EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems and products
Medicinal products – quality, safety and efficacy

Consultation document

Detailed Commission guidelines 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 sole purpose of this consultation is to collect views, relevant evidence and information from stakeholders to help the European Commission develop its thinking in this area with a view to preparing the required guidelines.

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

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1. INTRODUCTION TO THE PUBLIC CONSULTATION

Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC[1] requires in the second subparagraph of Article 63(1) that the Commission adopts and publishes detailed guidelines of good manufacturing practice (GMP) for investigational medicinal products for human use.

Such detailed guidelines are necessary to complement the high-level principles and guidelines on good manufacturing practice for investigational medicinal products for human use to be set out in a Delegated Act pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

Adherence to good manufacturing practice for investigational medicinal products for human use by manufacturers of such medicinal products is instrumental in ensuring the quality of the products which in turn will be an element in safeguarding the safety of the clinical trial subjects and in ensuring the reliability and robustness of the data generated in the trial.

As guidelines on good manufacturing practice for investigational medicinal products for human use already exists and is generally well-functioning, there is no need to reinvent the wheel and therefore, this consultation document refers, when relevant, to specific parts, chapters or annexes of EudraLex, Volume 4[2] or carries over relevant principles of Annex 13 to EudraLex, Volume 4. Annex 13 will be deleted from EudraLex Volume 4 when the new guidelines become operational.

The topics of this consultation document concerning detailed guidelines on good manufacturing practice for investigational medicinal products for human use should be read in conjunction with the consultation on the Commission Delegated Act on Principles and guidelines of good manufacturing practice for investigation medicinal products for human use and inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014, as the detailed Commission guideline will complement that Delegated Act.

Furthermore, on 23 July 2015, a targeted stakeholder consultation on the development of good manufacturing practice for advanced therapy medicinal products pursuant to Article 5 of Regulation 1394/2007 was launched with a deadline for comments on 12 November 2015. That consultation also addresses adaptations relevant to advanced therapy investigational medicinal products; the consultation can be found here: http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm.

With this public consultation on guidelines on good manufacturing practice for investigational medicinal products for human use, the Directorate-General for Health and Food Safety seeks the view of stakeholders regarding the content of such guideline as set out below.

[1] OJ L 158, 27.5.2014, p.1.

[2] http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

2. GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE

2.1. Introduction

These guidelines are based on the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

These guidelines complement the Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products for human use referred to in the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

These guidelines lay down appropriate tools to address specific issues concerning investigational medicinal products with regard to good manufacturing practice.

Article 63(1) of Regulation (EU) No 536/2014 provides that investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ("good manufacturing practice").

Good manufacturing practice for investigational medicinal products is set out in the Delegated Act referred to in the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 and in these guidelines. [The Delegated Act and these guidelines are developed in parallel.]

Furthermore, where applicable, the manufacturers and the competent authorities should also take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in the "Guide to good manufacturing practice for medicinal products and for investigational medicinal products" (EudraLex, Volume 4). Examples of applicable parts of EudraLex, Volume 4 to investigational medicinal products, not specifically mentioned in these guidelines, are Part I, Chapters 2, 4 and 6.

Procedures need to be flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product.

In clinical trials there may be added risk to the subjects compared to patients treated with authorised medicinal products. The application of GMP for the manufacture of investigational medicinal products is intended to ensure that subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison with authorised medicinal products by virtue of lack of fixed routines, variety of clinical trial designs and consequent packaging designs. Randomisation and blinding add to that complexity an increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation. Moreover,

authorised products may be used which have been re-packaged or modified in some way. These challenges require personnel with a thorough understanding of and training in the application of GMP to investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system.

For manufacturers to be able to apply and comply with GMP for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation may be described in a technical agreement.

2.2. Scope

These guidelines apply to manufacture of investigational medicinal products for human use. An investigational medicinal product is defined in Article 2(5) of Regulation (EU) No 536/2014 as a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial, and manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding) in Article 2(24) of said Regulation.

Reconstitution is not considered manufacturing when understood as the simple process of

- dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or

- diluting or mixing the investigation medicinal product with some other substance(s) used as a vehicle for the purpose of administering it to a trial subject.

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product.

An investigational medicinal product must exist before a process can be defined as reconstitution.

The process of reconstitution has to be undertaken as close as possible to administration and has to be defined in the clinical trial application/dossier and in the protocol, or related document, available at the clinical trial site.

These guidelines do not apply to the processes referred to in Article 61(5) of Regulation (EU) No 536/2014. Member States shall make those processes subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial.

Though not strictly in the scope of these guidelines, the guidelines do nevertheless address a few issues concerning auxiliary medicinal products, as defined in Article 2(8) of Regulation (EU) No 536/2014, as manufacturing – fully or partially – of those products has to take place according to good manufacturing practice or to at least an equivalent standard according to Article 65 of said Regulation.

