Investigational Products: IP Management and Accountability

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Investigational Drug Service

Department of Pharmacy

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Learning Objectives

- Describe the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP) guidelines as they pertain to study drugs.
- Describe national and state standards and laws applicable to study drugs.
- Describe the lifecycle of an investigational drug.
- Explain how the Investigational Drug Service (IDS) can help Investigators/Study Coordinators fulfill these requirements.

Regulations and Standards

- **Code of Federal Regulations (CFR)**
- **Good Clinical Practice (GCP)**
- **NY State Regulations**
- **Hospital Policy (IRB)**
- The Joint Commission (TJC)
- American Society of Health System Pharmacists (ASHP)
- Hematology Oncology Pharmacy Association (HOPA)

Code of Federal Regulations

General Responsibilities of Investigators

312.60 An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

Investigator Record Keeping and Retention

312.62(a) An investigator is required to maintain adequate records of the disposition of the drug.

312.62(b) An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

312.62(c) An investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or until 2 years after it is D/C and FDA is notified

Handling of Controlled Substances

312.69 If the investigational drug is subject to the CSA, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Cabinet must meet NYS regulations – NYS likely to inspect

NYS requires that the site / PI obtain a Class 4 Researcher's license

Good Clinical Practice

What is Good Clinical Practice?

1.24 A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

Roles and Responsibilities

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution

Record Keeping and Retention (IP Related)

4.6.3 Maintaining records of the product's delivery to the trial site, inventory at the site, use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include:

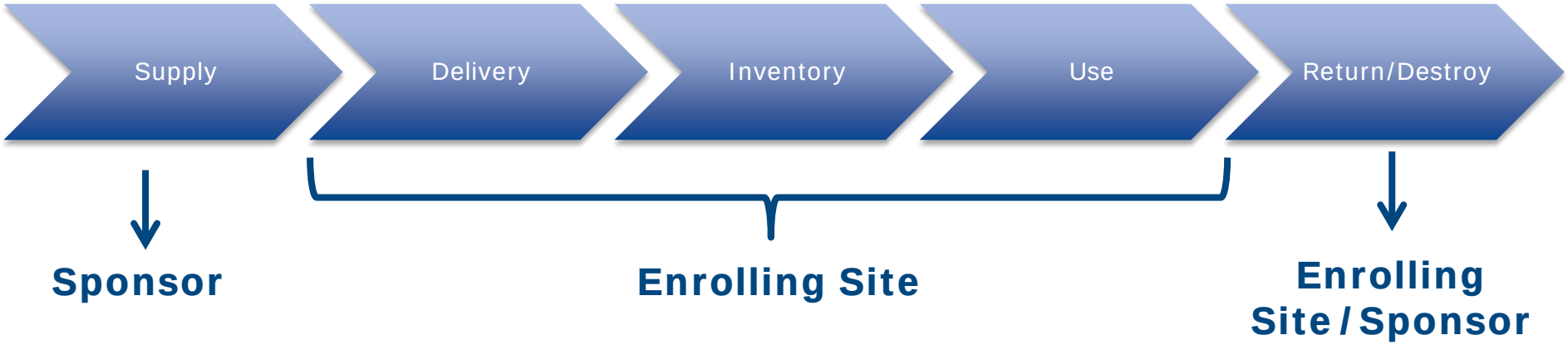
- Dates
- Quantities
- Batch/serial numbers
- Expiration dates
- Unique code number assigned to the product and trial subject

Record Retention (All)

