

Standard Operating Procedure Investigational Medicinal Product (IMP) management

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1. ABBREVIATIONS

ASST-PG23:	Azienda Socio Sanitaria Territoriale – Papa Giovanni XXIII
CRA:	Clinical Research Associate
FROM:	Fondazione per la Ricerca Ospedale Di Bergamo
GMP:	Good Manufacturing Practice
IMP:	Investigational Medicinal Product
IP:	Investigational Product
ISF:	Investigator Site File
PM:	Project Manager
SOP:	Standard Operating Procedure
TMF:	Trial Master File

2. SCOPE

This SOP defines the process for supplying an IMP (i.e. excluding Advance Therapy) to sites involved in a trial, managing the IMP accountability and destruction, and the IMP re-labelling if required during the trial.

3. FIELD OF APPLICATION

This SOP applies to clinical trials sponsored by FROM or ASST-PG23 and conducted at ASST-PG23 and collaborative sites. It does not apply to trials sponsored by other organizations (e.g. Pharmaceutical Company, Collaborative Groups etc.) for which the Sponsor provides own instructions/procedures.

4. RESPONSIBILITIES

Pharmaceutical Company/ delegate

- Ensures IMP manufacturing, packaging, labeling distribution and disposal (where agreed) according to GMP and other applicable regulation.
- Provides the Sponsor with written information related to any changes of IMP characteristics (e.g. stability).
- Ensures that all import/export requirements are met.

Project Manager

- Reviews and approved the draft of IMP labels
- Ensures that essential/trial approval documents are issued and collected before requesting the first IMP delivery to sites.
- Collects IMP(s) certificates (e.g. QP release certificate) from the Pharmaceutical Company/delegate and draws the forms to be used to track the IMP supply/resupplying to the involved sites.
- Estimates the amount of IMP to be supplied to each site according to the protocol design and the enrolment plan at each site.

- Manages the requests of the IMP supply to the sites.
- Organizes and supervises the process for the IMP labelling and relabelling.
- Organizes the pick-up at the sites for IMP disposal.
- Archives records of IMP handling and accountability in the Trial Master File.

Clinical Research Associate

- Informs Investigators on their obligations with respect to the IMP storage, management, accountability and return/disposal.
- Verifies the IMP storage, management and accountability and collects the relevant documentation duly completed by sites personnel.
- Checks the IMP availability at the sites to appropriately manage the resupply (i.e. in due time).
- Oversees the return of unused IMP to the Pharmaceutical Company/delegate (if required) in collaboration with the PM.
- Verifies and collects documentation of local IMP destruction, where applicable.
- Oversees or performs the IMP relabelling / additional labelling, if requested.

Pharmacist at the site

- Receives the IMP, checks integrity and temperature recorded during the transport, and verifies the compliance with the shipping documents.
- Documents IMP receipt, storage, preparation (if applicable), dispensing and return/destruction.
- Ensures IMP storage according to the IMP instructions until the release to the Investigator/patient.
- Prepares the IMP (e.g. in case of infusion) according to protocol and applicable regulation.
- Performs the IMP relabelling / additional labelling, if requested.

5. PROCEDURE

Any medicinal product tested or used as reference drug in a clinical trial is considered as an IMP, regardless of whether the IMP is already on the market or not.

The IMP is usually supplied by a Pharmaceutical Companies, also through a delegated provider. but FROM PM is involved in the coordination and supervision of the IMP ordering, distribution, and collection, or destruction of the unused IMP.

5.1 Agreement with the Pharmaceutical Company providing the IMP

A specific agreement between Pharmaceutical Company and FROM/ASST-PG23 should be executed to define the respective responsibilities for the manufacture (including packaging and labeling), storage, shipment, batch certification and testing together with responsibilities for handling complaints, quality deviation, return and regulatory issues.

An IMP ordering procedure should be agreed before the trial starts to ensure an adequate and timely IMP supply during the course of the trial and to avoid any delay in patient treatment due to lack of IMP at the sites.

The following items should be discussed between the PM and the Pharmaceutical Company regarding to the IMP:

- Packaging and labeling of the IMP;
- Supply, distribution, return of the IMP to the Pharmaceutical Company/delegate or local disposal of unused IMP.

5.2 IMP distribution to the investigational site

The PM must ensure that all the regulatory approvals and the trial documents mandatory for the first drug release are available; specifically, no IMP can be delivered to a site until at least the following essential documents are collected:

- trial protocol signed by the Principal Investigator;
- Clinical Trial Agreement between the Pharmaceutical Company and FROM/ASST-PG23;
- Competent Authority and Ethical Committee approvals of the trial;
- IMP handling instructions (either as part of the protocol or as a separate document);
- any other documents required by the Pharmaceutical Company or local regulations.

Shipping and storage are critical parts of any clinical trial. Compliance of shipment conditions to label instructions should be documented (e.g., by temperature monitoring device) and checked by the hospital personnel when the IMP arrives to the site and by the CRA during the Site Initiation Visit and the course of the trial.

An IMP with a marketing authorization could be ordered directly by the sites or be available at the hospital pharmacy before the documents listed above are issued. If this is the case it must be ensured and documented that they are delivered to patients according to the trial protocol only after the abovementioned essential documents are collected.

