CASE STUDIES FROM GCP INSPECTIONS 2011

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OUTLINE

- Case Studies
  - Informed Consent
    - Short Form Consent
    - Subjects unable to read the ICF
    - Sharing of Best Practices
  - Investigational Products
    - IP Management where site is involved in IP re-packaging
    - Sharing of Best Practices

CASE STUDY A

- **Informed Consent**
  - Short Form Consent
  - Subjects unable to read the ICF
  - Sharing of Best Practices

Case Study A

Protocol Title:

A phase 3, randomized, double-blind, placebo-controlled clinical trial comparing the safety and efficacy of Phantomine 100mg for the treatment of migraine.

Study Staff:

Principal Investigator: Dr James Lee

CRC : Ms Karen Tan

Study Pharmacist : Ms Laura Sim

Case Study A

Short Form Consent

Mrs Devi Muthu was a 60 year old Patient Services Associate who was screened for this clinical trial. She was literate only in Tamil.

As translated informed consent forms (ICFs) had been unavailable for this clinical trial, Dr Lee (PI) had explained the ICF to the subject and requested the subject to sign the Short Form Consent on 6 Dec 2011.

Case Study A - ANSWERS

Short Form Consent

Medicines (Clinical Trials) Regulation 11(4):

(4) Subject to paragraph (5), consents obtained for the purposes of these Regulations shall be —

(a) in written form approved by the licensing authority and signed and dated by the person giving his consent; or

(b) if the person giving his consent is unable to sign the written form, in any other form and manner as the licensing authority may approve.

SGGCP Section 4.8.8:

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

➔ **No legal provision for the use of Short Form Consent for clinical trials on Medicinal Products in Singapore.**

Case Study A - ANSWERS

Subjects unable to read the ICF

Medicines (Clinical Trials) Regulation 11(5):

(5) If the person giving his consent for the purposes of these Regulations is unable to read, the consent form referred to in paragraph (4) shall be read and explained to him in the presence of an impartial witness who shall sign and date the consent form to attest that the form was accurately explained to that person and that his consent thereto was freely given.

SGGCP Section 4.8.9:

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Case Study A - ANSWERS

Subjects unable to read the ICF

SGGCP Section 1.26

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Choice of impartial witness:

- ❑ Family member / friend
- ❑ Clinic staff (non-study staff)
- ❑ Lay person from the street

Role of impartial witness:

- ❑ Accurate explanation
- ❑ Understood
- ❑ Voluntary participation

INFORMED CONSENT

Sharing of Best Practices

- **Informed Consent Process:**
  - **WHO** can obtain informed consent?
  - **WHEN** should informed consent be obtained?
  - **WHICH** version of the informed consent form should be used?
  - **WHERE** should informed consent be explained?
  - **HOW** should the informed consent be explained?
    - Subjects who are illiterate in English but literate in another local language
      - *Use of translated Informed Consent Forms or Use of translator*
    - Subjects who are unable to read the Informed Consent Form
      - *Use of impartial witness*
    - Need for substituted consent?
      - *Paediatric subjects*
      - *Subjects who are unconscious*
      - *Subjects who are incapable of exercising rational judgment*

