Topic: Investigational Product (IP)

Contents

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Introduction

Welcome to the Topic: **Investigational Product.**

This topic will provide more information on how to manage and use Investigational Products (IP) at the Site during a clinical study. You will need approximately **20 minutes** to review the topic.

Why is this Topic important?

Short Version (Page text)
Testing IP on human subjects validates dosage and safety. This is why it is so important to handle IP with care and by following proper processes. During most phases of clinical studies, the IP is evaluated for efficacy and safety in human subjects. This is why it is so important to ensure integrity of IP at the site. IP must be received, stored, secured, dispensed, documented, reconciled, and any unused stock returned/ destroyed by following proper processes and regulations. Not doing so puts the quality of IP, safety of subjects, and integrity of study data at risk. To ensure inspection readiness, all IP related data must be documented in source documents as per Sponsor and local regulatory requirements. This includes accounting for any discrepancies in stock, dosage, etc.
Long Version (Audio text)
Hello! I am Dr. Paul Wang. I've been working as a Senior Investigator for more than ten years. Today, we're going to discuss the topic of Investigational Products, or IPs. A clinical study revolves around the investigational product it has set out to test. While the investigational product goes through pre-clinical testing before being tested on subjects, it is the process of having it tested in human subjects that validates its dosage and safety. This is why it is so important to handle IP with care and by following proper processes. Anything else might ultimately put our subjects at risk. During most phases of clinical studies, the IP is evaluated for efficacy and safety in human subjects. This is why it is so important to ensure integrity of IP at the site. IP must be received, stored, secured, dispensed, documented, reconciled, and any unused stock returned/ destroyed by following proper processes and regulations. Not doing so puts the quality of IP, the safety of subjects, and the integrity of study data at risk. To ensure inspection readiness, all IP related data must be documented in source documents as per Sponsor and local regulatory requirements. This includes accounting for any discrepancies in stock, dosage, etc.

Topic Details

Page text & Audio text
This topic will provide more information on: • Investigational Products (IP) • Non-Investigational medicinal products • Investigator responsibilities with reference to IP • Receipt and storage of IP at site • IP dispensation to subjects • Documentation, including IP Labelling/ Re-labelling • IP Reconciliation • Destruction of IP • Inspection readiness

Responsibilities of an Investigator

According to the European Commission Enterprise & Industry Directorate-general, an Investigational Product, or IP, is:

- a pharmaceutical form of an active ingredient, or,
- a 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.

Did You Know?

A placebo is a substance that has no therapeutic effect, and is used as a control in testing new drugs.

Non-Investigational Medicinal Products

There are different types of Non-Investigational Medicinal Products.

1. Rescue Medication

Rescue medication refers to quick-relief or fast-acting medication in clinical studies. Rescue medication may be given besides the IP and/ or placebo when:

- efficacy of the study treatment/ IP is unsatisfactory, and/ or
- effect of the IP is too great and is likely to cause hazard to the subject, and/ or
- exacerbated symptoms of the disease need to be alleviated

2. Challenge Agents

Medicinal product given to produce a physiological response necessary before the pharmacological action of the IP can be assessed.

Example: Skin prick test used to identify subjects with allergic responses to specific allergens. This test may be used as part of the inclusion criteria for a clinical study to control/ prevent symptoms from allergic reactions to the IP.

3. Products used to assess end-points

Medicinal product given as a tool to assess a relevant clinical endpoint (e.g: PET radiopharmaceuticals).

Example: PET radiopharmaceuticals administered to a clinical study population to measure the function of a certain organ before and after the subject has been given an IP.

4. Concomitant Medications

Medicinal products allowed by study protocol as part of standard of care for a condition that is not the indication for which the IP is being tested.

Example: Cancer patients need to receive, at minimum, the current standard of care. Medicinal product allowed under such current standard of care is not considered as IP.

5. Background Therapy

Medicinal product given to all subjects, regardless of randomization group, to treat the indication which is the object of the study. Background treatment is generally considered to be current standard of care for the indication, as defined by local or international consensus.

Receipt of IP at site

The Investigator's responsibility starts when the IP is received at the site. When the IP arrives at the site, the Investigator must verify the IP for correct amount, temperature, and integrity of product. The Investigator should ensure that all persons handling the medication are properly trained and delegated in their duties.

