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Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice

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Related content	***The clinical trial regulation (EU) No 536/2014*** http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp ***Detailed Commission guidelines No C(2017) 8179 on GMP for investigational medicinal products for human use*** https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guideline_adopted_1_en_act_part1_v3.pdf

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Table of contents

1. Introduction

This guideline complements the Delegated Regulation (EU) No 2017/1569 of 23 May 2017, on good manufacturing practice (GMP) for investigational medicinal products (IMP) and arrangements for inspections, that has as legal basis the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and the detailed Commission guidelines No C(2017) 8179 on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

The guideline lays down the principles for management of the investigational medicinal products by the sponsor for use in a clinical trial and in accordance with Good Clinical Practice (GCP) which are at the interface with, and complementary to, Good Manufacturing Practice.

This guideline is not applicable to operations related to direct-to-patient delivery of IMP. When direct-to-patient delivery of IMP is defined in national legislation the applicable provisions of this Guideline should be followed.

2. IMP release procedure

A clinical trial in the EU can only start after a clinical trial authorisation has been granted by the EU member states concerned, following fulfilment of the requirements of Chapter II (Authorisation procedure for a clinical trial) of Regulation (EU) No 536/2014. This involves the assessment of the site suitability adapted to the nature and use of the investigational medicinal product. The necessary documentation that needs to be submitted with the initial application or an application for a substantial modification to approve a new site is described in Annex I.N.67 of Regulation (EU) No 536/2014. An EU harmonised template for site suitability and the declaration of site suitability is published on Eudralex-10[1]. According to Article 15 of Regulation (EU) No 536/2014, the addition of a new site is always a substantial modification to the trial and therefore requires assessment and regulatory approval.

The release process consists of the batch certification by the Qualified Person (QP) followed by the regulatory release of the IMP by the sponsor to the sites for use in a clinical trial. These steps should be recorded and retained in the clinical trial master file. Investigational medicinal products should remain under the control of the sponsor until the release process is complete.

The certification of each batch by the QP ensures, in line with Article 62(1) of Regulation (EU) No 536/2014, that the provisions of 63(1) and 63(3) of Regulation (EU) No 536/2014 and those set out in Article 12 of the Commission Delegated Regulation (EU) No 2017/1569, have been complied with and documented.

The regulatory release is the verification of completion of batch certification by the QP and that the necessary authorisations are in place for the clinical trial, before supply of IMP to the clinical trial site.

In line with the detailed Commission guidelines No C(2017) 8179 on good manufacturing practice for investigational medicinal products for human use, where the manufacturer is delegated by the sponsor to perform the regulatory release of the IMP to the trial sites in addition to certification by the QP, the arrangements should be defined in an agreement between the sponsor and the manufacturer. The sponsor should provide all the necessary information to the manufacturer to allow the delegated regulatory release. The manufacturer should verify that the necessary clinical trial authorisations are in

[1] https://ec.europa.eu/health/system/files/2019-10/site_suitability_template_en_0.pdf

place prior to shipping the medicinal product for use in the trial (e.g. by consulting the Clinical Trials Information System (CTIS) referred to in Articles 80 and 81 of Regulation (EU) No 536/2014).

Importantly, un-blinding arrangements, according to Annex I.D.22 and Annex III of Regulation (EU) No 536/2014, should be available to the appropriate responsible clinical trial site personnel before, or at the same time, IMPs are received at the clinical trial site. The sponsor is responsible for ensuring that the investigator has appropriate access to systems for immediate un-blinding of each single treatment prior to the start of the trial.

3. Shipping

It should be ensured that the shipping of the IMPs minimises any risk of exposure to conditions that could impact quality and integrity of the product. This includes security of the product (e.g. against adulteration, tampering or theft), ensuring that the applicable principles of the guidelines on Good Distribution Practice (GDP) of medicinal products for human use are taken into consideration, including but not limited to, documentation, transportation (including selection of container and packaging, qualification and/or validation activities, monitoring of transport conditions) and outsourced activities.

Shipping of IMPs to the clinical trial site or pharmacy, where applicable, should be conducted according to detailed instructions given by, or on behalf of, the sponsor (e.g.in the shipping order). Any departures from these instructions should be reported to the sponsor and/or representative. Records to support the supply chain should be maintained, including evaluation of transportation time against any applicable limits. IMPs should be transported in accordance with the storage conditions defined in the product specification file. Equipment which is critical to maintaining the product under the required conditions during transportation should be qualified. Transport validation should be considered according to the stage of development of the IMP. Temperature monitoring of transport and storage conditions are necessary, and these records should also be maintained and evaluated at delivery. A risk assessment should be performed to identify variable conditions expected during transportation and determine continuous monitoring and recording of other critical environmental conditions to which the product may be subjected. Any deviation to the specified conditions during shipment should be recorded and formally investigated with assistance from the manufacturer in order to conclude on the quality implications for the IMPs. In addition, appropriate corrective and preventive actions should be identified, implemented and their effectiveness should also be monitored. Responsibility for the control of the IMPs during shipment remains with the sponsor (or representative) until it has been received and accepted by the clinical trial site or pharmacy, as applicable.

A detailed inventory of the shipments made should be maintained in order to assure traceability of the products during the shipment process in terms of product(s) identity and quantity. Shipping documentation should identify the intended recipient as well as any relevant contact information.

Transfers of IMPs from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer should be established, including review of trial monitoring reports and records of storage conditions at the original trial site. This should be part of the assessment of the product’s suitability for transfer and the advice of the certifying QP should be sought. If deemed appropriate, re-labelling or re-packaging of the product may be performed in accordance with the provisions under Article 61(5)(a) of Regulation (EU) No 536/2014 and any national legislation which may apply. Otherwise the product should be returned to the original manufacturer, or another authorised manufacturer, for re-labelling or re-packaging and certification by a QP. Records should be retained and full traceability ensured as described in Article 51 of Regulation (EU) No 536/2014.

4. Contractual arrangements or technical agreements

Responsibilities of the manufacturer and sponsor should be appropriately defined, agreed and controlled in a written contract or technical agreement, as mentioned in recital 4 to the Commission Delegated Regulation (EU) No 2017/1569 specifying principles and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections. The agreement should clearly establish the duties of each party, taking into account the guidance in EudraLex, Volume 4, Part I, Chapter 7, as applicable.

The detailed Commission guidelines No C(2017) 8179 on good manufacturing practice for investigational medicinal products for human use further mentions certain issues which could be covered by technical agreements, to ensure that all relevant responsibilities are clearly defined and documented (e.g. transport, storage, re-labelling or re-packaging, recall, return, destruction) where applicable, for example:

- Ensuring that any authorised products used in the clinical trial are sourced from an authorized vendor and that arrangements for recall are in place.
- Ensuring that the most up to date information is provided to the QP for consideration during the batch certification process in accordance with the documents set out in the clinical trial applications authorised by EU member states[2].
- Ensuring that any proposed revision of manufacturing and control methods are appropriately communicated between the manufacturer and the sponsor as this may require submission of a substantial modification to the clinical trial application.
- Ensuring that un-blinding arrangements and the respective responsibilities of each party are appropriately defined.
- Ensuring that any agreed responsibilities are not subcontracted to a third party without prior evaluation and approval from the contract giver.
- Ensuring that the documentation required in the clinical trial master file (e.g. IMP batch certification by the QP (https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/template_imp_batch_certification.docx), documentation related to assembly and packaging of IMPs, Certificate of Analysis) remains available to the sponsor, in accordance with 58 of Regulation (EU) No 536/2014, after the retention periods as defined in Article 8 of the Commission Delegated Regulation (EU) 2017/1569 on GMP for IMPs expires.
- Ensuring that storage condition and location of reference and retention samples is defined and documented.
- Clarifying the manufacturer's roles and deliverables regarding the regulatory release.
- Where the sponsor is not the IMP manufacturer and relies on chain of contracted manufacturers, specifying the exact role of each manufacturer (e.g. specific tasks and GMP and GDP related responsibilities) in the chain of manufacturers.
- Defining responsibilities for the handling of deviations during shipment to clinical trial sites.

[2] As described in chapters II, for initial applications, and chapter III, for substantial modifications, of the Regulation (EU) No 536/2014

- Defining requirements for the exceptional process of transferring IMPs from one clinical trial site to another.