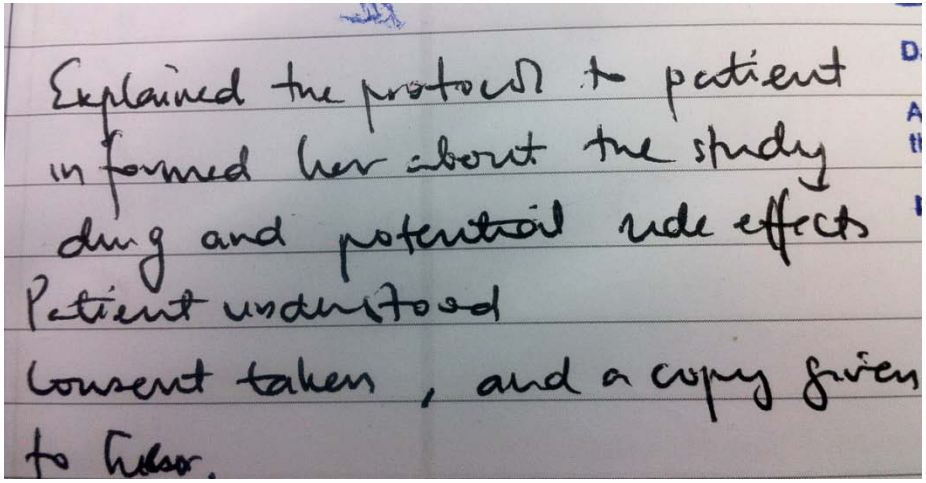
INFORMED CONSENT

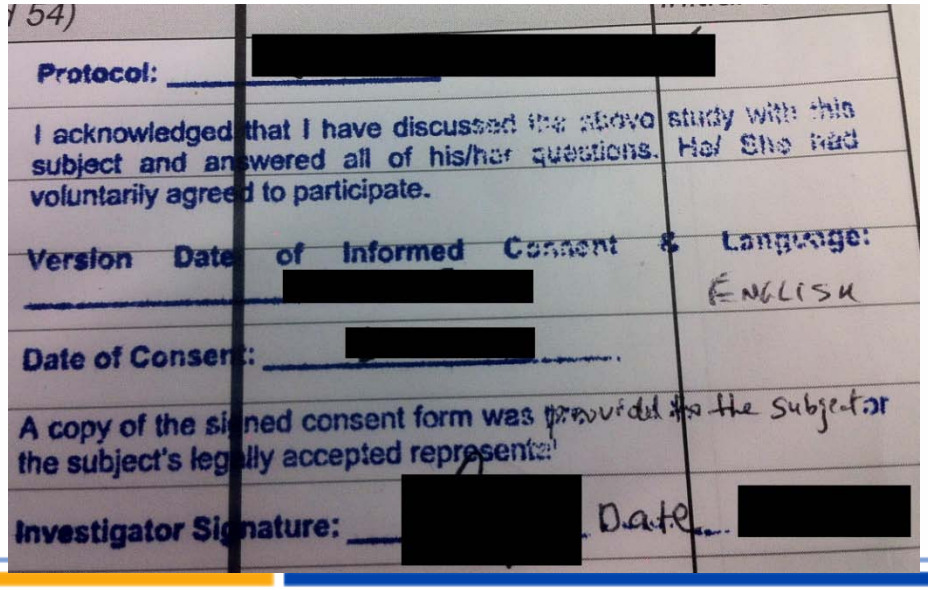
Sharing of Best Practices

- **Informed Consent Process (cont'd):**
  - **HOW** many copies of the Informed Consent Form should be signed?
    - *Subject*
    - *Investigator Site Files*
    - *Medical Records?*
  - **HOW** should Informed Consent Process be documented?
    - *Protocol Reference*
    - *Date of informed consent*
    - *Informed Consent Process (e.g. for use of substituted consent / impartial witness / translator)*
    - *Signed copy provided to subject*

Informed Consent Form

Sharing of Best Practices – ICF Documentation





CASE STUDY B

- Investigational Products
  - IP Management where site is involved in IP re-packaging
  - Sharing of Best Practices

CASE STUDY B

Protocol Title:

A phase 3, randomized, double-blind, placebo-controlled clinical trial comparing the safety and efficacy of Phantomine 100mg for the treatment of migraine.

Study Staff:

Principal Investigator: Dr James Lee

CRC : Ms Karen Tan

Study Pharmacist : Ms Laura Sim

- **IP :** Active or Placebo Phantomine 100mg
- **Recommended storage conditions:** Ambient Temperature

CASE STUDY B

SOURCE OF IP

- Since Phantomine 100mg could be sourced from the hospital pharmacy, Dr James Lee decided to approach ABC Pharmaceuticals to manufacture the placebo.
- As ABC Pharmaceuticals was unable to manufacture a matching placebo, Dr James Lee decided to request the Study Pharmacist to mask the outer packaging of the IP prior to dispensing to the subject.