1. Integrity

- Check content and condition of shipment.
- Observe and record any damage, leakage, etc.
- Review for any discrepancies in documents (name of Investigator, IP, wrong expiration date, etc).
- Observe and record any suspected counterfeits, especially for commercial products.
- Verify expiration/ retest dates match the Sponsor's most updated information.
- Verify that controlled substance requirements are being complied with (if required by the study).
- Report any observed deviations to the Sponsor immediately.
- Ensure that essential shipping documents are filed within the site files. Failure to do this may cause issues in the future, e.g: an insufficient record that the IP arrived in good condition may cause the IP to be put in quarantine.

2. Temperature

- Verify temperature conditions upon arrival, ensuring that the temperature during transport was within manufacturer's stability range.
- Sponsors may include a temperature measuring device in the package. Or, they may use temperature controlled containers validated for a determined amount of time.
- Store IP according to the label and/or protocol instructions.

- Follow Sponsor's instructions to report any temperature excursions (deviations) identified upon arrival.

3. Amount

- Verify if the correct amount of IP has been received.
- Unpack the shipment and compare amount received against the list in the acknowledgement of receipt.
- Match the lot numbers in the invoice against the actual delivery.
- Once satisfied, acknowledge receipt via the method set forth by the Sponsor.
- For IxRS studies, ensure that receipt of IP is completed via IxRS system (if applicable).

Did You Know?

Some studies use an Interactive Voice/ Web Response System to randomize subjects. These are respectively identified as IVRS/ IWRS System. Collectively, they are referred to as IxRS Systems.

IP Storage

IP storage conditions are globally regulated by the Guidelines on GDP (Good Distribution Practices) when delivered as per protocol requirements. Three main topics are assessed and evaluated:

1. Storage location
2. Temperature monitoring
3. Documentation

1. Storage Location

- Store the IP at the correct location: pharmacy/ site. In some countries, it is mandatory to store the IP in the pharmacy.
- Ensure that IP is stored separately from other products at the site.
- Storage facilities can include rooms, refrigerators, or freezers. Ensure the facility is clean and tidy!
- Ensure that access to the IP storage location is controlled.
- For studies where IP is not dispensed via an IXRS, implement the “first-in/ first-out” process so that IP is used up on time and expired IP is not dispensed.
- If temperature excursion is detected, do not use IP until Sponsor's written authorization is granted.
- Follow Sponsor's instructions on documentation/ notification, and quarantine.

2. Temperature Monitoring

- Place storage devices in a suitable location (e.g: refrigerator should not be located beside the incinerator, where it is hot).
- Ensure that the storage device has a current maintenance certificate.
- Ensure that the storage device is correctly calibrated. Calibration certificate must be readily available upon request.

- Keep a temperature log for each refrigerated/ ambient storage device.
    - Monitor and document temperature at regular intervals, including on weekends.
    - Install a reliable alarm system for early identification of temperature deviations.
    - The temperature monitoring device must be calibrated. There must be a connection between the records and the device they are referring to.

Did You Know?

Storing the IP at an incorrect temperature can cause potential risks like:

- Exposure to excessive heat/ light, causing protein degradation/ denaturation of proteins
- Reduction in the strength of the IP
- Micro-cracking of glass vials leading to contamination

3. Temperature Log

A well-documented Temperature Log includes:

- ID of storage location (this allows to connect the log to the correct storage location)
- Min/ max range of measuring device (to ensure measuring device is working properly)
- Investigator ID/ Site ID (to connect the log to the owner)
- Protocol number (owner may use one log for more than one protocol)
- Range of temperature (to remind the correct range within which IP must be kept)
- Deviation of temperature (to define the deviation ranges)
- Date (must be completed on a daily basis; using one log per month is recommended)
- Time of measure (as exactly as possible) if min/ max system is used
- Min/ max at time of measure (reset after documenting each measure)
- Signature or initials of person documenting (to ensure measuring device is properly calibrated)
- Comments, if any

Dispensing & Returning IP

Dispensing IP refers to the distribution of IP to subjects as per study protocol.

Returning IP refers to the returning of unfinished/ unused/ used up IP from subject to site, and from site to Sponsor.

Dispensing IP:

- Always dispense IP according to protocol.
- Follow IxRS, if applicable (also see #2, Dispensing IP for masked studies).
- During the informed consent process, ensure that subjects understand:
- IP administration by subject (if applicable)
- Correct storage procedures for IPs

- That they return ALL IP: empty/ partially used/ unused IP containers (e.g: bottles, blister cards, etc)
- During study visits, calculate IP compliance in the presence of the subject to confirm that IP is being taken in compliance with protocol.
- Follow up on any inconsistencies/ non-compliance and counsel the subjects on the correct dosing required by the protocol.