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Drug Accountability

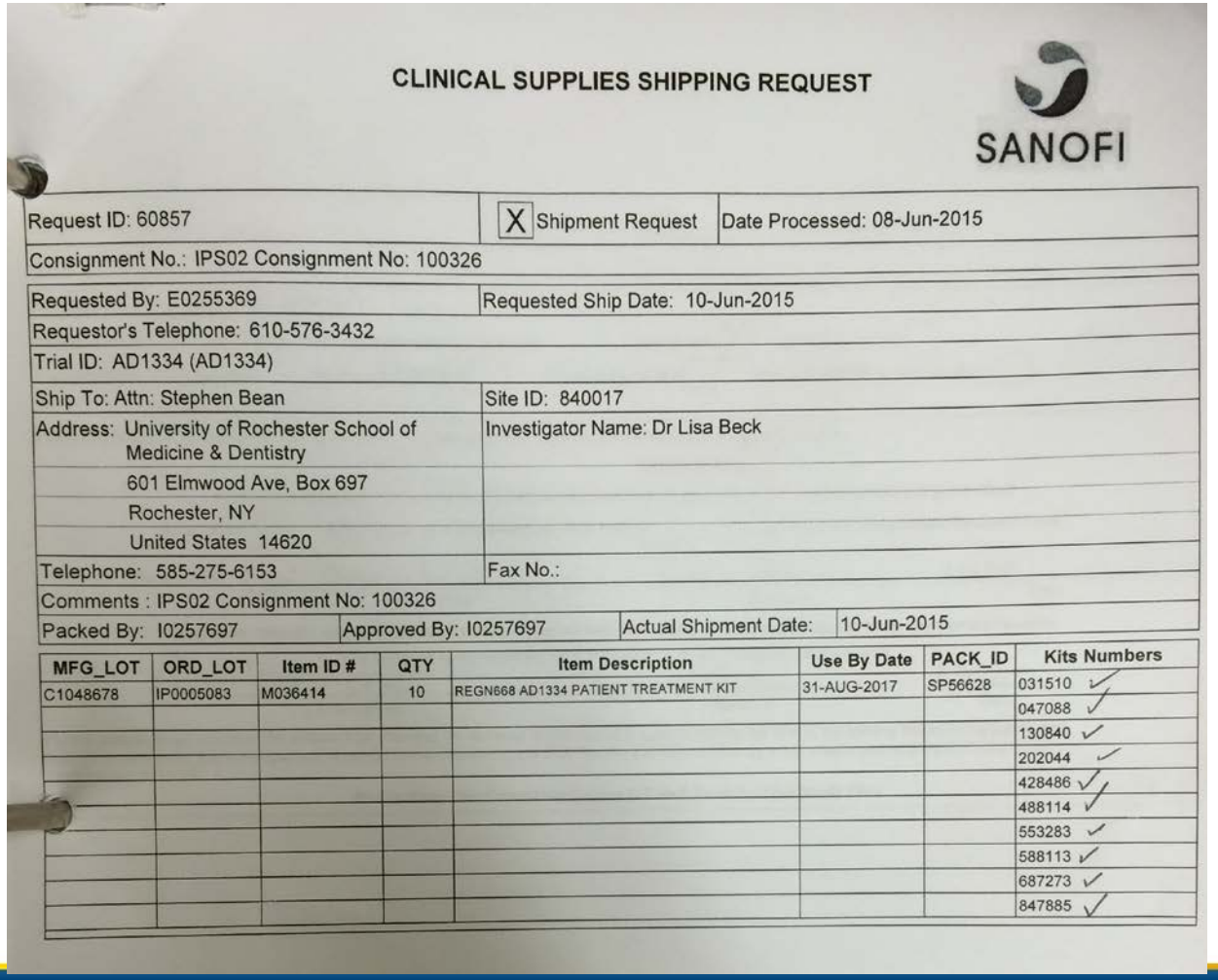
Drug Accountability Lifecycle



Investigational Drug Delivery

- Date of arrival
- Packing invoice
- Temperature tracker
- Acknowledgement

of receipt



CLINICAL SUPPLIES SHIPPING REQUEST

SANOFI

Request ID: 60857	[X] Shipment Request	Date Processed: 08-Jun-2015
Consignment No.: IPS02 Consignment No: 100326		
Requested By: E0255369	Requested Ship Date: 10-Jun-2015	
Requestor's Telephone: 610-576-3432		
Trial ID: AD1334 (AD1334)		
Ship To: Attn: Stephen Bean	Site ID: 840017	
Address: University of Rochester School of Medicine & Dentistry 601 Elmwood Ave, Box 697 Rochester, NY United States 14620	Investigator Name: Dr Lisa Beck	
Telephone: 585-275-6153	Fax No.:	
Comments : IPS02 Consignment No: 100326		
Packed By: I0257697	Approved By: I0257697	Actual Shipment Date: 10-Jun-2015

