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 (Text with EEA relevance)

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

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to 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[(1)], and in particular Article 63(1) thereof,

Whereas:

(1) The good manufacturing practice for investigational medicinal products for human use ensures 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 manufacturing of investigational medicinal products presents additional challenges comparing to the manufacturing of authorised medicinal products because there are no fixed routines, there is a variety of clinical trial designs and consequently packaging designs. Those challenges are due to the need, often, of randomisation and to disguise the identity of the investigational medicinal products for the purpose of clinical trial (blinding). The toxicity, potency and sensitising potential of investigational medicinal products for human use may not be fully understood at the time of the trial, and the need to minimise all risks of cross-contamination is therefore of even greater importance than for authorised medicinal products. Because of this complexity, the manufacturing operations should be subject to a highly effective pharmaceutical quality system.

(2) Good manufacturing practice as regards both medicinal products authorised to be placed on the market and investigational medicinal products are based on the same principles. The same manufacturing sites will often manufacture both investigational and medicinal products authorised to be placed on the market. For that reason the principles and guidelines of good manufacturing practice for investigational medicinal

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products for human use should be aligned as much as possible with those applicable to medicinal products for human use.

(3) In accordance with Article 61(5) of Regulation (EU) No 536/2014 certain processes do not require the authorisation referred to in Article 61(1) of that Regulation. In line with Article 63(2) of Regulation (EU) No 536/2014 good manufacturing practice for investigational medicinal products does not apply to those processes.

(4) For the manufacturer to be able to comply with good manufacturing practice for investigational medicinal products, cooperation between the manufacturer and the sponsor is necessary. Likewise, for the sponsor to comply with the requirements of Regulation (EU) No 536/2014 cooperation with the manufacturer is necessary. Where the manufacturer and the sponsor are different legal entities, the obligations of the manufacturer and sponsor vis-à-vis each other should be specified in a technical agreement between them. Such an agreement should provide for the sharing of inspection reports and exchange of information on quality issues.

(5) Investigational medicinal products imported into the Union should be manufactured by applying quality standards at least equivalent to those in the Union. For this reason, only products manufactured by a third country manufacturer that is entitled or authorised to do so in accordance with the laws of the country where the manufacturer is located, should be allowed to be imported into the Union.

(6) All manufacturers should operate an effective quality assurance system of their manufacturing or import operations. Such a system in order to be effective requires the implementation of a pharmaceutical quality system. Good documentation constitutes an essential part of a quality assurance system. The documentation system of manufacturers shall enable the history of the manufacture of each batch and any changes introduced during the development of an investigational medicinal product to be traced.

(7) Principles and guidelines of good manufacturing practice for investigational medicinal products should be set out in relation to quality management, personnel, premises, equipment, documentation, production, quality control, outsourced operations, complaints and recall, and self-inspections.

(8) It is appropriate to require a product specification file which brings together and contain 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.

(9) Due to the special characteristics of advanced therapy investigational medicinal products, the provisions on good manufacturing practice should be adapted to those products in accordance with a risk-based approach. As regards the advanced therapy medicinal products marketed in the Union, Article 5 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[(2)] provides for such adaptation. The Commission guidelines referred to in Article 5 of Regulation (EC) No 1394/2007 should also set out the requirements on good manufacturing practice applicable to advanced therapy investigational medicinal products.

(10) In order to ensure conformity with the principles and guidelines of good manufacturing practice for investigational medicinal products, provisions on inspections by the competent authorities of the Member States should be established. Member States should not be obliged to inspect third country manufacturers of investigational medicinal products routinely. The need for such inspections should be established according to a risk-based approach but third country manufacturers should be inspected at least if there is a suspicion that the investigational medicinal products are not manufactured by applying quality standards at least equivalent to those applicable in the Union.

(11) Inspectors should consider the Commission guidelines on good manufacturing practice for investigational medicinal products for human use. To achieve and maintain mutual recognition of inspection findings in the Union and facilitate the cooperation of the Member States, commonly recognised standards on the conduct of inspections on good manufacturing practice for investigational medicinal products in the form of procedures should be developed. The Commission guidelines and these procedures should be maintained and regularly updated, according to technical and scientific developments.

