

CH → Lobna et Georges

Procédure pour % aux référentiels thérapie génique

Contexte courant

- Product
 - Toutes
- Actor
 - Toutes
- Regulation
 - Europe: France_
- Comment
 - NO

if ne semble pas que la section "Specific References" prenne en compte les référentiels pour pds dérivés du sang (Vol. 4. Annexe 14) pour thérapie innovante (guidelines on GCP specific to advanced therapy... dec 2009)

Management of the Investigational Medicinal Products (IMPs)**1. Aim of the procedure**

The aim of this procedure is to describe the management of the Investigational Medicinal Products (IMPs) used in the clinical trials sponsored by LABO PHARMA.

2. Scope of the procedure

This procedure applies to all the clinical trials sponsored by LABO PHARMA in the European Union.

The management of the IMPs on site is defined in the procedure "Management of Investigational Medicinal Products on site" procedure.

3. Principles * cf feuille annexe

"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." (Note for Guidance on Good Clinical Practice, ICH E6, July 1996)

"Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures." (Annex 13, Manufacture of investigational medicinal products, July 2003) à revoir

"The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor." (Annex 13, Manufacture of investigational medicinal products, July 2003) idem.

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4. Specific References

- Directive 2001/20/EC
- ~~Annex 13, Manufacture of investigational medicinal products, July 2003~~
- CPMP/ICH/135/95, Note for guidance on Good Clinical Practice, July 1996
- ~~Décision du 11 décembre 2006 relative aux bonnes pratiques de fabrication et Bulletin officiel N° 2007/1 bis~~
- ~~Fascicule spécial : Bonnes Pratiques de Fabrication, ministère de la santé et des solidarités (Ligne directrice 12 : Bonnes Pratiques de Fabrication des médicaments expérimentaux)~~ 2011/8 bis 13
- ~~Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain~~
- ~~Bulletin officiel N° 2007/1 bis Fascicule spécial : Bonnes Pratiques de Fabrication, ministère de la santé et des solidarités (Ligne directrice 12 : Bonnes Pratiques de Fabrication des médicaments expérimentaux)~~ ?

5. Responsibilities

The Clinical Project Leader is responsible for :

- assessing the needs for IMPs, planning the IMPs shipment,
- ensuring compliance with the regulatory green light requirements,
- coordinating the return of the Investigational Medicinal products,
- requesting the destruction of the IMPs.

The IMP Manager is responsible for preparing the IMPs in accordance with the Clinical Trial Protocol, the list of requirements, and relevant regulatory requirements.

The Clinical Research Associate (CRA) is responsible for managing the IMPs on site.

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6 Assessing the needs for IMPs

In parallel with the design of the clinical trial, the Clinical Project Leader collects the necessary information to assess the needs for IMPs, taking into account:

- the posology and the treatment frequency,
- the clinical trial duration,
- the recruitment period,
- the number of expected patients,
- the number of centers.

The Clinical Project Leader defines the IMPs forecasts and provides them to the IMP Manager.

If needed, the Clinical Project Leader sets up a meeting with the relevant individuals (such as the IMP Manager) to consolidate the IMP forecasts.

The Clinical Project Leader ensures that sufficient IMP supplies with an appropriate expiry date are available. In the case of a long-term trial or IMPs with a short expiry date, the Clinical Project Leader plans the future orders for IMP request.

If necessary, the Clinical Project Leader informs the IMP Manager of the changes in the needs for IMPs.

7 Ordering the IMPs

7.1 Global IMP Order

At least three months before the clinical trial set-up, the Clinical Project Leader, in collaboration with the IMP Manager, prepares the initial order by filling in an "IMP Order Form", specifying:

- requested quantity (including samples to be reserved),
- active ingredients,
- dosage form,
- details of formulation, if applicable,
- date required.

The IMP Manager:

- ensures that the Product Specification File of each IMP is complete and updated,
- prepares the order:
 - in accordance with:
 - the Product Specification File,
 - the Study Protocol,
 - issuing an order letter,
 - including:
 - the IMP Order Form,
 - the reference to the Product Specification File,
 - the Clinical Trial Protocol,
- obtains the validation of the Order Form by:
 - the Qualified Pharmacist,
 - the Medical Director,
- transmits the Order Form to the IMP Manufacturer.

7.2 Import of IMPs

If IMPs and drugs needed for the trial have to be imported, the Clinical Project Leader follows the "Import Licence" procedure.

7.3 Manufacturing of IMPs

The IMP Manager:

- ensures that the IMPs are manufactured in accordance with:
 - Good Manufacturing Practices ("any applicable GMP", CPMP/ICH/135/95 - Good Clinical Practice),
 - information provided in the Clinical Authorization Request submitted to Competent Authority,
- informs the Clinical Project Leader when IMPs are available, specifying:
 - batch number,
 - expiry date,
 - total quantity available.

