thus, an auditor should carefully assess drug accountability. The

Warning Letters

Proper drug accountability procedures and regular drug accountability checks during monitoring visits could have prevented most of these drug accountability findings noted in recent FDA warning letters.

- Incomplete and/or inaccurate dispensing records.
- Failure to maintain an adequate drug inventory, such that records do not identify the recipients of a particular lot of the drug.
- Lack of drug accountability records regarding the transfer of drug between sites.
- Failure to maintain drug dispensing records during the study.
- Shipping invoices and dispensing/accountability records reflecting more drug administered than received.
- Discrepancies between drug administration forms and accountability records.
- Unavailability of drug distribution records.
- Missing or unaccounted-for study drug.
- Inadequate and inaccurate source documents, although CRO monitoring guidelines required 100 percent verification of source for completeness and accuracy.
- Failure of the CRO to adequately monitor the clinical study and to secure the compliance of or discontinue noncompliant clinical investigators.

accountability documentation should fully reconcile for all supplies received, dispensed, and returned. There should be evidence that entries on logs were made in real time (at the time the action took place). Documentation should support proper storage and security of the drug. Moreover, dispensing logs should be complete. The auditor should confirm that the monitor reviewed drug accountability periodically and that final drug reconciliation was performed. Copies of drug labels should be attached to the original CRF pages, and returns should be completely documented. In all, the documentation should provide a full and accurate explanation of drug handling from receipt through final disposition. Good documentation and records will facilitate any regulatory inspection.

FDA inspection findings

An FDA inspection is the biggest test of the drug accountability process. FDA inspectors assess two main areas: accountability and control of the test article. FDA inspectors also look at whether the drug was shipped to designated, authorized individuals listed on the Form FDA 1572. Moreover, FDA inspectors evaluate the way the monitor reviewed study progress, including use and accounting of supplies.

Many of the findings related to drug accountability from recent warning letters, as shown in the accompanying box, could be avoided with proper drug accountability procedures and regular drug accountability checks during monitoring visits.

Documentation is key to accountability

If the clinical investigator adequately maintains the study drug accountability documentation, and the monitor conducts ongoing reviews, then the records should reflect that the clinical investigator maintained proper control of administration and distribution of the study drug. The records, when kept according to the recommendations presented here, should also indicate that the clinical investigator met his or her regulatory obligations. The paper trail should show the receipt of the supplies at the site, the dispensing to each subject, the amount the subject used or did not use, the amount the subject returned, and the amount the monitor returned to the sponsor or destroyed on-site. Accurate drug accountability records provide assurance that the drug was dispensed and/or administered according to the protocol, and support study data validity and conclusions drawn from those data. At any stage of the study, the site staff, the monitor, and the sponsor should know where their drugs are.

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