EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

Consultation document

Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures, pursuant to the first 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 of preparing the required delegated act.

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

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 that the Commission adopt delegated acts to specify the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products.

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.

Currently, Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use[2] also sets out principles and guidelines for good manufacturing practice for investigational medicinal products for human use.

However, once Regulation (EU) No 536/2014 becomes applicable, manufacture and import of investigational medicinal products use in clinical trials carried out under that Regulation cannot follow the good manufacturing practice for investigational medicinal products for human use set out in Directive 2003/94/EC. Instead those investigational medicinal products have to be manufactured or imported under good manufacturing practice for investigational medicinal products for human use laid down by the Delegated Act provided for in Article 63(1) of Regulation (EU) No 536/2014.

The first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 further provides that the Commission shall adopt Delegated Acts on the detailed arrangements for inspections.

As 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 carries over the majority of the principles and guidance set out in Directive 2003/94/EC relating to investigational medicinal products for human use.

However, a new provision is proposed with regard to adaptation of good manufacturing practice for advanced therapy investigational medicinal products.

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

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

[2] OJ L 262, 14.10.2003, p. 22.

Article 63(4) of Regulation (EU) No 536/2014 puts an obligation on Member States to ensure compliance with good manufacturing practice for investigational medicinal products through inspections. For arrangements for inspections, inspiration for this consultation document is drawn from provisions on inspections of Directive 2001/83/EC and from already existing procedures (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf) agreed by the Member States.

With this public consultation, the Directorate-General for Health and Food Safety seeks the views of stakeholders regarding the content of such Delegated Acts.

2. PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE

2.1. Conformity with good manufacturing practice

The manufacturer shall ensure that the manufacturing or import operations for investigational medicinal products for human sue are carried out in accordance with good manufacturing practice for investigational medicinal products laid down in the Commission Delegated Regulation on good manufacturing practice for investigational medicinal products, with Regulation (EU) No 536/2014 and with the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014.

The importer of investigational medicinal products for human use shall ensure that the products have been manufactured by applying quality standards at least equivalent to those laid down by the Commission Delegated Regulation and in accordance with Regulation (EU) No 536/2014.

The importer of investigational medicinal products for human use shall ensure that the manufacturer located in a third country is entitled to manufacture the relevant type of investigational medicinal product in that country.

2.2. Compliance with the clinical trial authorisation

The manufacturer shall ensure that all manufacturing operations for investigational medicinal products for human use are carried out in accordance with the information provided by the sponsor pursuant to Article 25 of Regulation (EU) No 536/2014 and as authorised by the Member States.

The manufacturer shall regularly review his manufacturing methods in the light of scientific and technical progress and the development of the investigational medicinal product.

2.3. Pharmaceutical quality system

A pharmaceutical quality system means the total sum of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use.

The manufacturer shall establish, implement and maintain an effective pharmaceutical quality system, involving active participation of the management and personnel of the different departments.

2.4. Personnel

At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the objective of the pharmaceutical quality system.

The duties of managerial and supervisory staff, including the qualified persons, responsible for implementing and operating good manufacturing practice shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

The managerial and supervisory staff shall be given sufficient authority to discharge their responsibility correctly.

The personnel shall receive internal and on-going training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of pharmaceutical quality and good manufacturing practice, including in particular requirements for the manufacture of investigational medicinal products for human use.

Hygiene programmes adapted to the activities to be carried out shall be established and observed. These programmes shall, in particular, include procedures relating to health, hygiene practice and clothing of personnel.

2.5. Premises and equipment

Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended operations.

Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the investigational medicinal product.

Premises and equipment to be used for manufacturing operations, which are critical to the quality of the product, shall be subjected to appropriate qualification and validation.

2.6. Documentation

The manufacturer shall establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing or import operations performed. Documents shall be clear, free from error and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents on the manufacture of each batch of investigational medicinal products for human use. That set of documents shall enable the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product for human use to be traced.

Question 1a: Would a requirement for a 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) be useful to be introduced?

Question 1b: Do product specification files exist for manufacture of all investigational medicinal products in the EU?