MFG_LOT	ORD_LOT	Item ID #	QTY	Item Description	Use By Date	PACK_ID	Kits Numbers
C1048678	IP0005083	M036414	10	REGN668 AD1334 PATIENT TREATMENT KIT	31-AUG-2017	SP56628	031510 ✓
							047088 ✓
							130840 ✓
							202044 ✓
							428486 ✓
							488114 ✓
							553283 ✓
							588113 ✓
							687273 ✓
							847885 ✓

Temperature Monitoring (Onsite)

- Storage conditions must be monitored
- Secondary monitoring system should be in place
  - In the event of a temperature excursion the site must be able to provide details to sponsor including when, how long it lasted (ideally), and the "out of range temperatures" reached during the excursion
    - IDS utilizes a Min/Max manual recording system for each area
      - Considered to be the minimum accepted by most sponsors
- Temperatures must be monitored on a daily basis
- Records must be readily available to study monitors upon request
  - A continuous monitoring system with 24/7 alert functionality preferred
    - IDS system records temperatures every 15 minutes via Mobileview by Stanley Healthcare
      - Alerts IDS pharmacists via text messages in the event of an excursion

IDS Continuous Temperature Monitoring

Temperature History

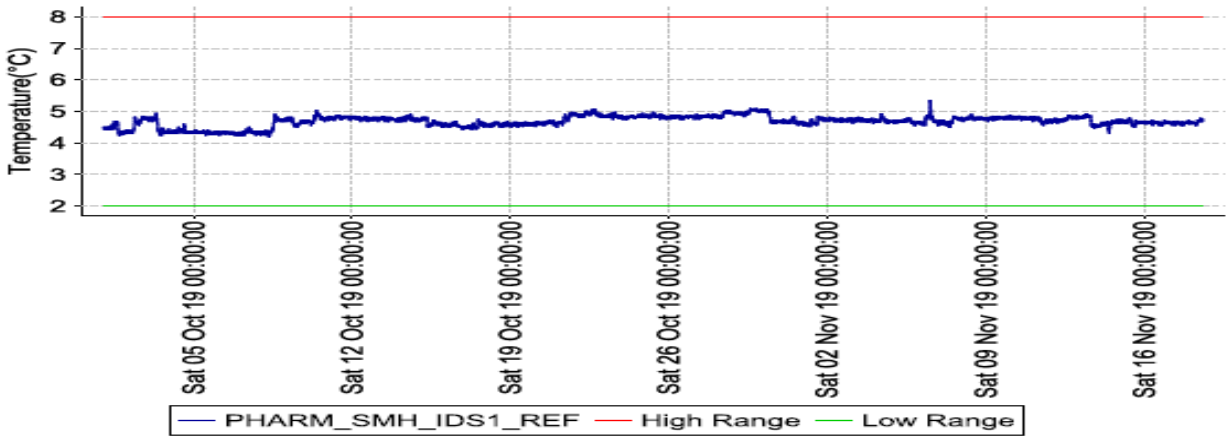
STANLEY Healthcare

Report run by: Steve Bean, Mon 18 Nov 19 14:22:26 — Signed By:

Period: Tue 01 Oct 19 00:05:00 - Mon 18 Nov 19 14:22:25

Asset: PHARM_SMH_IDS1_REF

Asset Name:	PHARM_SMH_IDS1_REF
Asset ID:	CMT-104PHID-003
Description:	56725 IDS Fridge #1 (A)
Category:	Medication Refrigerators
Range:	2.0 °C to 8.0 °C
Department:	SMH, SMH IDS Pharmacy



