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Guidelines

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

INTRODUCTION

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

These guidelines complement Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 on the good manufacturing practice for investigational medicinal products for human use and arrangements for inspections[2] that has as its legal basis 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. The tools are flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product.

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 that Regulation.

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 Commission Delegated Regulation (EU) No 2017/1569 and in these guidelines.

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[3], 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, and 6, and Part III.

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

[2] Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections (OJ L 238/12, 16.09.2017).

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.201, p. 67).

With regard to EudraLex, Volume 4, Part II, it should be noted that Regulation (EU) No 536/2014 does not lay down requirements for good manufacturing practice for active substances of investigational medicinal products. However, if a clinical trial is to be used to support the application for a marketing authorisation, Part II of EudraLex, Volume 4 would need to be considered.

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

In clinical trials there may be added risk to the subjects compared to patients treated with authorised medicinal products. The application of good manufacturing practice for the manufacture and import of investigational medicinal products is intended to ensure that subjects are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or import. 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 good manufacturing practice 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 good manufacturing practice for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation should be described in a technical agreement between the sponsor and manufacturer, as referred to in recital 4 of Delegated Regulation (EU) No 2017/1569.

1. SCOPE

These guidelines apply to manufacture or import of investigational medicinal products for human use.

For advanced therapy investigational medicinal products, Article 16 of Commission Delegated Regulation (EU) No 2017/1569 states that the requirements of good manufacturing practice shall be adapted to the specific characteristic of such products in accordance with a risk-based approach and consistent with good manufacturing requirements applicable to authorised advanced therapy medicinal products. Those adaptations are addressed in the Guidelines on good manufacturing practice for advanced therapy medicinal products[4]. Therefore, these detailed guidelines on good manufacturing

[4] Commission guideline on good manufacturing practice for advanced therapy medicinal products, Eudralex Volume 4, Part IV

practice for investigational medicinal products for human use do not apply to manufacture or import of advanced therapy investigational medicinal products.

Reconstitution of investigational medicinal products is not considered manufacturing, and therefore is not covered by this guideline.

The reconstitution is 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 in time as possible to administration and has to be defined in the clinical trial application dossier and 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 should 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.

2. PHARMACEUTICAL QUALITY SYSTEM

The pharmaceutical quality system required of the manufacturer according to Article 5 of Commission Delegated Regulation (EU) No 2017/1569 and designed, set-up and verified by the manufacturer should 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 documented and maintained. Deviations from any predefined specifications and instructions should be registered, investigated and corrective and preventive action measures initiated as appropriate.

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 falsified 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 documented and maintained.

2.1. Product specification file

Products specification file, in light of Article 2(3) of Commission Delegated Regulation (EU) No 2017/1569, brings together and contains all of the essential

reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. The products specification files is one of the essential elements of pharmaceutical quality system.

Applicable sections of the product specification file should 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 plan and reports;

viii. Details of plans and arrangements for reference and retention samples;

ix. Storage and transport conditions;

x. Details of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products, preferably in the format of a comprehensive diagram.

This list of documents is neither exhaustive nor exclusive.

The contents of the product specification file will vary depending on the product and the stage of development.

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 manufacturing site should have access to the necessary documentation of the product specification file, including changes, to enable the relevant activities to be performed.

3. PERSONNEL

The requirements as regards the personnel are defined in Article 6 of Commission Delegated Regulation (EU) No 2017/1569. The EudraLex, Volume 4, Part I, Chapter 2 should also be taken into account as appropriate.

All personnel involved with the manufacture, import, 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 or import 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, as per 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 further elaborated in Article 12 of Commission Delegated Regulation (EU) No 2017/1569.

The qualified person that certifies the finished batch of investigational medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.

4. 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 manufacturing, 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. physio-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 qualified in accordance with EudraLex, Volume 4, Annex 15.

5. DOCUMENTATION

Documentation should be generated and controlled in line with the principles detailed in EudraLex, Volume 4, Part I, Chapter 4. The retention period for instructions and records required to demonstrate compliance with good manufacturing practice should be defined according to the type of document while complying with the requirement of Article 8 of Commission Delegated Regulation (EU) No 2017/1569, where relevant. In line with Article 8(1) of the above mentioned Delegated Regulation the documentation shall be consisted with the Product Specification File. Documents which are part of the Products Specification File shall be retained for the period of at least 5 years as required by Article 8(3) of the Delegated Regulation.

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 at least 25 years after the end of the trial. If the sponsor and the manufacturer are not the same entity, the sponsor has to make appropriate arrangements with the manufacturer to fulfil the sponsor's requirement to retain the clinical trial master file. Arrangement for retention of such documents and the type of documents to be retained should be defined in an agreement between the sponsor and manufacturer.

5.1. 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 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 responsible 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.

5.2. Order

The manufacturer should retain the order for investigational medicinal products as part of the batch documentation. 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. The order 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.

5.3. 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 relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing, and storage, including storage conditions.

5.4. 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 that 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. Appropriate records should be maintained.

5.5. 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 at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used as set out in Article 8(3) of Commission Delegated Regulation (EU) No 2017/1569.

6. PRODUCTION

6.1. 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.

6.2. 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.

In line with Article 9(3) of Delegated Regulation, the manufacturing process is not to be validated to the extent necessary for routine production but shall be validated in its entirety, as far as is appropriate taking into account the stage of product development. It should be documented in accordance with the requirements detailed in EudraLex, Volume 4, Annex 15. Article 9(3) of Commission Delegated Regulation (EU) No 2017/1569 states also that the manufacturer shall identify the process steps that safeguard the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical study.

To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process should 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 and biological 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.

6.3. Modification of comparator products

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.