2.3. Pharmaceutical quality system

The pharmaceutical quality system required of the manufacturer according to the Delegated Act on GMP for investigational medicinal products pursuant to Article

63(1) of Regulation (EU) No 536/2014 and designed, set-up and verified by the manufacturer should also be described in written procedures taking into account EudraLex, Volume 4, Part I, Chapter 1 as applicable to investigational medicinal products.

The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained. Deviations from any predefined specifications and instructions shall be investigated and corrective and preventive action (CAPA) measures initiated.

The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system to ensure the integrity of the supply chain and protect against counterfeit products. The level of supervision should be proportionate to the risks posed by the individual materials, taking into account their source, manufacturing process, supply chain complexity and the final use to which the material is put in the investigational medicinal product. The supporting evidence for each supplier approval and material approval should be maintained.

2.4. Personnel

All personnel involved with the manufacture, storage or handling of investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

Even where the number of staff involved in the manufacturing of investigational medicinal products is small, there should be, for each batch, separate people responsible for production and quality control.

The qualified person has to fulfil the conditions of qualification set out in Article 49(2) and (3) of Directive 2001/83/EC, cf. Article 61(2)(b) of Regulation (EU) No 536/2014.

The responsibilities of the qualified person are set out in Article 62 of Regulation (EU) No 536/2015 and (anticipated) further elaborated in the Delegated Act on GMP for investigational medicinal products pursuant to Article 63(1) of said Regulation.

The final certifying qualified person should ensure that there are systems in place that meet the requirements of GMP and should have a broad knowledge of pharmaceutical development and clinical trial processes.

2.5. Premises and equipment

The toxicity, potency or sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection/test methods and acceptance limits to be used after cleaning should reflect the nature of these risks and take account of the quality risk management principles detailed in EudraLex, Volume 4, Part I, Chapters 3 and 5.

Consideration should be given to campaign working, where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

A quality risk management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the investigational medicinal products manufactured. Factors that should be taken into account include:

i. facility/equipment design and use;

ii. personnel and material flow;

iii. microbiological controls;

iv. physic-chemical characteristics of the active substance;

v. process characteristics;

vi. cleaning processes;

vii. analytical capabilities relative to the relevant limits established from the evaluation of the investigational medicinal products.

Premises and equipment are expected to be validated in accordance with EudraLex, Volume 4, Annex 15.

2.6. Documentation

2.6.1. Specification and instructions

Specifications for starting materials, immediate packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packing instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document. Any changes should be carried out according to a written procedure which should address any implications for product quality such as stability and bioequivalence. The approval process for instructions and changes thereof shall include management personnel at the manufacturing site.

Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and fully documented.

2.6.2. Order

The manufacturer should retain the order for investigational medicinal products. The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. It should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.

2.6.3. Product specification file

Applicable sections of the product specification file shall be available at the start of manufacturing of the first batch of investigational medicinal product for a clinical trial.

The product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include or refer to at least the following documents:

i. Specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product;

ii. Manufacturing methods;

iii. In-process testing and methods;

iv. Approved label copy;

v. Relevant clinical trial authorisations and amendments thereof, clinical trial protocol and randomisation codes, as appropriate;

vi. Relevant technical agreements with contract givers and acceptors, as appropriate;

vii. Stability data;

viii. Reference and retention sample plans;

ix. Storage and transport conditions.

The list of document is neither exhaustive, nor exclusive.

The contents of the product specification file will vary depending on the product and the stage of development. The information should form the basis for assessment of the suitability of certification and release of a particular batch by the qualified person and should therefore be accessible to him or her.

Where different manufacturing steps are carried out at different locations under the responsibility of different qualified persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The documentation of the product specification file, including changes, shall be accessible at the manufacturing site.

2.6.4. Manufacturing formulae and processing instructions

For every manufacturing operation or supply there should be clear and adequate written instructions and written records which are prepared using the specific clinical study information detailed in the product specification file. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted.

The information in the product specification file should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage, distribution conditions and storage conditions.

2.6.5. Packaging instructions

Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and for any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

Procedures should describe the specification, generation, testing, security, distribution, handling and retention of any randomisation code used for packaging investigational medicinal products as well as code-break mechanism. Appropriated records should be maintained.

2.6.6. Batch records

Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify procedures used and any changes made, enhance knowledge of the product, develop the manufacturing operations and document deviations from predefined requirements.

Batch manufacturing records should be retained by the manufacturer for the periods specified in the Delegated Act on GMP for investigational medicinal products pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

The sponsor has specific responsibilities for document retention of the clinical trial master file according to Article 58 of Regulation (EU) No 536/2014 and is required to retain such documentation for 25 years after the end of the trial. If the sponsor and the manufacturer are not the same entity, the sponsor has therefore to make appropriate arrangements with the manufacturer to fulfil his requirement to retain the clinical trial master file.