IDS Temperature Log (min/max log)

Temperature Log

Month: June, 2015

Investigational Drug Services: Strong Memorial Hospital
All medication storage areas need to be checked for proper temperature range on a daily basis.
Storage area ID = Refrigerator #2, room 5-6725
Temperature range: 2 to 8 degrees C
High/Low Thermometer Details
SN: 140495006
Calibration due date: 07/22/16

Date	*Low Temp*	*High Temp*	*Current temp*	*Time Recorded*	*Reset (Y/N)*	*Initials*
6/1/2015	6	6	6	11:00	Y	DC
6/2/2015	6	6	6	9:35	Y	DC
6/3/2015	6	6	6	8:55	Y	DC
6/4/2015	6	6	6	10:15	Y	DC
6/5/2015	6	6	6	8:00	Y	DC
6/6/2015	sat					
6/7/2015	sun					
6/8/2015	5	6	5	7:40	Y	DC
6/9/2015	5	7	5	9:00	Y	DC
6/10/2015	5	6	5	10:05	Y	DC
6/11/2015	5	6	5	9:20	Y	DC
6/12/2015	5	5	5	10:00	Y	DC

Investigational Drug Inventory

- Inventory log - at minimum must capture
  - Date received, dispensed, returned by patient, returned to sponsor or destroyed onsite (i.e. the lifecycle)
  - Subject information (dispensing's and returns)
  - Bottle/Kit number (if applicable)
  - Lot number
  - Expiration/Retest date (if applicable)

Investigational Drug Use – Subject Specific Product Accountability

Dispensing

- Subject ID
- Date dispensed
- Dose/quantity dispensed
- Lot number/package identifier
- Initials of study staff

Return

- Date of return
- Quantity returned
- Initials of study staff

May be required in addition the overall drug accountability log

Drug Accountability Record: Inventory Log

Protocol Title
Master Drug Accountibility Log

Investigator/ Site:_____/_____ **Page** _____ **of** _____

Investigational Drug: _____ **Package Size:** _____ **Storage Temperature:**_____

RECEIVED					DISPENSATION			RETURN/DESTRUCTION			
Shipment Number	Lot/Kit Number Received	Date Received	Expiration Date	Receipt Verified by Site (initials)	Date Dispensed	Subjects #/Initials	Dispensed by	Verified by Monitor (initials and date)	Lot/Kit Number Returned	Comments (e.g., unused, used, damaged IP, expired)	Returned to Sponsor (Monitor initials/date)

Investigational Drug Return / Destruction

- Written approval from the sponsor for ultimate disposition
  - Return to sponsor
  - On-site disposal/destruction
    - Must have formal SOP for on-site destruction

Investigational Drug Return / Destruction

Return to Sponsor

- Date of (return) shipment
- Detailed listing of contents of the shipment
  - Often via use of sponsor's return form
- Name/initial of study staff
- Place copy of return form in shipment and in study file/binder

Destroy Onsite

- Sponsor must provide authorization and guidelines
- Date, quantity, means of destruction
- Name/initial of study staff
- If a controlled substance → NYS, federal regulations apply as well

Investigational Drug Destruction Record

WILMOT CANCER CENTER

UNIVERSITY of ROCHESTER MEDICAL CENTER

JAMES P. WILMOT CANCER CENTER PHARMACY
INVESTIGATIONAL DRUG SERVICES
INVESTIGATIONAL AGENT DESTRUCTION RECORD

Study ID:

Subject #:

Investigational Agent:

Cycle	Day	Date	Lot	Component	Vials	Vial Status

I certify that the agent(s) referenced above has been disposed of or otherwise destroyed in a manner consistent with institutional policy/Cancer Center Investigational Drug Service policy and procedure.

