II

(Acts whose publication is not obligatory)

COMMISSION

COMMISSION DIRECTIVE

of 19 July 1991

modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products

(91/507/EEC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (1), as last amended by Directive 89/341/EEC (2),

Having regard to Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens (3), and in particular Article 5 thereof,

Having regard to Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals (4), and in particular Article 7 thereof,

Having regard to Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulations or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma (5), and in particular Article 6 thereof,

Whereas following the adoption of Directives 89/342/EEC, 89/343/EEC and 89/381/EEC, it is necessary to amend the Annex to Directive 75/318/EEC in order to lay down special requirements for the testing of immunological medicinal products, radiopharmaceuticals and medicinal products derived from human blood or human plasma;

Whereas it is further necessary to adapt to technical progress the existing requirements laid down in the Annex to Directive 75/318/EEC, in particular with regard to the special nature of medicinal products obtained through processes mentioned in list A and in the first indent of list B of the Annex of Council Directive 87/22/EEC (6);

Whereas the provisions of this Directive are in accordance with the opinion of the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Medicinal Products Sector established pursuant to Article 2b of Directive 75/318/EEC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The text of the Annex to Directive 75/318/EEC is hereby replaced by the text of the Annex to this Directive.

(1) OJ No L 147, 9. 6. 1975, p. 1.
(2) OJ No L 142, 25. 5. 1989, p. 11.
(3) OJ No L 142, 25. 5. 1989, p. 14.
(4) OJ No L 142, 25. 5. 1989, p. 16.
(5) OJ No L 181, 28. 6. 1989, p. 44.
(6) OJ No L 15, 17. 1. 1987, p. 38.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive, save Part 2, paragraph A, point 3.3 of the Annex, no later than 1 January 1992 ; they shall bring into force the provisions necessary to comply with Part 2, paragraph A, point 3.3 of the Annex no later than 1 January 1995. They shall forthwith inform the Commission thereof.

2. When the Member States adopt these provisions, the provisions shall contain a reference to this Directive or shall be accompanied by such a reference when they are published in official form. The arrangements for this reference shall be decided by the Member States.

Article 3

This Directive is addressed to Member States.

Done at Brussels, 19 July 1991.

For the Commission

Martin BANGEMANN

Vice-President

ANNEX

INTRODUCTION

The particulars and documents accompanying an application for marketing authorization pursuant to Article 4 of Council Directive 65/65/EEC (1) shall be presented in four parts, in accordance with the requirements set out in this Annex and taking account of the guidance published by the Commission in *The rules governing medicinal products in the European Community,* Volume II : *Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community.*

In assembling the dossier for application for marketing authorization, applicants shall take into account the Community guidelines relating to the quality, safety and efficacy of medicinal products published by the Commission in *The rules governing medicinal products in the European Community,* Volume III and its supplements : *Guidelines on the quality, safety and efficacy of medicinal products for human use.*

All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product. Moreover, in order to monitor the benefit/risk assessment after marketing authorization has been granted, any change to the data in the dossier, any new information not in the original application and all pharmacovigilance reports, shall be submitted to the competent authorities.

The general sections of this Annex give the requirements for all categories of medicinal products ; they are supplemented by sections containing additional special requirements for radiopharmaceuticals and for biological medicinal products, such as vaccines, serums, toxins, allergen products, medicinal products derived from human blood or plasma. The additional special requirements for biological medicinal products are also applicable to medicinal products obtained through processes mentioned in List A and the first indent of List B of the Annex to Directive 87/22/EEC.

Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC (2).

(1) OJ No 22, 9. 2. 1965, p. 369/65.
(2) OJ No L 358, 18. 12. 1986, p. 1.

PART 1

SUMMARY OF THE DOSSIER

A. Administrative data

The medicinal product which is the subject of the application shall be identified by name and name of the active ingredient(s), together with the pharmaceutical form, the method of administration, the strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active ingredient(s)), and where relevant the name and address of the importer.

The applicant shall identify the number of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorization as defined in Article 16 of Council Directive 75/319/EEC (1), together with a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 4a of Directive 65/65/EEC as approved by Member States and a list of countries in which an application has been submitted.

B. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 4a of Directive 65/65/EEC.

In addition the applicant shall provide samples or mock-ups of the packaging, labels and package leaflets for the medicinal product concerned.

C. Expert reports

In accordance with Article 2 of Directive 75/319/EEC, expert reports must be provided on the chemical, pharmaceutical and biological documentation, the pharmacotoxicological documentation and the clinical documentation respectively.

The expert report shall consist of a critical evaluation of the quality of the product and the investigations carried out on animals and human beings and bring out all the data relevant for evaluation. It shall be worded so as to enable the reader to obtain a good understanding of the properties, quality, the proposed specifications and control methods, the safety, the efficacy, the advantages and disadvantages of the product.

All important data shall be summarized in an appendix to the expert report, whenever possible including report formats in tabular or in graphic form. The expert report and the summaries shall contain precise cross references to the information contained in the main documentation.

Each expert report shall be prepared by a suitably qualified and experienced person. It shall be signed and dated by the expert, and attached to the report shall be brief information about the educational background, training and occupational experience of the expert. The professional relationship of the expert to the applicant shall be declared.

(1) OJ No L 147, 9. 6. 1975, p. 13.

PART 2

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL TESTING OF MEDICINAL PRODUCTS

All the test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures; results of the validation studies shall be provided.

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

A. Qualitative and quantitative particulars of the constituents

The particulars and documents which must accompany applications for marketing authorization, pursuant to point 3 of Article 4 (2) of Directive 65/65/EEC shall be submitted in accordance with the following requirements.

1. *Qualitative particulars*

1.1. 'Qualitative particulars' of all the constituents of the medicinal product shall mean the designation or description of:

— the active ingredient(s),

— the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,

— the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products — capsules, gelatine capsules, rectal capsules, etc.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the product.

1.2. In the context of a radiopharmaceutical kit, which is to be radiolabelled after supply by the manufacturer, the active ingredient is considered to be that part of the formulation which is intended to carry or bind the radionuclide. Details of the source of the radionuclide shall be stated. In addition, any compounds essential for the radiolabelling shall be stated.

In a generator, both mother and daughter radionuclides are to be considered as active ingredients.

2. The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions of point 3 of Article 4 (2) of Directive 65/65/EEC:

— in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC (1) of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products.

(1) OJ No L 11, 14. 1. 1978, p. 18.