2.7. Production

2.7.1. Packaging materials

Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

2.7.2. Manufacturing operations

During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions

and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.

The manufacturing process is not expected to be validated to the extent necessary for routine production but shall be validated in its entirety in so far as appropriate, taking into account the stage of product development.

To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process shall be available.

For sterile products, the validation of sterilising processes should be of the same standards as for authorised medicinal products and take account of the principles for the manufacture of sterile medicinal products detailed EudraLex, Volume 4, Annex 1. Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products by following the scientific principles and techniques defined in the available guidance in this area.

Validation of aseptic processes presents special problems where the batch size is small; in these cases, the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility so enhanced attention should be given to operator training and validating the aseptic technique of individual operators.

If a product is modified, data should be available, e.g. stability, comparative dissolution or bioavailability, to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

2.7.3. Blinding operations

Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products, when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

Where products are blinded, the expiry date assigned should be stated at the expiry of the shortest dated product so that the blinding is maintained.

2.7.4. Packaging

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. Documentation must be sufficient to demonstrate that appropriate segregation has been maintained during any packaging operations.

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 authorised medicinal products, particularly when "blinded" products with similar appearance are used. Precautions against mislabelling such as reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.

The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection. A suitable expiry date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such date should be justified and must not be later than the expiry date of the original package. There should be comparability of expiry dating and clinical trial duration.

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.

2.7.5. Labelling

Labelling of investigation medicinal products and auxiliary medicinal products should comply with the requirements of Article 66 and 67 of Regulation (EU) No 536/2014. A list of information which is to appear on the labelling is set out in Annex IV to said Regulation.

If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new expiry date and repeat the batch number and/or clinical trial reference number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number.

The re-labelling operation should be performed by appropriately trained staff in accordance with GMP principles and specific and standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mix-up, the additional labelling activity should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed with 100 %.

The re-labelling operation can be outsourced only if it is subject to a written contract.

2.8. Quality control

According to the Delegated Act on GMP for investigational medicinal products pursuant to Article 63(1) of Regulation (EU) No 536/2014 the manufacturer is required to establish and maintain a quality control system place under the authority of a person who has the requisite qualifications and is independent of production.

As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.

Quality control of the investigational medicinal product, including comparator product, should be performed in accordance with the information submitted according to Article 25 of Regulation (EU) No 536/2014 as authorised by the Member State.

Verification of the effectiveness of blinding should be performed and recorded.

Samples are retained to fulfil two purposes: firstly, to provide a sample for future analytical testing, and secondly, to provide a specimen of the finished product and may be used in the investigation of a product quality defect. Samples may therefore fall into two categories:

- Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise. Where stability permits, reference samples from critical intermediate stages, e.g. those requiring analytical testing and release, or intermediates which are transported outside of the manufacturer's control, should be kept.
- Retention sample: a sample of a packaged unit from a batch of finished product for each packaging run or trial period. It is stored for identification purposes. For example presentation, packaging, labelling, package leaflet, batch number, expiry date should the need arise.

For retention samples it is acceptable to store information related to the final packaging as written, photographic or electronic records, if such records provide sufficient information, e.g. examples of packaging, labelling and any accompanying documentation to permit investigations associated with the use of the product. In case of electronic records, the system should comply with the requirements of EudraLex, Volume 4, Annex 11. [Please note, that the public consultation on principles and guidelines on GMP for investigational medicinal products, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 poses questions about requirements for retention samples.]

Where reference samples and retention samples are presented identically, i.e. as fully packaged units, the samples may be regarded as interchangeable.

Samples are not expected of an investigational medicinal product which is an unblinded comparator in its original packaging and sourced from the authorised supply chain in the EU or of a product which holds a marketing authorisation granted by a national competent authority in the EU or by the European Commission.

The storage location of samples should be defined in a technical agreement between the sponsor and the manufacturer(s) and should allow timely access by the competent authorities.

Reference samples of finished product should be stored in the EU or in a third country where appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer of the investigational medicinal

product applies standards of good manufacturing practice at least equivalent to those laid down by the Union. In exceptional circumstances, the reference samples of the finished product may be stored by the manufacturer in another third country, in which case this should be justified and documented in a technical agreement between the sponsor, the importer in the EU and that manufacturer in the third country.

The reference sample should be of sufficient size to perform, on at least two occasions, all critical quality attribute tests as defined in the investigational medicinal product dossier accepted by the Member State. Any exception to this should be justified to, and agreed with, the national competent authority.

2.9. Release of batches

Release of investigational medicinal products should not occur until after the qualified person has certified that the requirements of Article 63 of Regulation (EU) No 536/2014 and those set out in the Delegated Act on GMP for investigational medicinal products pursuant to Article 63(1) of said Regulation are met.

The duties of the qualified person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below:

i. Product manufactured within EU but not subject to an EU marketing authorisation: the duties are laid down in Article 62 of Regulation (EU) No 536/2014;

ii. Product sourced from the open market within EU in accordance with Article 80(b) of Directive 2001/83/EC and subject to a marketing authorisation granted by a competent authority in the EU, regardless of manufacturing origin: the duties are as described above. However, the scope of the certification can be limited to assuring that the products are in accordance with the authorisation of the clinical trial and any subsequent processing for the purpose of blinding, trial-specific packaging and labelling.

iii. Product imported directly from a third country: the duties are laid down in Article 62 of Regulation (EU) No 536/2014. Where investigational medicinal products are imported from a third country and they are subject to agreements concluded between the Union and that country, such as a Mutual Recognition Agreement (MRA), equivalent standards of good manufacturing practice apply provided any such agreement is relevant to the product in question. In the absence of a MRA, the qualified person should determine that equivalent standards of good manufacturing practice apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through audit of the manufacturer's quality systems. In either case, the qualified person may then certify on the basis of documentation supplied by the manufacturer in the third country and document the rationale for certification.

Assessment by the qualified person of each batch for certification prior to release may include as appropriate:

i. Batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the

order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks and tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;

ii. Production conditions;

iii. Cleaning records;

iv. The validation status of facilities, processes and methods;

v. Examination of finished packs;

vi. The results of any analyses or tests performed after importation, where relevant;

vii. Stability reports;

viii. The source and verification of conditions of storage and shipment;

ix. Audit reports concerning the quality system of the manufacturer;

x. Documents certifying that the manufacturer is authorised to manufacture investigational medicinal product for export by the appropriate authorities in the country of export;

xi. Regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance, where relevant;

xii. All factors of which the qualified person is aware that are relevant to the quality of the batch;

The relevance of the above elements is affected by the country of origin of the product, the manufacturer, the status of the product, i.e. with or without a marketing authorisation granted by competent authorities in the EU or in a third country, and the phase of development of the product.

Where investigational medicinal products are produced and packaged at different sites under the supervision of different qualified persons, EudraLex, Volume 4, Annex 16 is applicable.

The qualified person is not required to certify re-packaging or re-labelling carried out pursuant to Article 61(5)(a) of Regulation (EU) No 536/2014.

2.10. Outsourcing

Activities which are outsourced by the manufacturer should be defined, agreed and controlled by written contracts in accordance with the principles detailed in EudraLex Volume 4, Part I, Chapter 7.

2.11. Complaints

There should be written procedures describing the actions to be taken upon receipt of a complaint at the manufacturing, storage or importation site. All complaints should be documented and assessed to establish if they represent a potential quality

defect or other issue. The procedures should ensure that the sponsor could assess the complaints to determine if they meet the requirements for serious breach reporting according to Article 52 of Regulation (EU) No 536/2014.

The quality defect investigation should be in accordance with the principles detailed in EudraLex, Volume 4, Part I, Chapter 8.

The conclusions of the investigation should be discussed between the manufacturer and the sponsor, if different, in a timely manner. This should involve the qualified person and those responsible for the relevant clinical trial in order to asses any potential impact on the trial, product development and on subjects.

2.12. Recalls and returns

2.12.1. Recalls

Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor in collaboration with the manufacturer, where different. The investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. The procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in EudraLex, Volume 4, Part I, Chapter 8.

2.12.2. Returns

Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of returned products should be kept.

2.12.3. Destruction

The manufacturer should destroy investigational medicinal products only with prior written authorisation by the sponsor.

Destruction of unused investigational medicinal products should be carried out only after reconciliation of delivered, used and recovered products and after investigation and satisfactory explanation of any discrepancies upon which the reconciliation has been accepted.

Recording of destruction operations should be carried out in such a manner that all operations may be accounted for.

When destruction of investigational medicinal products takes place the manufacturer provides a dated certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify or allow traceability to the batches and/or patient numbers involved and the actual quantities destroyed.

2.13. Glossary of terms

Terms	Definition
Comparator product	A medicinal product used as a reference, including as a placebo, in a clinical trial.
Preparation	Enclosing the product in a container which is labelled before the product is used in a clinical trial, or where the product is already in the container, in which it is to be supplied, labelling the container before the product is used in a clinical trial.
Manufacturer	Any person engaged in activities for which the authorisation referred to in Article 61 of Regulation (EU) No 536/2014 is required.
Order	Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).
Product specification file	A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.
Randomisation	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Shipping/distribution	The operation of packaging for transportation and sending of ordered medicinal products for clinical trials.
Transportation	Moving medicinal products between two locations without storing them for unjustified periods of time.