NAME / TITLE _____ SIGNATURE _____ DATE _____

WITNESS NAME / TITLE _____ SIGNATURE _____ DATE _____

Drug Accountability Record: Inventory Log

Protocol Title
Master Drug Accountibility Log

Investigator/ Site:_____/_____ **Page** _____ **of** _____

Investigational Drug: _____ **Package Size:** _____ **Storage Temperature:**_____

RECEIVED					DISPENSATION			RETURN/DESTRUCTION			
Shipment Number	Lot/Kit Number Received	Date Received	Expiration Date	Receipt Verified by Site (initials)	Date Dispensed	Subjects #/Initials	Dispensed by	Verified by Monitor (initials and date)	Lot/Kit Number Returned	Comments (e.g., unused, used, damaged IP, expired)	Returned to Sponsor (Monitor initials/date)

Study Team Tools/References

OHSP Study Documentation Tool Box

NCCIH Clinical Research Toolbox

NIDCR Toolkit for Clinical Researchers

NCI – Pharmaceutical Management Branch Investigational Drug Accountability Training Videos

PI Initiated "In-House Study" Thinking Points

- Where does the drug come from?
  - Who is responsible for ordering the drug?
- Who can prepare blinded dose forms?
- How to prepare blinded dose forms?
  - Is it even possible to blind doses?
    - Too bulky, hazardous, chemical instability
- What is required for control/storage of the drug?
  - Security
  - Temperature
  - Documents

PI Initiated "In-House Study" Thinking Points Cont.

- Preparing and dispensing to the patient
  - How/who prepares/dispenses the product?
  - Is maintenance of study blind required?
    - If so then what is dispensing plan?
  - Is it possible to ship the product to the patient at home?
    - Generally discouraged
- Drug returns by the patients
- Disposition/destruction of unused/expired/patient returned drugs

What is an Investigational Drug Service?

The IDS is a division of pharmacy ensuring that the handling, storage, packing, labeling, distribution, and inventory maintenance of investigational agents comply with Good Clinical Practices (GCP), Federal and State regulations, The Joint Commission (TJC) Standards, as well as per the recommendations of the American Society of Health-System Pharmacists (ASHP) and the Hematology Oncology Pharmacy Association (HOPA)

Responsibilities

- Reviewing study protocols before their submission to the institutional review board (IRB)
- Development of guidelines for appropriate dispensing of the study drug
- Development of drug information resources for use by health professionals involved with dispensing and/or administration of the drug (cancer center and inpatient based studies)
- Ensuring that supplies of investigational drugs are stored properly and kept in a secure pharmacy area separate from regular drug supplies
- Maintenance of accurate drug lifecycle and temperature records
- Managing study drug inventory

Services Provided

- Drug and Record Storage
  - Access limited to IDS staff
    - Enhances security and maintenance of blind
  - Archiving of study files via Iron Mountain
- Inventory Control via the “Vestigo Automated Accountability System”
  - Receipt
  - Returns/Destruction
  - Quality Assurance
- Patient randomization
- Dose Calculation/Preparation/Delivery
- Determine the budget for the study

Services Provided Cont.

- Regulatory forms
- Study Meetings
    - SEV/SIV/Monitoring/Close Out
    - Planning/design (in-house)
- Miscellaneous
    - Randomization schemes (with limitations)
    - Odd dosage form preparations
    - Drug packaging/shipping (with limitations)

References

1. Code of Federal Regulations: Selected Regulations & Guidance for Drug Studies. Book 1A. Philadelphia, PA 19103. Clinical Research Resources, LLC.

2. Shehab N, Tamer H. Dispensing Investigational Drugs: Regulatory issues and the role of the investigational drug service. Am J Health- Pharm – Vol 61 [internet] Sep 15, 2004. Available from: http://www.ajhp.org/content/61/18/1882.full.pdf

3. U.S. Department of Health and Human Services. Guidance for Industry SysteE6 Good Clinical Practice: Consolidated Guidance. Available at: http://www.ajhp.org/content/61/18/1882.full.pdf

4. Kim, J. PREP Workshop #20: Investigational Drug Accountability. Feinstein Institute of Medical Research. Available at: http://www.feinsteininstitute.org/wp-content/uploads/2014/09/PREP-20_2014-2015.pdf

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