ACTIVE

PLACEBO

CASE STUDY B

IP RECEIPT

Ms Karen Tan (CRC) signed on the IP Shipment Receipt for the bulk IP. She filed it together with the Certificates of Analyses (CoAs) in the Investigator Site File.

CASE STUDY B

IP STORAGE

Ms Karen Tan (CRC) locked up the bulk bottles in her filing cabinet located in her office, where central air-conditioning was available.

CASE STUDY B

IP RE-PACKAGING

- Ms Karen Tan requested Ms Laura Sim (Study Pharmacist) to prepare smaller bottles of Active and Placebo Phantomine 100mg since this was a double-blind clinical trial.
- The statistician handed over the Master Randomization List to Ms Laura Sim (Study Pharmacist) to re-package the IP.

CASE STUDY B

IP RE-PACKAGING

CASE STUDY B

IP DISPENSING AND ACCOUTABILITY

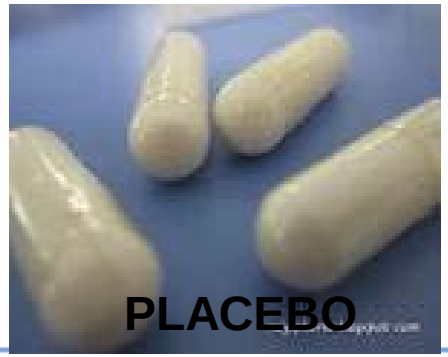
Subject ID	Treatment Kit No.	Qty Dispensed (tabs)	Dispensed By	Dispensed Date	Date Returned	Qty Returned (tabs)	Checked By
001	98765	30	KT	1/9/11	15/9/11	2	CRA
002	95678	30	KT	2/9/11	16/9/11	2	CRA

CASE STUDY B - ANSWERS

SOURCE OF IP : UNMATCHING PLACEBO

Note that even though the outer packaging was masked for the IP, the Active Phantomine capsules may be identifiable through the product code and capsule colour, thereby potentially compromising the study blind!
[Ref: SGGCP Sections 2.12, 5.13.1,5.13.4]

ACTIVE



PLACEBO

SGGCP 2.12, 5.13.1 and 5.13.4

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.

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s) (see Section 4.6.3).

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding. The key to the code/cipher shall be made known to the EC, the MCRC and the Ministry of Health and be readily accessible to any doctor (or dentist) in an emergency.

SOURCE OF IP

Points for consideration:

- **For Randomized, Double-Blind, placebo-controlled clinical trials where site is involved in IP re-packaging:**
  - *Try to source for an identical placebo.*
  - *Bulk IP should be labelled in accordance with Medicines (Clinical Trials) Regulation 18(1) and SGGCP 4.6.3.*

CASE STUDY B - ANSWERS

IP RECEIPT

- Roles and responsibilities of blinded and unblinded study staff were not clearly defined.
    - Blinded CRC should not have received the bulk IP.
    - Blinded CRC should not have maintained the IP Shipment Receipts and COAs.

[Ref: Sections SGGCP 2.12, 4.6.5, 5.14.3]

- Bulk Active and Placebo IP were not labelled in accordance with Medicines (Clinical Trials) Regulation 18(1) and SGGCP 4.6.3.