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[également valable pour
thérapie génique]

(If it is necessary to purchase a commercial drug product (competitor for instance), the Clinical Project Leader fills in the document "Specifications for a non LABO PHARMA Product". The Clinical Project Leader sends the document to the IMP Manager.)

8 Packaging and Labelling the IMPs

8.1 Packaging and Labelling

The Clinical Project Leader determines with the IMP Manager:

- the packaging specifications, taking into account the specific information which should be included for IMP labels, according to point 26 of the Annex 13, Manufacture of investigational medicinal products February 2010,
- the number of IMPs to be packaged, taking into account :
 - the expected number of subjects for the trial,
 - the number of units necessary for Quality Control,
 - any retention samples to be kept.

The Clinical Project Leader:

- prepares the appropriate label templates, in collaboration with Regulatory Affairs / information provided by Regulatory Affairs, taking into account:
 - in case of a multinational trial, that labelling is available in the language of each country involved in the trial,
 - country-specific requirements,
 - trial specificities:
 - blinded trial requiring procedures,
 - centralised electronic randomisation system, justifying the absence of one of the legal label mention (§26 Annex 13),
 - IMP with an immediate and outer packaging, requiring a complementary specific label for the immediate container (§28 Annex 13) and the case where the immediate container is too small to include legal label mentions (§30 Annex 13),
 - clinical trials with characteristics identified in Article 14 Directive 2001/20/CE, allowing a lighter labelling (§32 Annex 13),
 - leaflet provided to the patient, including the main contact for the trial (§27 Annex 13),
 - the need of pictograms and additional information (§31 Annex 13),
- fills in the "IMP Packaging Description Form", taking into account the previous information.
- (transmits the "IMP Packaging Description Form" to Regulatory Affairs with the label templates)

(Regulatory Affairs:

- approve the "IMP Packaging Description Form" and the label templates (signature and date),
- send back the approved form to the Clinical Project Leader.)

The Clinical Project Leader sends the approved "IMP Packaging Description Form" and the label templates to the IMP Manager and files a copy in the Trial Master File.

The IMP Manager:

- transmits the "IMP Packaging Description Form" with label templates to the IMP Manufacturer for designing the label samples in accordance with it,
- transmits the label samples received from the IMP Manufacturer, to Regulatory Affairs for validation,
- obtains from Regulatory Affairs the "ok to print proof" on label samples,
- informs the IMP Manufacturer and Clinical Project Leader.

The IMP Manager verifies that systems are in place, in order to ensure that:

- if applicable, the listing with randomisation codes has been transmitted to the IMP Manufacturer before packaging and blinding operations,
- if applicable, for blinded operations:
 - "the blind is achieved and maintained"
 - "Rapid identification of product" in case of emergency is available.
- packaging of IMPs is designed:
 - in an individual way for each subject,
 - to prevent any contamination and any damage during the transport and storage,
 - to optimize adhesion to the treatment.

9 Authorizing the IMPs shipment

9.1 General Principle

The IMP Manager / Clinical Project Leader is not allowed to ship the IMP without:

- pharmaceutical release,
 - Certification performed by the Chief Pharmacist ("Pharmacien Responsable" in France)
 - or Certification performed by the Qualified Person in the European Union or European Economic Area,
- regulatory release (regulatory green light).

*  + dispositions spécifiques prévues pour les OG-17
art. D.532-24 du Code de l'environnement

9.2 Process for Authorizing IMPs shipment

The IMP Manager:

- informs the Clinical Project Leader that IMPs are available and ready for shipment (after pharmaceutical release),
- transmits a copy of the Certificate(s) of Analyses and the Release Certificate(s), when available, to the Clinical Project Leader.

The Clinical Project Leader ensures that certification of IMPs takes into account information related to pharmaceutical, chemical and biologic quality of IMP included in the Clinical Authorization Request submitted to the Competent Authority (Afssaps in France).

The first shipment to the trial Center depends on the documentation of the completion of the following regulatory steps (= regulatory green light):

- the internal approval of the Clinical Trial Protocol (identified by a trial number), → *je approuverais ce point car on en a l'autorisation de l'AC + avis CE*
- the favourable opinion of the Ethics Committee, for the study and the concerned Investigator/Center,
- the authorization of the Competent Authority, for the study and the concerned Investigator/Center,
- others specific regulatory steps (according to local regulation), such as:
 - submission to the French Medical Council,
 - authorization related to protection of personal data...
- signed financial arrangements with the Investigator(s), the Hospital Director, the Hospital Pharmacist...
- collection of documents related to the center:
 - if applicable, the specific authorization for the center (article L. 1121-13 CSP),
 - Investigator's CV,
 - normal values of laboratory,
- if applicable, availability of blinded devices,
- if the trial is conducted in an Hospital:
 - the information letter to the Hospital Director,
 - the information letter to the Hospital Pharmacist,
 - if applicable, the specific trial authorization for the hospital pharmacy.

cela implique qu'il y avait au préalable l'accord interne

[If a distribution of IMPs between Investigators is foreseen in a specific Center (previously defined with many trial sites), the Clinical Project Leader follows the Procedure "distribution between Investigators"]

10 IMP shipment to the investigational Centers

The IMPs should be shipped to the center just after the Site Initiation Visit (if this has not been waived) in order to guarantee that the study could not start (patient inclusion) before all essential documents are obtained. [Choix SUNNIKAN d'envoyer les produits après la visite de mise en place]

(In some situations (e.g. a trial with a long run-in period) the IMPs can be shipped to the site later, after subject enrolment has started, provided it has been assured that the IMPs will be available when required.)