Dispensing IP for Masked Studies:

- For masked studies, an IP management system like an IxRS is often used to manage IP distribution. This is to ensure that:
- dispensation of IP follows the mask design of the study (single/ double/ triple masked)
- randomization of medication stays unbiased
- IP supply is timely
- If an IxRS is used, please remember to file evidence of IP assignment.
- If the mask has to be 'broken' for emergency reasons (e.g: AE or potential AE to the subject), contact the Sponsor immediately to discuss changes in future IP dispensation.
- Some IP may use tear off labels to unmask the treatment. Ensure such labels remain intact.

Documenting IP Dispensation:

- If an IxRS system is being used, remember to keep it updated as per the Sponsor's instructions.
- Document dispensation information in CRF, if applicable.
- Investigators are responsible to conduct due diligence to ensure that subjects are in compliance. Ensure subjects return study medication at every visit.
- Update IP accountability log (and CRF when applicable), including comments on inconsistencies.

For more details, review the upcoming page in this topic, IP Details for Documentation.

Returning IP:

IP Return refers to subjects returning unfinished/ unused/ used up IP to the study site. It also refers to the subsequent returning of these items from the study site to the Sponsor.

IP Labelling/ Re-labelling

Labelling: The IP label contains important information on composition of the IP, storage requirements, expiration date (if applicable), etc. Review the IP label to ensure that the same expiration date appears on both Acknowledgement of Receipt and IP container. Expired and/ or un-labelled IP must be quarantined and should not be dispensed among subjects.

Explain expiration and retest dates to the subject.

Re-labelling: At the site, the IP may need to be re-labelled to show updated details (e.g: extension of expiration date). If expiration date is extended, Sponsor will notify sites with new date. Always follow re-labelling instructions and document the re-labelling procedure. New label should not obscure previous label.

IP Details for Documentation

The IP details recommended for documentation at various stages of the study are:

1. Inventory at the site (in case inventory is not tracked in IxRS)
2. IP name, strength, form
3. Quantities received, dispensed, returned from subject, returned to Sponsor, destroyed
4. Batch/ serial numbers
5. Expiration date (if applicable)
6. Temperature control records
7. Investigator, site, and protocol number
8. Unique code numbers for all IP and subjects (if applicable)
9. Initials of site staff dispensing/ administering IP
10. Dosing instructions as per protocol
11. Subject's compliance
12. Inconsistencies, and explanations provided by Subject
13. Action taken to address inconsistencies
14. Date of destruction/ return to Sponsor

Reconciliation details

IP Reconciliation

IP Reconciliation is the process of accounting for all the IP provided by the Sponsor to the site throughout the study. The amount of IP used, unused, destroyed, and returned to Sponsor must add up to the total amount of IP received.

The Investigator is accountable for IP Reconciliation at the site even if specific tasks are delegated. The reconciliation can either be conducted periodically or at the end of the study (as per Sponsor's Standard Operating Procedures). Generally, the process is:

- Calculate the total amount of IP received from Sponsor as per signed receipts.
- Count empty, partially empty, and unused packaging units returned by subjects.
- Compare A) and B). Any missing units must have a documented explanation.

In order for reconciliation to be conducted, it is important that proper documentation is maintained throughout the study. The Investigator must sign the IP return forms (for IP to be returned to Sponsor) or onsite destruction records (for IP to be destroyed).

Inspection Readiness

If your IP documentation is up to date, you will always be prepared for audits and inspections!

- Highlight any IP related issues to Sponsor as soon as they occur.
- Have dispensing and accountability logs available for Sponsor representative to review.
- Have IP available for Sponsor Representative to conduct drug accountability review during monitoring visits.
- If IP is kept in the pharmacy, make arrangements for Sponsor Representative to visit the pharmacy.

Destroying IP

IP can be destroyed only with prior written authorization from Sponsor.

Unused IP can be returned to the Sponsor or destroyed, as guided by Sponsor requirements and local regulatory requirements. Destruction can be conducted at:

- Investigational Site
- Local third party contractor
- Sponsor facilities

The destruction facility must be able to safely handle and destroy the IP as per Sponsor requirements and local regulatory requirements.

- Written destruction procedures must be available for review.
- Evidence of destruction must be provided. Evidence must account for every unit of the destroyed IP.
- Investigator must retain evidence of destruction.