(12) During inspections of a site the inspectors should check whether a site respects good manufacturing practice as regards both investigational medicinal products and medicinal products authorised to be placed on the market. For that reason, and in order to ensure the effective supervision, procedures and powers to carry out inspections to verify that good manufacturing practice for investigational medicinal products for human use is followed should be aligned as much as possible to those for medicinal products for human use.

(13) To ensure that inspections are effective, inspectors should be appropriately empowered.

(14) Member States should be able to take action in case of non-compliance with good manufacturing practice for investigational medicinal products for human use.

(15) The competent authorities should be required to set up quality systems to ensure that the inspection procedures are observed and consistently monitored. A well-functioning quality system should comprise an organisational structure, clear processes and procedures, including standard operating procedures to be followed by inspectors when performing their tasks, clearly defined details of the inspectors' duties and responsibilities and ongoing training requirements, as well as adequate resources and mechanisms which aim to eliminate non-compliance.

(16) This Regulation should apply from the same date as Commission Directive (EU) 2017/1572[(3)],

HAS ADOPTED THIS REGULATION:

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CHAPTER I

GENERAL PROVISIONS

Article 1

Subject matter

This Regulation specifies the principles and guidelines of good manufacturing practice for investigational medicinal products for human use the manufacture or import of which requires an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014 and lays down arrangements for inspections of manufacturers in relation to compliance with good manufacturing practice in accordance with Article 63(4) of that Regulation.

Article 2

Definitions

For the purposes of this Regulation, the following definitions shall apply:

(1) ‘manufacturer’ means any person engaged in activities for which an authorisation is required in accordance with Article 61(1) of Regulation (EU) No 536/2014;

(2) ‘third country manufacturer’ means any person established in a third country and engaged in manufacturing operations in that third country;

(3) ‘product specification file’ means a reference file containing, or referring to files containing, all the information necessary to draft detailed written instructions on processing, packaging, quality control, testing and batch release of an investigational medicinal product and to perform batch certification;

(4) ‘validation’ means action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

CHAPTER II

GOOD MANUFACTURING PRACTICE

Article 3

Conformity with good manufacturing practice

1 The manufacturer shall ensure that manufacturing operations are carried out in accordance with good manufacturing practice for investigational medicinal products specified in this Regulation and subject to an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014.

2 When importing an investigational medicinal products, the holder of the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014 shall ensure that the products have been manufactured by applying quality standards at least equivalent to those laid down by

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this Regulation and in Regulation (EU) No 536/2014, and that the third country manufacturer is authorised or entitled to in accordance with the laws of that country to manufacture that investigational medicinal products in that third country.

Article 4

Compliance with clinical trial authorisation

1 The manufacturer shall ensure that all manufacturing operations for investigational medicinal products are carried out in accordance with the documentation and information provided by the sponsor pursuant to Article 25 of Regulation (EU) No 536/2014 and as authorised in accordance with the procedure laid down in Chapter II, or if documentation and information was subsequently amended, in Chapter III of abovementioned Regulation (EU) No 536/2014.

2 The manufacturer shall regularly review his manufacturing methods in the light of scientific and technical progress and experience gained by the sponsor during the development of the investigational medicinal product.

The manufacturer shall inform the sponsor of his reviews of the manufacturing methods.

Where, following a review, an amendment to the clinical trial authorisation is necessary, the application for the amendment shall be submitted in accordance with Article 16 of Regulation (EU) No 536/2014 where the change to the clinical trial is a substantial modification or the amendment shall be carried out in accordance with Article 81(9) of that Regulation where the change to the clinical trial is not a substantial modification.

Article 5

Pharmaceutical quality system

1 The manufacturer shall establish, implement and maintain effective organised arrangements to ensure that the investigational medicinal products are of the quality required for their intended use. Those arrangements shall include the establishment of a good manufacturing practice and a quality control.

2 Senior management and personnel from different departments shall participate in the establishment of the pharmaceutical quality system.

Article 6

Personnel

1 At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to ensure that the investigational medicinal products are of the quality required for their intended use.

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