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, or be compatible with the product. A suitable retest date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the product may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

A reference sample of comparator product, which has been repackaged or over encapsulated for blinding purposes, should be taken at a point representative of the additional processing and retained, as the additional processing step could have an impact on stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.

6.4. 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 the manufacturer has been delegated the responsibility for generation of randomisation codes, the manufacturer should enable that unblinding information is available to the appropriate responsible investigator site personnel before investigational medicinal products are supplied.

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.

6.5. 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 unintentional mixing (mix-ups) 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 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.

Re-packaging operations may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of Article 61(5)(a) of Regulation (EU) No 536/2014.

6.6. Labelling

Labelling of investigation medicinal products shall comply with the requirements of Article 66, 67, 68 and 69 of Regulation (EU) No 536/2014. A list of information which shall appear on the labelling is set out in Annex VI to the said Regulation. The labelling operation should be performed at an authorised manufacturing site that complies with the requirements of Article 61(1) of Regulation (EU) No 536/2014.

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 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 good manufacturing practice principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes 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. Any discrepancies observed during reconciliation should be investigated and accounted for before release.

The re-labelling operation may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of Article 61(5)(a) of Regulation (EU) No 536/2014.

7. QUALITY CONTROL

According to Article 10 of Commission Delegated Regulation (EU) No 2017/1569, the manufacturer is required to establish and maintain a quality control system placed 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.

Retention periods for samples of investigational medicinal products have to fulfil the requirements of Article 10(4) of Commission Delegated Regulation (EU) No 2017/1569.

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 investigational medicinal product which 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 fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, package leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.

There may be exceptional circumstances where this requirement can be met without retention of duplicate samples, e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

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.

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 under defined storage conditions 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 authorised by the Member State. Any exception to this should be justified to, and agreed with, the national competent authority.

8. RELEASE OF BATCHES

Release of investigational medicinal products should not occur until after the qualified person has certified in line with Article 62(1) of Regulation (EU) No 536/2014 that the requirements of Article 63(1) and (3) of Regulation (EU) No 536/2014 and those set out in Article 12 of the Commission Delegated Regulation (EU) No 2017/1569 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 the EU but not subject to an EU marketing authorisation: the duties are laid down in Article 62 of Regulation (EU) No 536/2014 and Article 12(1)(a) of the Delegated Regulation;

ii. Product sourced from the open market within the 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 carried out by the manufacturer 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 and Article 12(1)(b) of Delegated Regulation. 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 operational for investigational medicinal products. 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.

The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the qualified person and should therefore be accessible to him or her.

Assessment by the qualified person of each batch for certification prior to release should take account of the principles detailed in EudraLex, Volume 4, Annex 16 and 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 qualification status of facilities, validation status of processes and methods;

v. Examination of finished packs;

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

vii. Stability plan and 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 third country;

xi. Where relevant, regulatory requirements for marketing authorisation, good manufacturing practice standards applicable and any official verification of compliance with good manufacturing practice;

xii. Verification of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products;

xiii. 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, sharing of responsibilities amongst qualified persons in relation to compliance of a batch must be defined in a document formally agreed by all parties.

Where required to support certification, the qualified person has to ensure that investigational medicinal products have been stored and transported under conditions to maintain product quality and supply chain security. Relevant situations may include short expiry date products released prior to final qualified person certification, or where return of investigational medicinal products to an authorised manufacturer for re-labelling and re-packaging remains a possibility.

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.

Where the manufacturer is delegated by the sponsor to perform the regulatory release in addition to certification by the qualified person, the arrangements should be defined in an agreement between the sponsor and the manufacturer. Relevant clinical trial authorisation and amendment information should be available for reference in the

product specification file and the manufacturer should ensure the necessary clinical trial authorisations are in place and prior to shipping product for use in the trial.

After certification by the qualified person, investigational medicinal products should be stored and transported under conditions to maintain product quality and supply chain security.

9. OUTSOURCED OPERATIONS

Activities which are outsourced should be defined, agreed and controlled by written contracts between the contract giver and the party to whom the operations are outsourced in accordance with Article 13 of Delegated Regulation and the principles detailed in EudraLex Volume 4, Part I, Chapter 7.

10. 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 is able to assess the complaints to determine if they justify the reporting of a serious breach, as required by Article 52 of Regulation (EU) No 536/2014.

The investigation of quality defect should be performed 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.

11. RECALLS AND RETURNS

11.1. Recalls

Procedures for retrieving investigational medicinal products and documenting this retrieval should in line with Article 14 of the Delegated Regulation be agreed by the sponsor in cooperation with the manufacturer, where different. The manufacturer, 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.

To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.

11.2. 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.

11.3. Destruction

The manufacturer or sponsor's representative should destroy investigational medicinal products only with prior written authorisation by the sponsor. The arrangements for destruction of investigational medicinal products have to be described in the protocol. Any arrangement between sponsor and manufacturer in this regard should be defined in their technical agreement.

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.

Records of destruction operations should be retained, including 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.

564 **GLOSSARY OF TERMS APPLICABLE TO THESE GUIDELINES**

Terms	Definition
Campaign manufacturing	Manufacturing a series of batches of the same product in sequence in a given period of time followed by an appropriate (validated) cleaning procedure.
Comparator product	An investigational medicinal product used as a reference, including as a placebo, in a clinical trial.
Expiry date	The date placed on the container/labels of an investigational medicinal products designating the time during which the investigational medicinal products is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
Order	The order should request the processing and/or packaging of a certain number of units and/or their shipment and be given by or on behalf of the sponsor to the manufacturer.
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.
Retest date	The date when a material should be re-examined to ensure that it is still suitable for use.
Shipping	The operation of packaging for and sending of ordered medicinal products for clinical trials.

565