HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

INVESTIGATIONAL PRODUCT REPACKAGING AT THE INVESTIGATOR SITE

GN-CT-09 Rev. No. 004

HSA Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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SUMMARY OF KEY AMENDMENTS

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1. INTRODUCTION

1.1. Purpose

The purpose of this guidance is to provide guidance for the repackaging of Investigational Products (IP) at investigator sites.

1.2. Background

IP repackaging at the investigator site is sometimes necessary to maintain trial blinding, for example, in blinded clinical trials where the test product is compared with a placebo or an active comparator product. When the IP supplied differs in packaging or labelling from the comparator product, repackaging at the investigator site may be required to ensure that investigators, site staff and participants remain blinded to treatment allocation.

This guidance aims to provide guidance on IP repackaging at investigator sites to ensure that such activities are conducted appropriately and do not compromise the following essential goals of IP management:

(i) To ensure protection of the trial participant and product tracking;
(ii) To ensure identification of the product and the trial;
(iii) To facilitate proper use and storage of the product; and
(iv) To ensure the reliability and robustness of the data generated in the trial.

2. CONSIDERATIONS FOR IP REPACKAGING AT THE INVESTIGATOR SITE

2.1. Blinded and Unblinded Teams

2.1.1. For blinded trials, it is important to clearly delineate the roles and responsibilities of blinded and unblinded study staff involved in IP management to protect the integrity of the study blind.

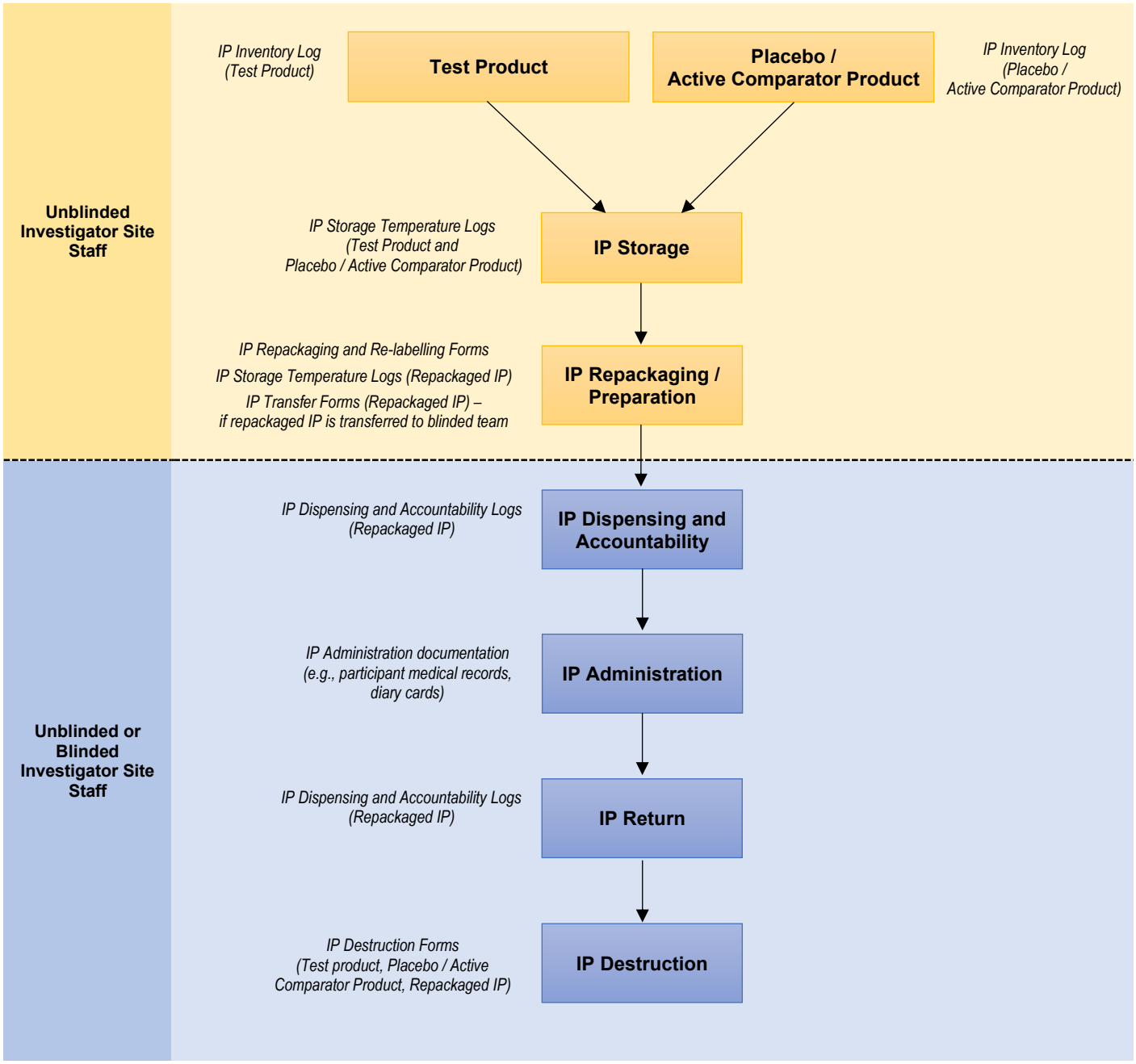
2.1.2. The Principal Investigator (PI) should ensure that the roles and tasks of the blinded and unblinded teams are clearly segregated and documented in the delegation log.

