Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (Text with EEA relevance)

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(Text with EEA relevance)

THE EUROPEAN COMMISSION,

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

Having regard to 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[(1)], and in particular the first paragraph of Article 47 thereof,

Whereas:

(1) Commission Directive 2003/94/EC[(2)] applies to both medicinal products for human use and investigational medicinal products for human use.

(2) In accordance with Article 63(1) of Regulation (EU) No 536/2014 of the European Parliament and of the Council[(3)] the Commission is empowered to adopt a delegated act laying down principles of good manufacturing practice for investigational medicinal products for human use. It is therefore necessary to adapt the provisions of Directive 2003/94/EC by deleting the references to investigational medicinal products for human use.

(3) The definition of a pharmaceutical quality system and some terminology should be updated to reflect the international developments or the actual usage of that terminology of inspectors and manufacturers.

(4) All medicinal products for human use manufactured or imported into the Union, including medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice. However, for the manufacturer to be able to comply with those principles and guidelines, cooperation between the manufacturer and the marketing authorisation holder, when they are different legal entities, is necessary. The obligations of the manufacturer and marketing authorisation holder vis-à-vis each other should be defined in a technical agreement between them.

(5) The manufacturer of medicinal products has to ensure that they are fit for their intended use, comply with the requirements of the marketing authorisation and do not place

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patients at risk due to inadequate quality. To achieve this quality objective reliably the manufacturer must implement a comprehensively designed and correctly implemented pharmaceutical quality system incorporating good manufacturing practice and quality risk management.

(6) In order to ensure conformity with the principles and guidelines of good manufacturing practice, it is necessary to lay down detailed provisions on inspections by the competent authorities and on certain obligations of manufacturer.

(7) It is necessary to ensure that all medicinal products available on the EU territory comply with the same quality standards, therefore medicinal products imported into the Union should be manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down in the Union.

(8) In order to ensure the consistent application of the principles of good manufacturing practice, manufacturers of medicinal products for human use and inspectors should consider the guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC. However, for advanced therapy medicinal products, the guideline referred in Article 5 of Regulation (EC) No 1394/2007[(4)] should be applied. Principles and guidelines of good manufacturing practice for medicinal products for human use should be set out in relation to quality management, personnel, premises and equipment, documentation, production, quality control, outsourced operations, complaints, product recall, and self-inspections. As regards the advanced therapy medicinal products those principles and guidelines should be adapted to the specific characteristic of those products in accordance with the risk-based approach.

(9) Since many of the provisions of Directive 2003/94/EC need to be adjusted, for the sake of clarity, that Directive should be repealed.

(10) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Subject-matter

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture or import requires the authorisation referred to in Article 40 of Directive 2001/83/EC.

Article 2

Definitions

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

(1) ‘manufacturer’ means any person engaged in activities for which the authorisation referred to in Article 40(1) and (3) of Directive 2001/83/EC is required;

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(2) '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;

(3) 'good manufacturing practice' means the part of the quality assurance which ensures that medicinal products are consistently produced, imported and controlled in accordance with the quality standards appropriate to their intended use.

Article 3

Inspections

1 By means of the repeated inspections referred to in Article 111(1a) of Directive 2001/83/EC, the Member States shall ensure that manufacturers authorised in accordance with Article 40(1) and (3) of Directive 2001/83/EC respect the principles and guidelines of good manufacturing practice laid down by this Directive.

Member States shall also take into account the compilation, published by the Commission, of Union procedures on inspections and exchange of information.

2 For the interpretation of the principles and guidelines of good manufacturing practice, manufacturers and the competent authorities shall take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC. In the case of advanced therapy medicinal products, the guidelines on good manufacturing practice specific to advanced therapy medicinal products referred to in Article 5 of Regulation (EC) No 1394/2007 on advanced therapy medicinal products shall be taken into account.

3 Member States shall establish and implement in their inspectorates a properly designed quality system that shall be complied with by inspectorates' personnel and management. The quality system shall be updated as appropriate.

Article 4

Conformity with good manufacturing practice

1 The Member States shall ensure that the manufacturing operations are carried out by manufacturers in accordance with good manufacturing practice and with the manufacturing authorisation. This provision shall also apply to medicinal products intended only for export.

2 For medicinal products imported from third countries, the Member States shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down in the Union and that such products have been manufactured by manufacturers duly authorised to do so.

Article 5

Compliance with marketing authorisation

1 The Member States shall ensure that all manufacturing or import operations for medicinal products subject to a marketing authorisation are carried out by manufacturers in accordance with the information provided in the application for that marketing authorisation.

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2 The Member States shall oblige the manufacturer to regularly review his manufacturing methods in light of scientific and technical progress.

If a variation to the marketing authorisation dossier is necessary, the variation shall take place by the arrangements established in accordance with Article 23b of Directive 2001/83/EC.

Article 6

Pharmaceutical quality system

The Member States shall ensure that the manufacturers establish, implement and maintain an effective pharmaceutical quality system, involving the active participation of the senior management and the personnel of the different departments.

Article 7

Personnel

1 The manufacturer shall be obliged to have at each manufacturing or import site a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the objective of the pharmaceutical quality system.

2 The duties of the managerial and supervisory staff, including the qualified persons referred to in Article 48 of Directive 2001/83/EC, 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.

3 The staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibility correctly.

4 The personnel shall receive initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance and good manufacturing practice.

5 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.

Article 8

Premises and equipment

1 As regards the premises and manufacturing equipment the manufacturer shall be obliged to ensure that they are located, designed, constructed, adapted and maintained to suit the intended operations.

2 The Member States shall require that the premises and manufacturing equipment are laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.

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

Article 9

Documentation

1 The manufacturer shall be obliged to establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed. The documentation system shall ensure data quality and integrity. 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 for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch to be traced.

The manufacturer shall be required to retain the batch documentation for at least 1 year after the expiry date of the batches to which it relates or at least 5 years after the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

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

Article 10

Production

1 The Member States shall ensure that the manufacturers carry out the different production operations in accordance with pre-established instructions and procedures and in accordance with good manufacturing practice. Adequate and sufficient resources shall be made available by the manufacturer for the in-process controls. All process deviations and product defects shall be documented and thoroughly investigated.

2 The manufacturers shall be required to take appropriate technical and organisational measures to avoid cross contamination and mix-ups.

3 Any new manufacturing or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly revalidated.