EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

Consultation document

Commission Implementing Act on Principles and guidelines on good manufacturing practices for medicinal products for human use, pursuant to the first paragraph of Article 47 of Directive 2001/83/EC

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.

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

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] provides in 1st paragraph of Article 47 an obligation for the Commission to adopt principles and guidelines of good manufacturing practice for medicinal products for human use in the form of a Directive.

This delegation is the legal basis for 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].

However, 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[3] 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.

It is therefore necessary that Directive 2003/94/EC is repealed and replaced by a Delegated Act on principles and guidelines of good manufacturing practice for investigational medicinal products with its legal basis as Article 63(1) of Regulation (EU) No 536/2014 and a new Implementing Directive on principles and guidelines of good manufacturing practice for medicinal products for human use with 1st paragraph of Article 47 of Directive 2001/83/EC as its legal basis.

With this public consultation, the Directorate-General for Health and Food Safety seeks the view of stakeholders regarding the content of a new Implementing Directive on principles and guidelines of good manufacturing practice for medicinal products for human use.

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

Manufacturers have to comply with the principles and guidelines of good manufacturing practice for medicinal products for human use. Compliance with good manufacturing practice for medicinal products for human use is instrumental in ensuring the quality of the products.

Currently, Directive 2003/94/EC provides the principles and guidelines for manufacturing practice for medicinal products for human use.

As good manufacturing practice for 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 medicinal products for human use.

[1] OJ L 311, 28.11.2001, p. 67.

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

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

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

2.1. Inspections

By means of the repeated inspections referred to in Article 111(1a), the Member States shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by the new Implementing Directive concerned by this consultation.

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

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, published by the Commission in the EudraLex, Volume 4.

2.2. Conformity with good manufacturing practice

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

For medicinal products imported from third countries, the importer 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 by the Union.

In addition, an importer of medicinal products shall ensure that such products have been manufactured by manufacturers duly authorised to do so.

2.3. Compliance with marketing authorisation

The manufacturer shall ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as granted by the competent authorities.

The manufacturer shall regularly review his manufacturing methods in light of scientific and technical progress.

If a variation to the marketing authorisation dossier is necessary, the application for modification shall be submitted to the competent authorities.

2.4. Pharmaceutical quality system

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

2.5. 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 the 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 initial and on-going 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.

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.

2.6. 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 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.

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

2.7. 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 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 for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch.

For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall 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 at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer to another storage system, against loss or damage or data, and audit trails shall be maintained.

2.8. 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 and organisational measures shall be taken to avoid cross contamination and mix-ups.

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 re-validated.

2.9. 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.

That 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 packaging materials and the testing of intermediate and finished products.

For medicinal products, including those imported from third countries, contract laboratories may be used if authorised by written contract, see below in section 2.10, and point (b) of Article 20 of Directive 2001/83/EC.

During the final control of the finished product before its release for sale or distribution, the quality control system 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 and the conformity of the product to its specifications, including the final finished pack.

Samples of each batch of finished medicinal product shall be retained for at least one year after the expiry date.

Unless a longer period is required under the law of the Member State of manufacture, samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained 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.

2.10. Work contracted out

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

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 and shall submit to inspections carried out by competent authorities pursuant to Article 111 of Directive 2001/83/EC.

2.11. Complaints and product recall

The manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or an abnormal restriction on supply and, in so far as possible, indicate the countries of destination.

Any recall shall be made in accordance with the requirements referred to in Article 123 of Directive 2001/83/EC.

2.12. Self-inspection

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

2.13. Advanced therapy medicinal products

The requirements provided for in the Directive shall be adapted to the specific characteristics of advanced therapy 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; the consultation can be found here:

http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm.