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

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

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], as last amended by Commission Directive 2003/63/EC [2], and in particular Article 47 thereof,

Whereas:

(1) All medicinal products for human use manufactured or imported into the Community, including medicinal products intended for export, are to be manufactured in accordance with the principles and guidelines of good manufacturing practice.

(2) Those principles and guidelines are set out in Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use [3].

(3) Article 13(3) of 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 [4] requires that detailed guidance be drawn up, in accordance with the guidelines on good manufacturing practice, on the elements to be taken into account when evaluating investigational medicinal products for human use with the object of releasing batches within the Community.

(4) It is therefore necessary to extend and adapt the provisions of Directive 91/356/EEC to cover good manufacturing practice of investigational medicinal products.

(5) Since most of the provisions of Directive 91/356/EEC need to be adjusted, for the sake of clarity that Directive should be replaced.

(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 the manufacturer.

(7) All manufacturers should operate an effective quality management system of their manufacturing operations, which requires the implementation of a pharmaceutical quality assurance system.

(8) Principles and guidelines of good manufacturing practice should be set out in relation to quality management, personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self-inspection.

(9) In order to protect the human beings involved in clinical trials and to ensure that investigational medicinal products can be traced, specific provisions on the labelling of those products are necessary.

(10) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use, set up under Article 121 of Directive 2001/83/EC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Scope

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 40 of Directive 2001/83/EC and in respect of investigational medicinal products for human use whose manufacture requires the authorisation referred to in Article 13 of Directive 2001/20/EC.

Article 2

Definitions

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

1. 'medicinal product' means any product as defined in Article 1(2) of Directive 2001/83/EC;

2. 'investigational medicinal product' means any product as defined in Article 2(d) of Directive 2001/20/EC;

3. 'manufacturer' means any person engaged in activities for which the authorisation referred to in Article 40(1) and (3) of Directive 2001/83/EC or the authorisation referred to in Article 13(1) of Directive 2001/20/EC is required;

[1] OJ L 311, 28.11.2001, p. 67.
[2] OJ L 159, 27.6.2003, p. 46.
[3] OJ L 193, 17.7.1991, p. 30.
[4] OJ L 121, 1.5.2001, p. 34.

4. 'qualified person' means the person referred to in Article 48 of Directive 2001/83/EC or in Article 13(2) of Directive 2001/20/EC;

5. 'pharmaceutical quality assurance' means the total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use;

6. 'good manufacturing practice' means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use;

7. 'blinding' means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;

8. 'unblinding' means the disclosure of the identity of a blinded product.

Article 3

Inspections

1. By means of the repeated inspections referred to in Article 111(1) of Directive 2001/83/EC and by means of the inspections referred to in Article 15(1) of Directive 2001/20/EC, the Member States shall ensure that manufacturers 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 Community procedures on inspections and exchange of information.

2. For the interpretation of the principles and guidelines of good manufacturing practice, the 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 'Guide to good manufacturing practice for medicinal products and for investigational medicinal products'.

Article 4

Conformity with good manufacturing practice

1. The manufacturer shall ensure that 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.

2. For medicinal products and investigational 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 Community.

In addition, an importer of medicinal products shall ensure that such products have been manufactured by manufacturers duly authorised to do so. An importer of investigational medicinal products shall ensure that such products have been manufactured by a manufacturer notified to the competent authorities and accepted by them for that purpose.

Article 5

Compliance with marketing authorisation

1. 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 accepted by the competent authorities.

In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information provided by the sponsor pursuant to Article 9(2) of Directive 2001/20/EC as accepted by the competent authorities.

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

If a variation to the marketing authorisation dossier or an amendment to the request referred to in Article 9(2) of Directive 2001/20/EC is necessary, the application for modification shall be submitted to the competent authorities.

Article 6

Quality assurance system

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

Article 7

Personnel

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

2. 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.

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, and, where appropriate, the particular requirements for the manufacture of investigational medicinal products.

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

2. 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.

3. 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.

Article 9

Documentation

1. 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 and the changes introduced during the development of an investigational medicinal product to be traced.

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.

For an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation.

2. 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 on to another storage system, against loss or damage of data, and audit trails shall be maintained.

Article 10

Production

1. 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.

2. Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups. In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.

3. For medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated.

4. For investigational medicinal products, the manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development. At least 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.

Article 11

Quality control

1. 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 the starting materials and packaging materials and the testing of intermediate and finished products.

2. For medicinal products, including those imported from third countries, contract laboratories may be used if authorised in accordance with Article 12 of this Directive and point (b) of Article 20 of Directive 2001/83/EC.

For investigational medicinal products, the sponsor shall ensure that the contract laboratory complies with the content of the request referred to in Article 9(2) of Directive 2001/20/EC, as accepted by the competent authority. When the products are imported from third countries, analytical control shall not be mandatory.

3. During the final control of the finished product before its release for sale or distribution or for use in clinical trials, 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.

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

For an investigational medicinal product, sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished product batch shall be retained 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.

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 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.

Article 12

Work contracted out

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

2. 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.

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

4. The contract-acceptor shall comply with the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities pursuant to Article 111 of Directive 2001/83/EC and Article 15 of Directive 2001/20/EC.

Article 13

Complaints, product recall and emergency unblinding

1. In the case of medicinal products, 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 abnormal restriction on supply and, in so far as is 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. In the case of investigational medicinal products, the manufacturer shall, in cooperation with the sponsor, implement a system for 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.

In the case of investigational medicinal products, all trial sites shall be identified and, in so far as is possible, the countries of destination shall be indicated.

In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised medicinal product.

3. The sponsor shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall as referred to in paragraph 2. The sponsor shall ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

Article 14

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 action subsequently taken.

Article 15

Labelling

In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.

Article 16

Repeal of Directive 91/356/EEC

Directive 91/356/EEC is repealed.

References to the repealed Directive shall be construed as references to this Directive.

Article 17

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 30 April 2004 at the latest. They shall forthwith communicate to the Commission the text of the provisions and correlation table between those provisions and the provisions of this Directive.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. The Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 18

Entry into force

This Directive shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

Article 19

Addressees

This Directive is addressed to the Member States.

Done at Brussels, 8 October 2003.

For the Commission

Erkki LIIKANEN

Member of the Commission