Upon IMP receipt the hospital pharmacist should:

- verify the IMP conditions, complete the shipping document with the requested information (e.g. IMP name, batches, amount received for each batch, etc.) and return it to Pharmaceutical Company/delegate to confirm that the IMP was received in good order;
- store, register and prepare the IMP(s) for use (where applicable) according to the IMP instructions;
- deliver the IMP to the concerned clinical unit (i.e. Principal Investigator) when no further processing/preparation for use are requested (e.g. home therapy). In this case the clinical unit should have refrigerator/freezer equipped with a device recording the storing temperature and a central alarm for a prompt alert in case of malfunctioning.

5.3 IMP handling instructions and IMP accountability

Written instructions for IMP storage, preparation, dispensing and disposition should be provided by the FROM/ASST-PG23 to the sites either as part of the trial protocol or as a separate document.

Drug accountability allows the reconstruction of the trial (i.e. the patients received the correct IMPs, in the correct formulation and strength according to protocol) and documents:

- IMP(s) received by the site.
- IMP(s) received by the patient.

- IMP(s) returned to the Pharmaceutical Company/delegate or destroyed.

In case of FROM/ASST-PG23 sponsored trials the PM provides the involved sites the **IMP Accountability Form (T.CLI11.1/2)** to record the IMP(s) received, used and unused. The form is filled in by the site personnel and checked by the CRA during the monitoring visits.

If the IMP is a home-therapy a diary is provided to patients to record details of the IMP intake in addition to other information (e.g. adverse events). The diary is used to verify the patient treatment compliance.

5.4 IMP re-labelling

If the IMP expiry date is extended during the trial period, the Certificate of Analysis or alternative written communication documenting the new expiry date should be filed in the TMF and a copy sent to the involved sites for information and archive in the ISF.

Therefore, the IMP should be re-labelled to document the extension of the expiry date.

The re-labelling can be performed after having obtained the approvals of the Competent Authority and the Ethics Committee.

The additional label recording the batch number and the new expiry date is produced by the Pharmaceutical Company/delegate as sticker to be superimposed on the old expiry date without masking the original batch number.

The re-labelling is performed by the Pharmaceutical Company/delegate for the IMP not yet delivered to the sites. Otherwise the re-labelling of the IMP stored at the sites is performed locally by trained personnel (i.e. by the pharmacist and verified by the CRA or by the CRA and verified by the PM).

Trial specific instructions are drafted and distributed to the involved site when the re-labelling activities must be implemented.

5.5 IMP reconciliation and destruction

At the end of the trial the sites personnel completes the **IMP Accountability Form (T.CLI11.1/2)**. Then the CRA checks and delivers a copy of the form to the FROM/ASST-PG23 PM.

Based on agreement with the Pharmaceutical Company, the PM can authorize the local destruction of unused or expired IMP. The CRA is responsible for collecting at the involved site the certificate of destruction to be shipped to the PM for archive.

In some cases (e.g. the centers not able to destroy the unused IMP) the PM collaborates with the Pharmaceutical Company/delegate in organizing the IMP collection and delivery to the organization in charge of the IMP destruction. The DM or Pharmacist fills in the **IMP Return Form (T.CLI11.02/2)** and transmits it to the PM. The PM verifies the amount of unused IMP to be returned, organizes the IMP collection and delivery, and informs the Pharmaceutical Company/delegate.

The organization in charge of the IMP destruction should confirm the receipt and provide the certificate of destruction to the involved site and to the PM.

5.6 IMP transfer between centers

During the trial conduct, a temporary lack of IMP could lead to transfer the IMP from a site to another one. The transfer is organized by the PM. A courier for appropriate IMP transportation is contacted by the PM. The pharmacist located at the delivery site ensures adequate IMP storage conditions during the transfer

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with the support of the CRA, if deemed necessary. All information about IMP transfer are recorded by the Pharmacist in the first part of **IMP Transfer Form (T.CLI11.03/2)** to be placed in the IMP delivery package. A copy of the form is remitted to the PM for archive.

The pharmacist of receiving site checks the integrity and the amount of the transferred IMP, and completes the second part of **IMP Transfer Form (T.CLI11.03/2)**. Then the completed form is sent to the PM with temperature log recorded during the IMP transportation to document that the IMP was transferred according to the storage conditions.

5.7 Complains

Complaints, IMP mislabeling, concerns as well as any potential IMP recall by a Pharmaceutical Company/delegate should be promptly brought to the attention of the PM who will take the appropriate actions.

5.8 Records

Records of shipment, receipt, transfer, return / destruction and dispensed to patients must be maintained by the Sponsor in the TMF and by the Investigators in the ISF. Records should document that the IMP was delivered to patients according to the protocol as well as not used outside the concerned clinical trial.

6. REFERENCES

- Guideline for good clinical practice E6(R2) (CPMP/ICH/135/95).
- Legislative Decree no. 211 of 24 June 2003 - Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use.
- Eudralex Volume 10 ANNEX 13 - Good Manufacturing Practice for the manufacture of investigational medicinal products.

7. TEMPLATES

T.CLI11.01/2 IMP Accountability Form.

T.CLI11.02/2 IMP Return Form.

T.CLI11.03/2 IMP Transfer Form.

8. VERSION HISTORY

Version	Date	Reason for revision
1	20 Dec 2016	Starting document.
2	15 Dec 2019	<ul style="list-style-type: none"> • Rewording of SOP text. • Inclusion of two new forms (T.CLI11.02/2-IMP Return Form and T.CLI11.03/2-IMP transfer Form) and one form (T.CLI11.01/2-IMP Accountability Form) moved from the SOP CLI04/1 Monitoring.