Learning Objectives

At the end of this activity, learners should be able to:

1. Understand FDA Regulations and ICH GCP Guidelines for disposition of Investigational Product in Clinical Trials
2. List the stages of the IP management cycle
3. Identify the documentation requirements and pitfalls at each stage of the IP management cycle
4. Identify situations where it is necessary to use the Investigational Drug Service (IDS) for outpatient trials
“Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under §312.59.”
ICH E6 Good Clinical Practice: Consolidated Guidance

Section 4.6.3

“The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.”
Steps Taken Throughout an IP’s Life Cycle

**MANUFACTURER**
- Batch/Lot
- Amount manufactured
- Samples—QA, QC, stability, analytical, etc.
- Rejected/Destroyed

**PACKAGER**
- Batch/Lot
- Amount of bulk drug received
- Amount packaged
- Samples
- Rejected/Destroyed
- Amount released to warehouse, depot or site by kit #

**WAREHOUSE/DEPOT**
- Batch/Lot
- Qty of kits received
- Qty of kits released
- **All kits tracked by Kit # and Site #**
- Site-to-warehouse-to-site distribution

**SITES**
- Kit # received
- Site #
- Patient #
- Kit # assigned per patient
- Date assigned
- Date returned
- Qty returned

**WAREHOUSE/DEPOT**
- Return # (including site # and kit #)
- Qty of kits received
- Qty within kits

**ENVIRONMENTAL WASTE MANAGEMENT**
- Pounds of waste destroyed
- Destruction date

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Material characterization and classification
Material Safety Data Sheets
Regulated or unregulated medical waste

Certificate of Destruction
Receiving Investigational Drugs

At the end of a trial, all drug assigned to a site must be accounted for, whether dispensed to patients, lost or damaged in transit, or returned to sponsor unused.

An accurate investigational drug accounting process begins with the sponsor's shipping records.

When possible, request that sponsor, CRA, or shipping vendor send a supply notice to the site before sending IP.
Receiving Investigational Drugs
Receiving Investigational Drugs

Upon opening the package:

- Verify that the contents are intact and undamaged.
- Check temperature monitor for alerts, if present.
- Compare the invoice to the lot number, expiration date, quantity, and dosage on each kit.
- Retain all shipping documents in site files.
- Register shipment as received in IWRS (or protocol specific inventory log).
Receiving Investigational Drugs

Report damage, temperature excursions, and content discrepancies to the sponsor immediately.

Assess current inventory: You may need to reschedule patients if a damaged IP shipment leaves you with insufficient supply!
Maintaining Record of Inventory

Record all kits shipped on Master IP log. You may need to specify:

- Shipment ID number
- Receipt date
- Quantities - # of pills or volume per dispensable unit
  - Best practice - Record each unit received on its own line; do not batch receipt of multiple units in a single line
- Dosage or strength
- Production lot or batch numbers
- Individual kit/bottle numbers
- Expiration dates
Master IP Log, Example

### DRUG ACCOUNTABILITY LOG

**Protocol:** Protocol #

Study Drug: ___________________________ Lot #: ___________________________ (A separate log must be maintained for each lot of product received.)

Drug Supplier: ___________________________ PI: ___________________________

<table>
<thead>
<tr>
<th>Received From Drug Supplier</th>
<th>Dispensed to Subject</th>
<th>Site Inventory</th>
<th>Subject Returned</th>
<th>Product Destruction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Received</td>
<td>Date Dispensed</td>
<td>Subj #</td>
<td># Bottles Dispensed</td>
<td>Running Balance</td>
<td>Date Returned</td>
</tr>
<tr>
<td>Ship- ment #</td>
<td>Init</td>
<td></td>
<td></td>
<td></td>
<td>Init</td>
</tr>
<tr>
<td># of bottles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PI: ___________________________ Date: ______________

Signature

CRC: ___________________________ Date: ______________

Page ___ of ___

Signature
IP Storage

Store IP according to protocol-specified conditions. This may include temperature, humidity, and sunlight restrictions.

You may need proof of temperature and/or humidity conditions:

• Manual logging is inexpensive but risks missing records and unknown excursions
• Consider electronic data logging devices for convenience, accuracy, and 24/7 coverage
IP Storage

Store IP in a dedicated room or cabinet accessible only to research staff.

Controlled substances should also be secured in a locked cabinet with access further limited only to the specific individuals delegated to dispense the medication.

