IMP management at site

Dmitry Semenyuta
TOP 5 FDA inspections finding 1999-2009
Center of Drug Evaluation and Research (CDER)

- Failure to follow the protocol
- Failure to keep adequate and accurate records
- Problems with the informed consent form
- Failure to report adverse events
- Failure to account for the disposition of study drugs

10 years without any changes....
Most recurrent IMP audit findings

Drug accountability:
- Inadequate records for IMP dispensing, accountability and reconciliation
- Monitor completed IP accountability log instead of site staff

Management at site:
- No/inadequate record of temperature monitoring of IMP storage facility
- No/inadequate documentation of IMP receipt at site

Violation of Protocol, GCP or Regulations:
- Dosage regime not followed
- Transfer of IMP between sites
- Expired IMP used
- IMP label does not meet Annex 13 requirements
Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. ICH 1.33
2.12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
IP Management During the Trial

Every time IP ‘changes hands’ there must be written documentation

Lost trial medication

% compliance

Investigator may delegate some or all duties to a pharmacist

IP=drug being studied and comparator or placebo
Sponsor Obligation  ICH 5.14

- 5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

- 5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

- 5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product (for the trial and documentation thereof). The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).
Before IP is at site

- CRA must ensure that site staff is trained. Good practice - the training should be documented. TCR would be ok
- Site staff - check equipment for IP storage. Freezer and min/max thermometer as example
- Site staff should be aware about expected date and time for IP shipment
- Immediate reporting required. Specially for IP with cool storage requirements
- CRA should support site staff for all questions/concerns
Investigational Product

• Once received by the site...
## Investigator Responsibilities

- Receipt and Inventory
- Storage requirements
- Dispensing & administering
- Return of unused supplies
- Alternative disposition
- Final accountability

**Remember....**

*If it isn’t documented, it didn’t happen. Records must be kept.*
Receipt/Inventory/Storage

- Recipient verifies shipment and signs receipt
- Inventory logs are maintained by Investigator/ staff
- Storage conditions
Storage Conditions

Room Temperature Storage

- Min/Max thermometer should be read, temperature recorded on a temperature log and thermometer reset at least once per week.
- Temp Logs should be reviewed by second person once per month.
- Thermometer should be calibrated or at least come with a “certificate of conformity with the accuracy requirements” issued by the manufacturer. Device needs to have accuracy of +/- 0.5 degrees. The recommended supplier can provide these thermometers in the required amount along with the necessary documentation.
Cold storage

• Min/Max thermometer should be read, temperature recorded on a temperature log and thermometer reset at least once daily.
• Temp Logs should be reviewed by second person once per week.
• Thermometer needs to be calibrated annually, calibration certificate is required, device needs to have accuracy of +/- 0,5 degrees.
• There is a recommended supplier for calibrated thermometers.
Use of Data Loggers

• The most comprehensive temperature monitoring at a site can be achieved by using so called data loggers. These are devices that continuously record the temperature in the room they are placed in. The temperature is measured and recorded at pre-defined intervals (can be anything between 1 Sec to several hours, recommended interval: once or twice per hour).

• In regular intervals (typically once per month) the data is downloaded onto a computer with the adequate software (which has to be purchased separately). On the computer the data can be reviewed either as tables or graphs, which also can be printed and filed as appropriate.

• N.B. If data logger software will be installed on computers at site, it will be necessary to confirm this upfront with the investigator sites.
Dispensing, Administering, and Documenting IP accountability

- **Investigator responsibilities:**
  - Dispense only to subjects enrolled in the study
  - Perform patient compliance checks

- **Documentation of IP includes:**
  - Patient diaries, Case Report Form entries
  - Inventory log entries, Source documentation
Documentation

Must exist as written evidence of
• how the activity was performed
• what actually happened - planned and unplanned
• when it happened
• who was involved
• training - all involved were trained to perform their roles
CRA Responsibilities for IP (ICH 5.18)

- During routine monitoring visits, the monitor will:
  - Review dispensing procedures and documentation with pharmacy and/or clinical staff at regular intervals
  - Check storage conditions, including any measurement logs (temp, humidity, light)
  - Check adequacy of supplies
  - Ensure IP dispensed to eligible trial subjects only
CRA Responsibilities for IP

During routine monitoring visits, the monitor will:

- Ensure documentation that subjects received instruction in using, handling, storing, and returning IP
- Check that receipt, use, and return of IP are controlled and documented
- Verify that IP labels remain unopened (protect the *blind)
- Check that disposition of unused IP at sites complies with applicable regulatory requirements
- Document monitoring of IP in the site visit report and follow up letter
Inventory Records of IMPs at Investigator Sites

- Quantity
  - Received
  - Dispensed to subject 1 = used + returned
  - Dispensed to subject 2 = used + returned
  - Dispensed to subject 3 = used + returned

Reconciliation 100%
Subject Compliance & Accountability

Compliance is a measure of how well the subject adheres to specified treatment regime.

Assessment of subject compliance may determine whether a negative clinical trial resulted from subject failure to take IP or from other influencing factors.
Relabeling at Investigator Site

- IPs highlighted as approaching retest/expiry date.
- Additional label applied with **NEW USE BY DATE** and **BATCH NUMBER** repeated.
- May be superimposed on old use date **BUT NOT** on original batch number.
- Labeling activity can be performed at supply centre or at investigator site in accordance with SOPs.
- Performed by one person (e.g., monitor, Pharmacist) and checked by a second person.
- Following approved instructions and all instructions documented as being performed.
- 100% label accountability, excess labels destroyed.
- Any deviation/incidents recorded.
IP Recordkeeping at Sites

- ALL shipping and receiving invoices indicating the type and quantity of the drug or device, and the date of shipment
- Sponsor letters that extend expiration dates
- Record of dispensing, waste and return reflecting the subject, reason and batch or lot number
- Destruction done according to institutional policy (if applicable)
Intersite Transfer

• Exceptional circumstances as detailed in Annex 13
• In accordance with Standard Operating Procedures
• Considerations before IMP can be re-distributed
  - Product history through trial monitoring reports
  - Storage conditions
  - Security
  - return to supply centre for visual inspection
  - return to supply centre for re-labelling

• Documented and re-certified by Qualified Person (QP)
Code Breaks Identified at Site

Coding system should allow rapid identification of the product in case of a medical emergency but should not permit undetectable breaks of the blinding.

Investigator to ensure the code is broken only in accordance with the protocol.

If the code is broken prematurely or accidentally, the investigator must promptly document this with an explanation.

Codes need to be accessible 24 hrs a day with ‘limited access’; however, they should not be locked away in a private office.
Final Accountability/Reconciliation

- Responsibility
- Records required to perform
- Formula
- Final reconciliation
Final Accountability

- Sponsor accounts for all supplies
  - Shipped to the site
  - Used for the study
  - Returned to the sponsor
  - Destroyed by site
Return of IP from Site

- Sponsor responsibility with **investigator cooperation**
- All unused/partially used supplies
- Drug return form (disposition form)
  - Copy in investigator file
  - Sponsor copies
- Confirmation of receipt
Destruction of IMPs

- written authorization by the Sponsor. (i.e. contract)
- reconciliation performed, and documented, at each trial site.
- certificate of destruction containing quantities destroyed, batch numbers and/or subject numbers. i.e. traceable to IMP destroyed
Thank you