Topic Summary

In summary, IPs must be carefully reviewed to ensure integrity when received at site. The IP storage facility, including storage temperature must be continually monitored throughout the clinical study. IP dispensation details like dosage, subject ID, details of site staff administering IP, etc, must be documented following local and Sponsor regulatory requirements. To prevent any misuse, the Investigator must account for, or reconcile, IP stock for the entire study, and account for any discrepancies. Any unused IP must be returned or destroyed following local regulatory and sponsor requirements. To ensure inspection readiness, all IP related data must be documented in prescribed templates. This includes accounting for any discrepancies in stock, dosage, etc.

Remember

During a clinical study, the IP is still in the process of having its efficacy and safety validated in human subjects.

To ensure the safety of such subjects, IP must be received, stored, secured, dispensed, documented, and reconciled following local and Sponsor guidelines.

Review Question 1 of 5

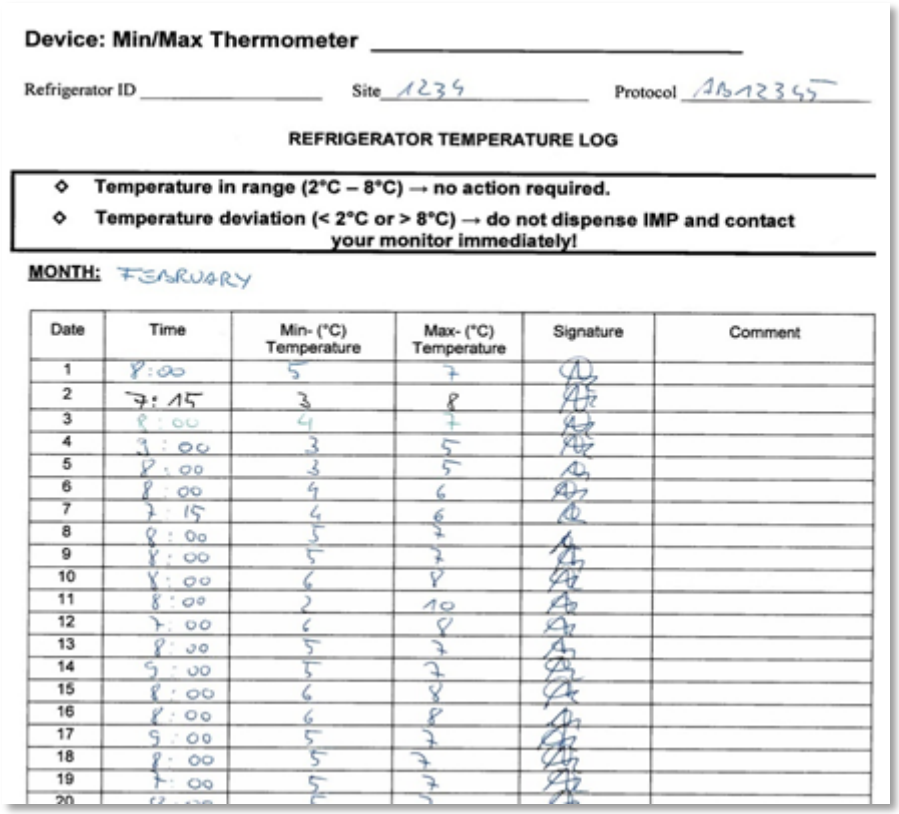
What are the Site staff's responsibilities when the IP arrives at Site??

All answers are correct.

1. Unpack the shipment and compare against receipt.
2. Check content and condition of the shipment.
3. Store IP according to label instructions.
4. Complete acknowledgment form/ update IxRS.
5. Report IP deviations immediately.

Review Question 2 of 5

What critical information is missing from this log?



Device: Min/Max Thermometer _____

Refrigerator ID _____ Site 1234 Protocol AB12345

REFRIGERATOR TEMPERATURE LOG

- **Temperature in range (2°C – 8°C) → no action required.**
- **Temperature deviation (< 2°C or > 8°C) → do not dispense IMP and contact your monitor immediately!**