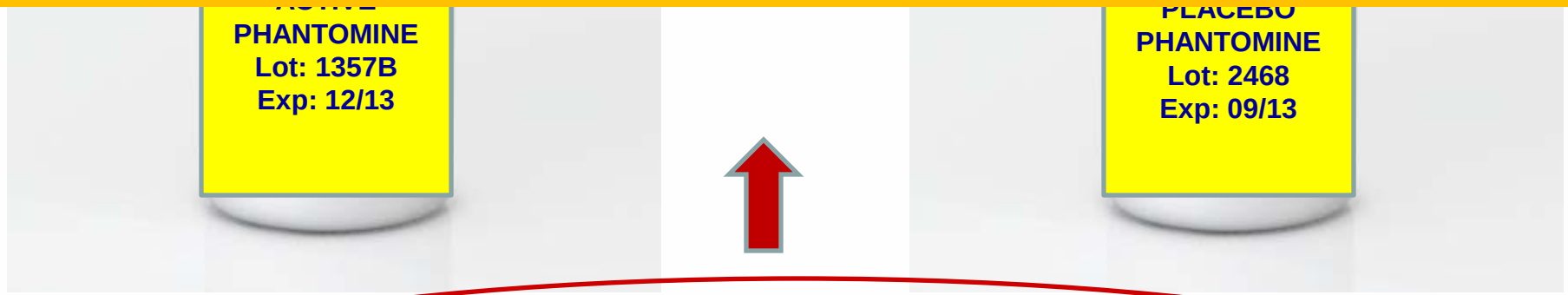
Ms Karen Tan (CRC) signed on the IP Shipment Receipt for the bulk IP. She filed it together with the Certificates of Analyses (CoAs) in the Investigator Site File.

CASE STUDY B - ANSWERS

IP STORAGE

- Roles and responsibilities of blinded and unblinded study staff were not clearly defined.
  - Blinded CRC should not have maintained IP Storage Temperature Records of bulk IP.

[Ref: SGGCP Sections 2.12, 4.6.4, 5.14.3]



Ms Karen Tan (CRC) locked up the bulk bottles in her filing cabinet located in her office, where central air-conditioning was available.

SGGCP 2.12, 4.6.4, 4.6.5, 5.14.3

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.

4.6.4 The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

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(s) 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 authorised by the sponsor and in compliance with the applicable regulatory requirement(s)).