Consider using the Pharmacy’s Investigational Drug Service if your facilities do not provide adequate security.
Dispensing IP to Subjects

Medication may be dispensed only by appropriately trained and delegated study personnel.

Dispensation records usually record the same set of information in multiple places:

- Subject source
- Subject-specific IP Log
- Master IP Log
- Completion of IP label
Dispensing IP to Subjects

Source documents should be completed to meet the documentation requirements of the protocol and may include:

- Dosage and frequency ordered
  - Best practice: Confirmatory statement from PI or Co-I
    - ex. “Patient may start/continue study drug at [dosage]”
    - “Patient should titrate up/down to [new dosage]”
- Individual bottle/kit/vial numbers dispensed *
- Number of pills or volume per bottle/kit/vial
- Record of any instructions or education to patient concerning dosing instructions
Additional Labeling, Examples
### Additional Labeling, Examples

<table>
<thead>
<tr>
<th>Shipment (Consignment Number)</th>
<th>Lot Number</th>
<th>Blister Card Number</th>
<th># of Capsules Received</th>
<th>Date Received (dd/mm/yy)</th>
<th>Date Confirmed in IVRS (dd/mm/yy)</th>
<th>Recorder’s Initials and Date (dd/mm/yy)</th>
<th>Comments*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE000101/001</td>
<td>P000105</td>
<td>1</td>
<td>20</td>
<td>30-SEP-15</td>
<td>NA</td>
<td>NA</td>
<td>CARD 1 of 40</td>
</tr>
<tr>
<td>BE000101/001</td>
<td>P000105</td>
<td>1</td>
<td>30</td>
<td>30-SEP-15</td>
<td>30-SEP-15</td>
<td>NA</td>
<td>CARD 1 of 40</td>
</tr>
<tr>
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<td>P000105</td>
<td>1</td>
<td>30</td>
<td>30-SEP-15</td>
<td>30-SEP-15</td>
<td>ML</td>
<td>CARD 6 of 40</td>
</tr>
<tr>
<td>BE000101/001</td>
<td>P000105</td>
<td>1</td>
<td>30</td>
<td>30-SEP-15</td>
<td>30-SEP-15</td>
<td>ML</td>
<td>CARD 7 of 40</td>
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<td>ML</td>
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<td>CARD 10 of 40</td>
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<td>30-SEP-15</td>
<td>ML</td>
<td>CARD 11 of 40</td>
</tr>
</tbody>
</table>

*Please explain any study drug discrepancies in this column – example study drug never returned by subject, or loss, etc.
Dispensing IP to Subjects

IP Labels must be completely filled out where any site-specific information is left blank by sponsor and may include:

- Subject ID
- Visit Number
- Date Dispensed
- Site Identifier and PI Name
- Contact Phone Number
- Dosage and Administration Frequency
Collecting Used IP

ALL dispensed IP should be accounted for at time of return.

Useful techniques:
• Calculate the amount of drug that patient should have used since last visit, if applicable.
• Count returned IP while the patient is still at the visit and before dispensing additional IP.
• Compare to patient records (diaries, calendars, etc.) and calculate compliance; anything other than 100% compliance may need to be explained and documented.
Returning IP for Destruction

Used and expired IP is typically reviewed on site by a monitor who will arrange for return to sponsor or depot.

Reminders:
• Resolve discrepancies in pill counts immediately.
• Confirmation of return may be documented in multiple places: Patient IP log; Master IP log; IWRS. Ensure that monitor signs off on all relevant forms.
• File copy of return documentation completed by monitor.
Investigational Drug Service

IDS must be used for inpatient trials, but it may be necessary to use their services for outpatient trials when:

- Study drug(s) require preparation on the date of use (weight dependent dosage; infusions)
- Study drugs require blinding services
- Site does not have proper facilities to store controlled substances or maintain required environmental conditions
Investigational Drug Service

When IP is managed by IDS, their staff:

- Reviews protocol for feasibility
- Prepares pharmacy budget
- Maintains drug accountability logs
- Monitors inventory levels
- Prepares dispensing procedures
- Maintains required environmental conditions and logs
- Participates in Initiation, Monitoring, and Closeout visits; internal and regulatory audits
Resources

**Reference Documents**
- FDA 21CFR 312
- ICH E6 Guideline for Good Clinical Practice, Section 4.6

**Temperature Monitoring**
- TJU IDS Email Address: IDS-Service.Pharmacy@jefferson.edu