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