CASE STUDY B - ANSWERS

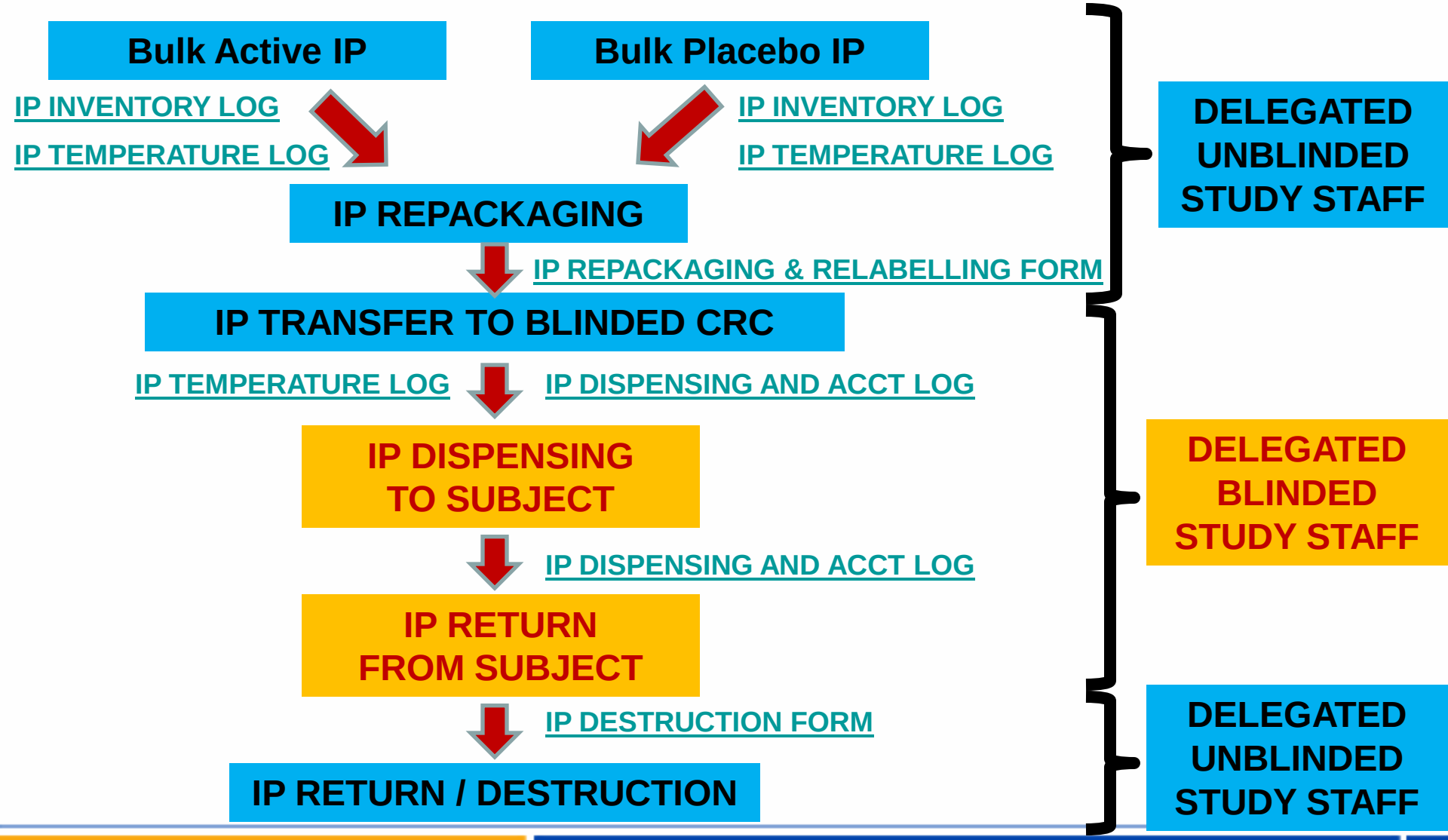
IP RE-PACKAGING

• IP re-packaging was not performed in accordance with GMP guidelines. [Ref: SGGCP 2.12, 5.13.1]

- Ms Karen Tan requested Ms Laura Sim (Study Pharmacist) to prepare smaller bottles of Active and Placebo Phantomine 100mg since this was a double-blind clinical trial.
- The statistician handed over the Master Randomization List to Ms Laura Sim (Study Pharmacist) to re-package the IP.

For sites involved in blinding process

Points for consideration:



PICS Annex 13

Packaging

23. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mix up must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.

24. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed products, particularly when "blinded" products with similar appearance are used. Precautions against mis-labelling such as label reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.

25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

CASE STUDY B - ANSWERS

IP DISPENSING AND ACCOUTABILITY

- IP Dispensing and Accountability Log was maintained electronically without any audit trail.
[Ref: SGGCP 2.13]
- Lot Number and Expiry Date of IP was not captured on IP Dispensing and Accountability Log.
[Ref: SGGCP 4.6.3]

Subject ID	Treatment Kit No.	Qty Dispensed (tabs)	Dispensed By	Dispensed Date	Date Returned	Qty Returned (tabs)	Checked By
001	98765	30	KT	1/9/11	15/9/11	2	CRA
002	95678	30	KT	2/9/11	16/9/11	2	CRA

SGGCP 2.13 and 4.6.3

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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. The investigator shall ensure that all test materials have the following particulars written on the containers :

a) the designation, reference number or other identification mark of each item of such material;
b) the name and address of the manufacturer;
c) the name or other identification mark of the subject for whom the test material is intended;
d) the expiry date or retest date of the test material;
e) the storage conditions appropriate for each item of test material as may be indicated by the manufacturer; and
f) the words : "This product shall only be used under strict medical surveillance" or "This product shall be used under strict dental surveillance" as the case may be, or the words "For clinical trial use only".

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.

IP MANAGEMENT

SHARING OF BEST PRACTICES

GOALS OF IP MANAGEMENT

- Ensure protection and safety of trial subjects, so that they are not placed under unnecessary risk
- Ensure traceability of the investigational product
- Ensure accuracy clinical trial data, that it is unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, handling and storage of the investigational product
- Ensure that there is consistency between batches of the same investigational product used in the same or different clinical trials

IP MANAGEMENT

SHARING OF BEST PRACTICES

USEFUL REFERENCES

- Medicines (Clinical Trials) Regulation 18
- Singapore Guideline for Good Clinical Practice (SGGCP)

