COMMISSION DIRECTIVE

of 13 June 1991

laying down the principles and guidelines of good manufacturing practice for medicinal products for human use

(91/356/EEC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], as last amended by Directive 89/381/EEC [2], and in particular Article 19a thereof,

Whereas all medicinal products for human use manufactured or imported into the Community, including medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice;

Whereas, in accordance with national legislation, Member States may require compliance with these principles of good manufacturing practice during the manufacture of products intended for use in clinical trials;

Whereas the detailed guidelines mentioned in Article 19a of Directive 75/319/EEC have been published by the Commission after consultation with the pharmaceutical inspection services of the Member States in the form of a *'Guide to good manufacturing practice for medicinal products';*

Whereas it is necessary that all manufacturers should operate an effective quality management of their manufacturing operations, and that this requires the implementation of a pharmaceutical quality assurance system;

Whereas officials representing the competent authorities should report on whether the manufacturer complies with good manufacturing practice and that these reports should be communicated upon reasoned request to the competent authorities of another Member State;

Whereas the principles and guidelines of good manufacturing practice should primarily concern personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self inspection;

Whereas the principles and guidelines envisaged by this Directive are in accordance with the opinion of the Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector set up by Article 2b of Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [3], as last amended by Directive 89/341/EEC [4],

HAS ADOPTED THIS DIRECTIVE:

CHAPTER I

GENERAL PROVISIONS

Article 1

This Directive lays down the principles and guidelines of good manufacturing practice for medicinal products for human use whose manufacture requires the authorization referred to in Article 16 of Directive 75/319/EEC.

Article 2

For the purposes of this Directive, the definition of medicinal products set out in Article 1 (2) of Council Directive 65/65/EEC [5], shall apply.

In addition,

— 'manufacturer' shall mean any holder of the authorization referred to in Article 16 of Directive 75/319/EEC,

— 'qualified person' shall mean the person referred to in Article 21 of Directive 75/319/EEC,

— 'pharmaceutical quality assurance' shall mean the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use,

— 'good manufacturing practice' shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.

[1] OJ No L 147, 9. 6. 1975, p. 13.
[2] OJ No L 181, 28. 6. 1989, p. 44.
[3] OJ No L 147, 9. 6. 1975, p. 1.
[4] OJ No L 142, 25. 5. 1989, p. 11.
[5] OJ No 22, 9. 2. 1965, p. 369/65.

Article 3

By means of the repeated inspections referred to in Article 26 of Directive 75/319/EEC, the Member States shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by this Directive.

For the interpretation of these principles and guidelines of good manufacturing practice, the manufacturers and the agents of the competent authorities shall refer to the detailed guidelines referred to in Article 19a of Directive 75/319/EEC. These detailed guidelines are published by the Commission in the '*Guide to good manufacturing practice for medicinal products*' and in its Annexes (Office for Official Publications of the European Communities, *The rules governing medicinal products in the European Community,* Volume IV).

Article 4

The manufacturer shall ensure that the manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorization.

For medicinal products imported from third countries, the importer shall ensure that the medicinal products have been manufactured by manufacturers duly authorized and conforming to good manufacturing practice standards, at least equivalent to those laid down by the Community.

Article 5

The manufacturer shall ensure that all manufacturing operations subject to an authorization for marketing are carried out in accordance with the information given in the application for marketing authorization as accepted by the competent authorities.

The manufacturer shall regularly review their manufacturing methods in the light of scientific and technical progress. When a modification to the marketing authorization dossier is necessary, the application for modification must be submitted to the competent authorities.

CHAPTER II

PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE

Article 6

Quality management

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

Article 7

Personnel

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

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

3. Staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibilities correctly.

4. Personnel shall receive initial and continuing training including 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 include procedures relating to health, hygiene 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. Lay out, design and operation must aim to minimize the risk of errors and 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 intended to be used for manufacturing operations which are critical for the quality of the products shall be subjected to appropriate qualification.

Article 9

Documentation

1. The manufacturer shall have a system of documentation based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations that they perform. Documents shall be clear, free from errors and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be available, together with specific documents

for the manufacture of each batch. This set of documents shall make it possible to trace the history of the manufacture of each batch. 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 22 (2) of Directive 75/319/EEC whichever is the longer.

2. When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall have validated the systems by proving that the data will be appropriately stored during the anticipated period of storage. Data stored by these systems shall be made readily available in legible form. The electronically stored data shall be protected against loss or damage of data (e.g. by duplication or back-up and transfer onto another storage system).

Article 10

Production

The different production operations shall be carried out according to 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.

Appropriate technical and/or organizational measures shall be taken to avoid cross contamination and mix-ups.

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

Article 11

Quality control

1. The manufacturer shall establish and maintain a quality control department. This department shall be placed under the authority of a person having the required qualifications and shall be independent of the other departments.

2. The quality control department shall have at its disposal one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of starting materials, packaging materials and intermediate and finished products testing. Resorting to outside laboratories may be authorized in accordance with Article 12 of this Directive after the authorization referred to in Article 5b of Directive 75/319/EEC has been granted.

3. During the final control of finished products before their release for sale or distribution, in addition to analytical results, the quality control department shall take into account essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the products to their specifications (including the final finished pack).

4. Samples of each batch of finished products shall be retained for at least one year after the expiry date. Unless in the Member States of manufacture a longer period is required, samples of starting materials (other than solvents, gases and water) used shall be retained for at least two years after the release of the product. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. All these samples shall be maintained at the disposal of the competent authorities.

For certain medicinal products manufactured individually or in small quantities, or when their storage could raise special problems, other sampling and retaining conditions may be defined in agreement with the competent authority.

Article 12

Work contracted out

1. Any manufacturing operation or operation linked with the manufacture which is carried out under contract, shall be the subject of a written contract between the contract giver and the contract acceptor.

2. The contract shall clearly define the responsibilities of each party and in particular the observance of good manufacturing practice by the contract acceptor and the manner in which the qualified person responsible for releasing each batch shall undertake his full responsibilities.

3. The contract acceptor shall not subcontract any of the work entrusted to him by the contract giver without the written authorization of the contract giver.

4. The contract acceptor shall respect the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities as provided for by Article 26 of Directive 75/319/EEC.

Article 13

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 the medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The competent authority shall be informed by the manufacturer of any defect that could result in a recall or abnormal restriction on the supply. In so far as possible, the countries of destination shall also be indicated. Any recall shall be made in accordance with the requirements referred to in Article 33 of Directive 75/319/EEC.

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 of such self-inspections and any subsequent corrective action shall be maintained.

CHAPTER III

FINAL PROVISIONS

Article 15

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 1 January 1992. They shall forthwith inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 16

This Directive is addressed to the Member States.

Done at Brussels, 13 June 1991.

For the Commission

Martin BANGEMANN

Vice-President