MONTH: FEBRUARY

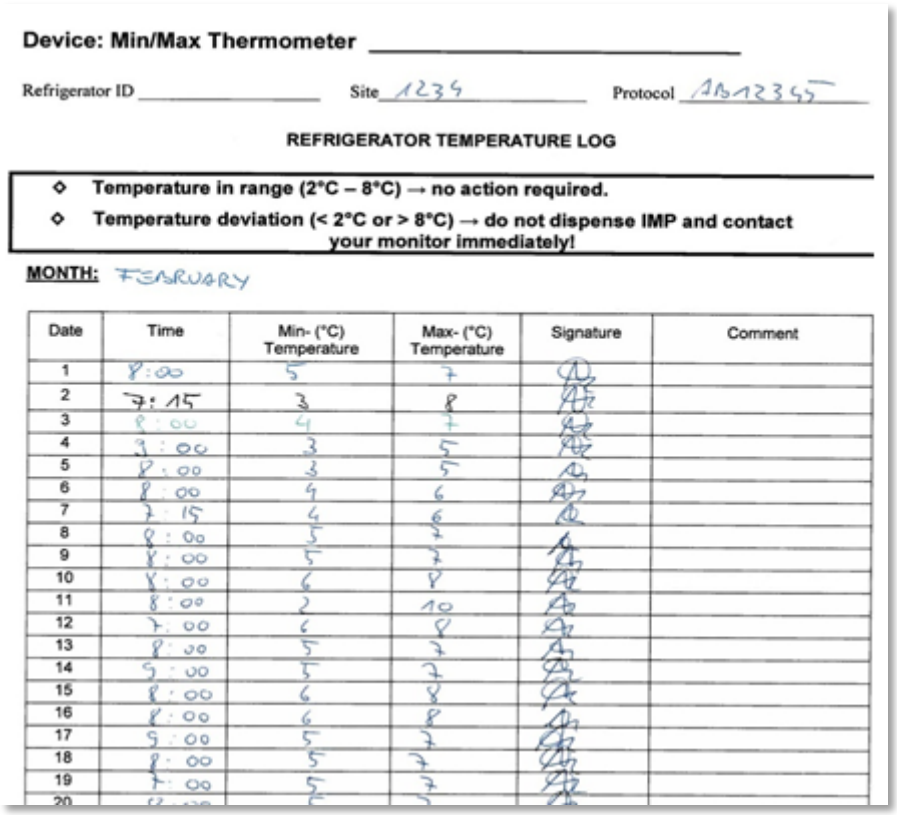
Date	Time	Min- (°C) Temperature	Max- (°C) Temperature	Signature	Comment
1	8:00	5	7		
2	7:15	3	8		
3	8:00	4	7		
4	9:00	3	5		
5	8:00	3	5		
6	8:00	4	6		
7	7:15	4	6		
8	8:00	5	7		
9	8:00	5	7		
10	8:00	6	8		
11	8:00	2	10		
12	7:00	6	8		
13	8:00	5	7		
14	9:00	5	7		
15	8:00	6	8		
16	8:00	6	8		
17	9:00	5	7		
18	8:00	5	7		
19	7:00	5	7		
20					

Answers 3 & 4 are correct.

1. Protocol number is missing.
2. Site number is missing.
3. Year is missing.
4. Refrigerator ID is missing.

Review Question 3 of 5

According to the instructions provided in the log, what action should the site staff have taken for temperature recorded on Feb 11?



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9	8:00	5	7		
10	8:00	6	8		
11	8:00	2	10		
12	7:00	6	8		
13	8:00	5	7		
14	9:00	5	7		
15	8:00	6	8		
16	8:00	6	8		
17	9:00	5	7		
18	8:00	5	7		
19	7:00	5	7		
20					

Answers 1, 2, & 4 are correct.

1. Stopped dispensing IP.
2. Added a comment with information/ explanation in the Comments column.
3. Closed down the refrigerator for repairs.
4. Contacted the Sponsor Representative immediately.
5. No action was required from the site staff.

Review Question 4 of 5

While conducting IP reconciliation activities, you find a discrepancy in the IP inventory. What should be your immediate next step?

Answer 3 is correct.

1. Notify the Sponsor immediately and put the study on hold.
2. Unmask the study for all subjects as they are all at risk from potential AEs.
3. Review documentation to see if such discrepancy is accounted for.
4. Ignore the discrepancy. Not all subjects return their IP containers.

Review Question 5 of 5

Which of the following statements is correct about destruction of IP?

Answers 2 & 4 are correct.

1. Unused IP can be destroyed by the Sponsor only.
2. If allowed under Sponsor and local regulatory requirements, unused IP can be destroyed at the study site.
3. Empty IP containers should be thrown out by Subject after IP administration at home.
4. Unused IP can be sent back to Sponsor for destruction.