  SGGCP Sections 2.12, 4.6, 5.12-14, 8.2.13 to 8.2.18, 8.3.8, 8.3.9, 8.4.1 and 8.4.2
- PICS Annex 13 (Good Manufacturing Practice)

IP MANAGEMENT

SHARING OF BEST PRACTICES

- **DOCUMENTATION**
  - Written instructions for storage and handling of IP
    - ✓ *To be developed by the Sponsor*
  - Signed Signature Sheet
    - ✓ *To delegate the roles, responsibilities and signatures of study staff*
  - IP Shipment Receipt
  - IP Inventory Log
  - IP Storage Temperature Log
  - IP Storage Temperature Excursion Report
  - IP Dispensing and Accountability Log
  - IP Destruction Form

FROM THE GCP INSPECTOR'S DESK

HEALTH PRODUCTS REGULATION GROUP | HEALTH SCIENCES AUTHORITY | ISSUE NO. 2 | SEP 2011

IP *INVESTIGATIONAL PRODUCTS OR Intensively Puzzling???*

This issue will provide you with an insight to the salient points and common issues encountered with Investigational Product (IP) management.

RESPONSIBILITY

✓Ensure that study staff have been delegated the responsibility for IP management on the Signed Signature Sheet [Medicines (Clinical Trials) Regulation 19(3) and SGGCP 4.1.5, 4.6.1, 4.6.2, 4.9.1 and 8.3.24]

✓Study staff responsible for IP management should not be referred to as 'Pharmacists', unless they are locally registered Pharmacists in accordance with the Pharmacist Registration Act.

IP RECEIPT

✓Check that the IP Shipment Receipts have been signed and dated by a responsible study staff [SGGCP 8.2.15 and 8.3.8].

✓Ensure that the IP Inventory Log has been maintained [SGGCP 4.6.3]. An IP Inventory Log should still be maintained for the clinical trial even if the IP has been sourced from the hospital pharmacy.

✓IP Inventory and IP Dispensing and Accountability Logs should not be maintained electronically unless it is a validated system [SGGCP 2.13].

IP STORAGE

✓Ensure that the Sponsor has provided written instructions for handling and storage of IP [SGGCP 5.14.3].

✓Temperature monitoring is required to provide assurance that the IP has been stored as per Sponsor requirements [SGGCP 4.6.4, 5.14.5].

✓Ensure that the temperature monitoring device has been calibrated and maintained [SGGCP 2.13].

✓ Ensure that there is traceability between various temperature monitoring devices, temperature logs and calibration and maintenance certificates [SGGCP 2.13].

✓Check that appropriate actions have been taken to quarantine the IP and alert the Sponsor for any temperature excursions.

IP DISPENSING & ACCOUNTABILITY

✓Verify that the IP Accountability Logs have been maintained in accordance with SGGCP 4.6.3.

IP DESTRUCTION

✓If the IP is to be destroyed by the site, ensure that the disposal method has been authorized by the Sponsor, and is in compliance with applicable regulatory requirements [SGGCP 5.14.3].

✓The disposal of IP should comply with NEA requirements if disposal is to be done locally. For more information, please refer to the CTB FAQs on the HSA website.

IP LABELLING

✓Check that the IP Label complies with the Medicines (Clinical Trials) Regulation 18(1) and SGGCP 4.6.3.

✓ The labeling requirements also applies to comparator drugs.

ATTENTION!

✧*Re-PACKAGING OF IP*

If the site is involved in re-packaging of the IP, the Sponsor should provide written instructions for handling of the IP [SGGCP 5.14.3]. The IP re-packaging process should have line clearance [SGGCP 5.13.3], IP label re-conciliation, performed and witnessed by delegated study staff, and documented accordingly.

✧*LOCALLY REGISTERED MEDICINAL PRODUCTS*

✧If the IP used in a clinical trial is a locally registered medicinal product, the IP label must still comply with local regulatory requirements. The common outstanding information usually is 'For Clinical Trial Use Only'.

USEFUL REFERENCES

GCP Inspection Framework

CTB Frequently Asked Questions

WE WELCOME YOUR FEEDBACK!