The manufacturer shall retain batch documentation for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

Question 2: Different options exist for the retention period of batch documentation:

a) Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period.

b) Retention for at least 25 years after the end of the clinical trial in line with the retention period of the clinical trial master file.

Please indicate the preferred option with justification.

When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems showing that the data will be appropriately stored during the anticipated period of storage. Data stored in those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained.

2.7. Production

The different production operations shall be carried out in accordance with pre-established instructions and procedures and in accordance with good manufacturing practice. Adequate and sufficient resources shall be made available for the in-process controls. All process deviations and product defects shall be documented and thoroughly investigated.

Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups. Particular attention shall be paid to the handling of products during and after any blinding operation.

The manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development.

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 trial. The critical process steps, such as sterilisation, shall be validated.

All steps in the design and development of the manufacturing process shall be fully documented.

2.8. Quality control

The manufacturer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

The person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of starting materials and packing materials and the testing of intermediate and finished investigational medicinal products for human use.

The manufacturer shall ensure that the contract laboratory complies with the content of the dossier referred to in Article 25 of Regulation (EU) No 536/2014 as authorised by the Member State. When products are imported from third countries, analytical control in the Union shall not be mandatory.

Question 3: Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please elaborate your answer to this question.

During the final control of the finished investigational medicinal product before its release for use in clinical trials, the quality control system of the manufacturer shall take into account, in addition to analytical results, essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents, the conformity of the product with its specifications and conformity with the clinical trial authorisation, including the final finished pack.

Sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished investigational medicinal product batch shall be retained by the manufacturer for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

Question 4a: Should retention samples also be required to be retained by the manufacturer?

Question 4b: If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify.

Unless a longer period is required under the law of the Member State of manufacture, the manufacturer shall retain samples of starting materials, other than solvents, gases or water, used in the manufacturing process for at least two years after the release of the product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. All those samples shall be maintained at the disposal of the competent authorities.

Other conditions may be defined, by agreement with the competent authority, for the sampling and retaining of starting materials and certain products manufactured

individually or in small quantities, or when their storage could raise special problems.

2.9. Responsibilities of the qualified person

The qualified person referred to in Article 61(2)(b) of Regulation (EU) No 536/2014 shall be responsible for ensuring:

(1) In the case of investigational medicinal products for human use manufactured in the Member State concerned, that each production batch has been manufactured and checked in compliance with the requirements of the Delegated Regulation on good manufacturing practice for investigational medicinal products for human use and with the information provided pursuant to Article 25 of Regulation (EU) No 536/2014;

(2) In case of investigational medicinal products for human use manufactured in a third country, that each production batch has been manufactured and checked in accordance with quality standards at least equivalent to those laid down in the Union for good manufacturing practice for investigational medicinal products for human use and with the information provided pursuant to Article 25 of Regulation (EU) No 536/2014.

Question 5a: In how many clinical trials authorised under the Clinical Trials Directive[3] has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

Question 5b: In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorised in an ICH country (EU, US, Japan, Canada and Switzerland)? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

In all cases, the qualified person shall certify in a register or equivalent document provided for that purpose that each production batch satisfies the requirements of good manufacturing practice for investigation medicinal products or at least equivalent quality standards and the information provided in the application for the authorisation of the clinical trial. The register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for at least five years after the completion or formal discontinuation of the last trial in which the batch was used. The retention period of the register will follow that of the batch documentation mentioned in section 2.6.

2.10. Work contracted out

Any manufacturing operation or operation linked thereto which is carried out under contract shall be the subject of a written contract.

[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.05.2001, p. 34.

The contract shall clearly define the responsibilities of each party and shall define, in particular, the observance of good manufacturing practice to be followed by the contract acceptor and the manner in which the qualified person responsible for certifying each batch is to discharge his responsibilities.

The contract acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract giver.

The contract acceptor shall comply with the principles and guidelines of good manufacturing practice laid down in the Delegated Act for good manufacturing practice for investigational medicinal products and in accordance with Regulation (EU) No 536/2014 and shall submit to inspections carried out by the Member States pursuant to Article 63(4) of Regulation (EU) No 536/2014.