2.1.2.1. The unblinded team should be responsible for all unblinded aspects of IP management (e.g., IP shipment receipt, storage of the IP prior to repackaging, IP repackaging), whilst the blinded team should only be involved in the blinded aspects of the clinical trial.

2.1.2.2. The PI should ensure that at least two unblinded investigator site staff are delegated for IP repackaging at the investigator site, wherein one would perform the IP repackaging and the other would witness the IP repackaging process (refer to Section 2.2.2 for further details on in-process control checks).

2.1.2.3. Refer to Figure 1 for the roles, tasks and required IP documentation for IP repackaging at the investigator site for blinded trials.

Figure 1. Roles, tasks and required documentation for IP repackaging at the investigator site for blinded trials



2.2. Principles of Good Manufacturing Practice (GMP)

2.2.1. IP repackaging may be performed outside of a GMP-certified facility. However, the principles of GMP should be adhered to, where applicable.

2.2.2. The following GMP principles for IP packaging apply to IP repackaging at the investigator site:

(i) Line clearance: Only one type of IP should be repackaged at a time to minimise the risk of unintentional product mix-ups.

(ii) In-process control checks: IP repackaging should be performed and witnessed by delegated and trained unblinded investigator site staff to ensure that the IP repackaging aligns with the treatment assignment. One unblinded investigator site staff should perform the IP repackaging and a second unblinded investigator site staff should witness the IP repackaging process.

(iii) Label reconciliation: The number of IP labels used, destroyed and remaining should be reconciled with the number of IP labels issued as a precaution against mislabelling.

(iv) Documentation: The IP repackaging process should be documented by the unblinded investigator site staff to demonstrate that appropriate safeguards had been implemented to protect the blinding and ensure product integrity.

2.3. Written instructions for IP repackaging

2.3.1. The sponsor should ensure that clear written instructions for IP management (e.g., Pharmacy Manual or documented procedure), including for IP receipt, storage, repackaging, dispensing, return and destruction, are provided to the investigator site.

2.3.2. The written instructions should consider adequate safeguards to blind individuals to the identity of the IP and to prevent and detect inappropriate unblinding.

2.3.3. Template forms for IP Management are available on the HSA website and may be customised to align with the specific requirements of your protocol and trial design.

2.4. IP labelling

2.4.1. The IP labels must comply with the applicable regulatory requirements for IP labelling.

2.4.2. The test product and placebo / active comparator product to be repackaged should be labelled in accordance with the IP labelling requirements for ‘wholesale supply’, and the repackaged products should be labelled in accordance with the IP labelling requirements for ‘supply to participant’. Refer to the Regulatory Guidance on Labelling of Investigational and Auxiliary Products in Clinical Trials for further guidance on IP labelling.

2.4.3. The IPs should be coded and labelled in a manner that protects the blinding.

(i) The name of each IP (i.e., test product and placebo / active comparator product) should be replaced with the name of the repackaged IP (i.e., test product / placebo, or test product / active comparator product) on the IP label for the repackaged IP.

For example:

- Name of IPs: Paracetamol 500mg, Placebo
- Name of repackaged IP: Paracetamol 500mg / Placebo

(ii) The batch numbers and expiry dates of each IP (i.e., test product and placebo / active comparator product) should be replaced by a

dummy batch number and dummy expiry date on the IP label for the repackaged IP.

For example:

- The dummy batch number may be set as 'YYYYMMDD' based on the date of IP repackaging,
- The dummy expiry date may be set as the earlier expiry date of the test product and placebo / active comparator product.

2.5. Documentation

2.5.1. The unblinded investigator site staff should maintain the following essential records relating to the test product and placebo / active comparator product prior to repackaging (where applicable) in a separate file (e.g., pharmacy binder) at the investigator site, with access secure and limited to the unblinded investigator site staff:

(i) Certificates of Analysis / COA (for unregistered products);
(ii) Master Randomisation List;
(iii) IP receipts;
(iv) IP Inventory Logs – maintained separately for each product;
(v) IP Storage Temperature Logs;
(vi) IP Storage Temperature Excursion Reports;
(vii) Calibration and maintenance reports for temperature monitoring equipment;
(viii) IP Repackaging and Re-labelling Forms;
(ix) IP Destruction Forms.

2.5.2. The blinded investigator site staff should maintain the following essential records relating to the repackaged IP (where applicable) in the Investigator Site Files:

(i) IP Dispensing and Accountability Logs – combined for the repackaged IP;
(ii) IP Administration documentation (e.g., diary cards);

(iii) IP Transfer Forms – for transfer of repackaged IP from unblinded investigator site staff to blinded investigator site staff;

(iv) IP Destruction Forms.

3. INVESTIGATOR SITE MONITORING

3.1. For blinded clinical trials where IP repackaging is performed at the investigator site, it is recommended that separate Monitors are appointed for investigator site monitoring, wherein the Unblinded Monitor would monitor the unblinded aspects of IP management, and the Blinded Monitor would monitor the blinded aspects of the clinical trial.

4. REFERENCES

(i) Health Products (Clinical Trials) Regulations

(ii) Medicines (Clinical Trials) Regulations

(iii) ICH E6 (R3) Good Clinical Practice (GCP) Guideline

(iv) Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme (PIC/S) Annex 13

(v) Regulatory Guidance on Labelling of Investigational and Auxiliary Products in Clinical Trials

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