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FROM THE GCP INSPECTOR'S DESK

HEALTH PRODUCTS REGULATION GROUP | HEALTH SCIENCES AUTHORITY | ISSUE NO. 3 | DEC 2011

RE-PACKAGING OF INVESTIGATIONAL PRODUCTS

| Right Drug | Right Dose | Right Subject |

40% of the sites inspected in 2011 had been involved in re-packaging of the Investigational Product (IP) on site. Out of these sites inspected, 80% had major GCP Inspection Findings concerning re-packaging of IP! Most of these sites inspected had initially been unaware that secondary assembly is a form of manufacturing and thus the need to conform with Good Manufacturing Practice (GMP) guidelines, in addition to Singapore Guideline for Good Clinical Practice (SGGCP). ***SGGCP 2.12 requires IP to be manufactured, handled and stored in accordance with applicable GMP and should be used in accordance with the approved protocol.***

GOALS OF IP MANAGEMENT

❑ ***Ensure protection and safety of trial subjects, so that they are not placed under unnecessary risk***

❑ ***Ensure traceability of the investigational product***

❑ ***Ensure accuracy of clinical trial data, that it is unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, handling and storage of the investigational product***

❑ ***Ensure that there is consistency between batches of the same investigational product used in the same or different clinical trials.***

ROLES AND RESPONSIBILITIES

It is critical to delineate the roles and responsibilities of blinded and unblinded study staff involved in IP management so as not to compromise the study blind for blinded clinical trials. Unblinded study staff should be involved in IP management from IP shipment, receipt, storage and re-packaging, whilst blinded study staff should be involved in IP Dispensing, Accountability, Return and Destruction.

DOCUMENTATION

❑***Written instructions for handling and storage of IP*** – to be developed by the Sponsor.

❑ ***Signed Signature Sheet*** – to document the roles, responsibilities and signatures of unblinded and blinded study staff involved in IP management

❑ ***Master Randomization List, IP Shipping Records, IP Inventory Logs, IP Storage Temperature Logs and IP Re-packaging Forms*** – to be maintained by unblinded study staff in an unblinded manner (i.e. for each IP).

❑ ***Transfer of blinded IP, IP Dispensing and Accountability Logs, IP Return and/or Destruction Records*** – to be maintained by blinded study staff in a blinded manner.

IP RE-PACKAGING

IP Re-packaging can be done outside of a GMP-certified facility. However, the principles of GMP should be adhered to, where applicable. Sections 23 to 25 of EU GMP Vol 4 Annex 13 provide guidance on IP re-packaging.

❑ ***Line clearance*** : Pack one type of Investigational Product at a time.

❑ ***In-process control checks*** : IP re-packaging should be performed and witnessed by delegated and trained unblinded study staff.

❑ ***Label re-conciliation*** : No. of IP labels issued = No. of IP labels used + destroyed + remaining; The Sample IP Label must comply with Medicines (Clinical Trials) Regulation 18 and SGGCP 4.6.3

❑ ***Documentation*** : The IP re-packaging process should be documented and signed off by the unblinded study staff. It would be recommended to affix the sample IP label(s) onto this documentation for reference purposes.

USEFUL REFERENCES

✓Medicines (Clinical Trials) Regulation 18

✓SGGCP 2.12, 4.6, 5.12-14, 8.2.13 to 8.2.18, 8.3.8, 8.3.9, 8.4.1 and 8.4.2

✓EU GMP Vol 4 Annex 13

REFERENCES

- **Medicines (Clinical Trials) Regulations**

  http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/legislation/medicines_act.Par.41439.File.dat/MEDICINES%20(CLINICAL%20TRIALS)%20REGULATIONS.pdf
- **Singapore Guideline for Good Clinical Practice**
- **PICS Annex 13**
- **CTB FAQs**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/faqs.html
- **From the GCP Inspector's Desk Newsletter**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/guidelines/gcp_compliance_inspection.html
- **HSA Industry Communication**

  http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/industry_communication.html

Thank You!

www.hsa.gov.sg