2.11. Complaints, product recall and emergency unblinding

The manufacturer shall, in cooperation with the sponsor, implement a system or recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products which have already entered the distribution network. The manufacturer shall record and investigate any complaint concerning a defect and shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply.

All trial sites shall be identified and, in so far as possible, the countries of destination shall be indicated.

In addition, for an authorised investigational medicinal product, the manufacturer of such product shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised investigational medicinal product.

Where required by the protocol of a clinical trial, the manufacturer shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The manufacturer shall ensure that the procedure discloses the identity of the blinded product only in so far as it is necessary.

2.12. Self-inspection

The manufacturer shall conduct repeated self-inspections as part of the pharmaceutical quality system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective actions or preventive actions. Records shall be maintained of such self-inspections and any corrective action or preventive action subsequently taken.

2.13. Advanced therapy investigational medicinal products

The requirements of good manufacturing practice shall be adapted to the specific characteristics of advanced therapy investigational medicinal products in accordance with a risk-based approach.

The adaptation to the specific characteristics of those products will be elaborated in a Commission guideline. 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.

3. INSPECTIONS

3.1. Supervision by inspection

By means of repeated inspections the Member States shall ensure that manufacturers comply with the principles of good manufacturing practice laid down by Union law.

Member States shall carry out inspections of manufacturers located in third countries to ensure that investigational medicinal products imported into the Union are manufactured by applying quality standards at least equivalent to those laid down in Union law. The frequency of such inspections shall be based on an assessment of risk, but shall in any case take place if the Member States have grounds for suspecting that the quality standards are lower than those laid down in Union law.

Inspections may, if necessary, be unannounced.

3.2. Inspection reports

Following an inspection, an inspection report shall be drawn up and made available to the inspected entity and the sponsor in accordance with Article 78(6) of Regulation (EU) No 536/2014.

Before adopting the report, the Member State under whose responsibility the inspection has been conducted shall give the inspected entity the opportunity to submit comments.

3.3. Inspectors' empowerment

Inspections shall be carried out by officials (inspectors) representing the Member State. The inspectors shall be empowered to:

(1) Inspect the manufacturing or commercial establishments of manufacturers of investigational medicinal products for human use, and lay laboratories employed by manufacturer to carry out quality control;

(2) Take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose in a Member State;

(3) Examine any documents relating to the object of the inspection;

(4) Inspection the premises, records and document of the manufacturer.

Inspectors shall be provided with suitable means of identification.

3.4. Inspectors' competence and obligations

In addition to the qualifications set out in Article 49(2) and (3) of Directive 2001/83/EC and adequate training, the inspectors shall also have the following:

(1) Experience and knowledge of the inspection process;

(2) The ability to make professional judgments as to the conformance of the inspected entity with the requirements of good manufacturing practice as laid down in Union law;

(3) The ability to apply the principles of quality risk management;

(4) Knowledge of current technology relevant for inspections;

(5) Knowledge of the current technology for the product manufactured.

The inspectors shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of their inspections in accordance with applicable Union legislation, national legislation or international agreements.

The qualifications, training and experience of each inspector shall be documented and those records shall be maintained up to date.

Each inspector shall have access to a document setting out standard operating procedures and giving details of duties, responsibilities and on-going training requirements. These procedures shall be maintained up to date.

3.5. Impartiality of inspectors

Inspectors shall have no conflicts of interest and be independent of the sponsor, of the clinical trial site, of the investigators involved, of persons financing the clinical trial and of the manufacturer, as well as free of any undue influence that could affect their impartiality.

Each inspector shall sign a statement declaring any financial or other link to the entities inspected. The statement shall be taken into consideration when inspectors are assigned to a specific inspection.

3.6. Obligation for manufacturer to allow access to his premises

The manufacturer shall allow inspectors access to his premise, records and documents at all times.

3.7. Consequence of non-compliance with GMP

If an inspection reveals that the manufacturer seriously fails to comply with good manufacturing practice as set out by Union law, the Member State shall suspend or revoke the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014 as a whole or in part.