In order to request a shipment to an Investigational Center, the Clinical Project Leader fills in a "IMP Shipment Request Form", including the documentation of preliminary regulatory steps and transmits the signed "IMP Shipment Request Form" to the IMP Manager, with the detailed name and address of the recipient(s) and the expected date for shipment.

The IMP Manager sends to the concerned CRA the "IMP Shipment Acknowledgement of Receipt" filled in by the investigational site at the IMPs receipt.

The CRA verifies the conformity of the receipt to the request (quantity, recipient identity...).

The CRA regularly assesses the IMPs need of IMP at the investigational Center and sends, if applicable, to the IMP Manager a "IMP Shipment Request Form", specifying:

- that it concerns a "Re-supply",
- the date of first request shipment.

11 Return of the Investigational Medicinal Products (IMPs)

During the periodic monitoring visits / the closure visit, the Clinical Research Assistant (CRA):

- ensures that:
 - treatment units not used by subjects are really returned to trial centre,
 - return of treatment units is controlled and documented,

- storage of treatment returned to trial centre is in conformity with applicable regulation and requirements of LABO PHARMA,
- registers on the "Investigational Medicinal Products (IMPs) Return Form" the IMPs to return:
 - treatment units not used,
 - treatment units not totally used,
 - empty packages.

The "Investigational Medicinal Products (IMPs) Return Form" contains the following information (if relevant):

- study identification,
- trial site identification,
- treatment units identification:
 - treatment number,
 - batch number and expiry date,
 - treatment period,
 - quantity returned.

The CRA:

- packages in one or more sealed boxes the IMPs to return, by putting only the products of a same clinical trial and of a same site in the same box,
- adds a copy of the "Investigational Medicinal Products (IMPs) Return Form" (the original remaining in the Trial Investigator's File),
- identifies the boxes with "Investigational Medicinal Products (IMPs) Return Labels", specifying the following information:
 - address of the Investigational Medicinal Products Unit,
 - study identification,
 - product identification,
 - trial site identification,
 - mention "Waiting for destruction authorization",
 - return request date,
 - name of the CRA requesting the return,
- organizes the return by a conveyor.

Under no circumstances, the CRA is authorized:

- to transport IMPs himself/herself,
- to address them elsewhere than to the Sponsor IMP Unit.

The Clinical Project Leader ensures:

- that the returned treatment units are managed in an appropriate way by the IMPs Unit:
 - "clearly identified",
 - "stored in an appropriately controlled, dedicated area" (Annex 13, Manufacture of investigational medicinal products, Juillet 2003),
- obtains from IMP Unit the inventories of returned IMPs:
 - performs the global reconciliation of IMPs accountability for the whole clinical trial,
 - files the inventories in the Trial Master File.

12 Destruction of the Investigational Medicinal Products by the Sponsor IMPs Unit

Destruction of unused and returned Investigational Medicinal Products (IMPs) is performed only after all the discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.

The Sponsor IMPs Unit stores the returned IMPs in a specific "Returned IMPs - Waiting for destruction" area.

After validation and signature of the Study Report, the Clinical Project Leader:

- fills in a "Investigational Medicinal Products (IMPs) Destruction Request Form" for the study IMPs,
- sends it to the Sponsor IMPs Unit.

After destruction, the Sponsor IMPs Unit addresses to the Clinical Project Leader a Destruction Certificate dated and signed.

The Clinical Project Leader files the Destruction Certificate in the Trial Master File.

13 Documentation

The Clinical Project Leader files in the appropriate part of the Trial Master File:

- the copy of the IMP Order Forms,
- the signed IMP Packaging Description Forms,
- the Certificate(s) of Analyses and the Release Certificate(s),
- the copy of the IMP Shipment Request Forms.

The CRA checks that the following documents are filed in the appropriate part of the Investigational Site File:

- the copy of the filled IMP Shipment Acknowledgement of Receipt,
- the copy of the Request for Re-supplying.
- the original sample of the "Investigational Medicinal Products (IMPs) Return Form",
- the acknowledgement of receipt from the IMP Unit,
- the documentation related to any discrepancy.

Appendices

- General IMP CL
- "Investigational Medicinal Products (IMPs) Return Form"
- "Investigational Medicinal Products (IMPs) Return Labels"
- "Investigational Medicinal Products (IMPs) Destruction Request Form"

Other Linked documents

- "Management of Investigational Medicinal Products on site"
- "Import License"