COMMISSION OF THE EUROPEAN COMMUNITIES

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Extension of the Pharmaceutical Directives to Medicinal Products not yet covered

(Communication from the Commission)

Com 697

INFORMATION POLICY SHEET

EXTENSION OF PHARMACEUTICAL DIRECTIVES TO MEDICINAL PRODUCTS NOT YET COVERED

1. PEOPLE OR GROUPS AFFECTED.

The primary objective of this package of proposals is to extend the scope of the Community pharmaceutical directives to cover immunological medicinal products, medicinal products derived from human blood, radiopharmaceuticals and non-proprietary (generic) medicinal products and as such it will be of particular interest to the manufacturers of the products concerned .
In addition, the package contains a series of general amendments to the pharmaceutical directives relating to information for patients about medicines, manufacturing standards and exports to the third world, which will be of interest to all pharmaceutical manufacturers, to other health professionals and to consumers.

2. PREPARING THE PROPOSALS.

a) Innovative aspects

This package of proposals would bring immunological medicinal products (sera, vaccines, toxins, allergens etc.) blood products and radio-pharmaceuticals within the scope of the Community Directives on medicinal products for the first time.

b) Consultation by the Commission's services

This package of proposals results not only from a commitment in the White Paper on the Internal Market but also from a mandate unanimously conferred to the Commission by the Council in Article 5 of Directive 87/22/EEC. All the Member States support the objectives of the package the details of which have been drafted in close consultation with national and industry experts and representatives of other interested groups. These consultations will continue during the elaboration of the very detailed implementing directives on the testing of each of the categories of medicines concerned.

3. PARTICULAR INFORMATION ACTIVITIES.

Press release for specialist journals in medical/pharmaceutical field.
Summary mention in more general press releases dealing with the implementation of the internal market.

TIMETABLE ANNEX

Given the importance of attaining the White Paper target date of 1992 for the realisation of the internal market and the public health importance of the categories of product covered by these proposals, it is desirable that these proposals should come into effect by 1 January 1991 at the latest. To this end, the following timetable is proposed :

Opinion of the Economic and Social Committee	30 April 1988
Opinion of the European Parliament	30 September 1988
Adoption of a common position by Council	30 April 1989
Conclusion of cooperation procedure with European Parliament and adoption of directives by the Council	31 December 1989
Entry into force of the directives	1 January 1991

EXTENSION OF PHARMACEUTICAL DIRECTIVES
TO MEDICINAL PRODUCTS NOT YET COVERED

PROPOSAL FOR A COUNCIL DIRECTIVE

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

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PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

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PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for medicinal products derived from human blood

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PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for radiopharmaceuticals

EXTENSION OF PHARMACEUTICAL DIRECTIVES TO MEDICINAL PRODUCTS NOT YET COVERED

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EXTENSION OF PHARMACEUTICAL DIRECTIVES TO MEDICINAL PRODUCTS NOT YET COVERED

EXPLANATORY MEMORANDUM

1. INTRODUCTION

When it adopted Directive 75/319/EEC[1] on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, the Council considered that the provisions of that Directive and those of the earlier Directive 65/65/EEC[2], "although appropriate, are inadequate for vaccines, toxins and serums, proprietary medicinal products based on human blood or blood constituents, proprietary medicinal products based on radio-active isotopes and homeopathic proprietary medicinal products". Article 34 of Directive 75/319/EEC therefore excludes these products from the scope of the Community Directives.

The inclusion of these categories of products within Community rules relating to medicinal products was identified by the Commission as a priority in the legislative programme annexed to the White Paper on the Completion of the Internal Market. This work was given further impetus following the adoption of Council Directive 87/22/EEC of 22 December 1986[3], Article 5 of which requires the Commission to present proposals within one year to harmonise, along the lines of Directive 75/319/EEC, the conditions for authorizing the manufacture and placing on the market of the proprietary medicinal products excluded by Article 34, and of the veterinary medicinal products referred to in Article 2(2) of Directive 81/851/EEC[4], in view of in particular, the safety problems arising in production and use.

This package of proposals is presented as a first step towards the implementation of that mandate. It covers medicinal products based on radio-active isotopes (radiopharmaceuticals); vaccines, toxins, serums and allergens (immunological products); and medicinal products derived from human blood. In addition, the Commission is proposing several detailed but important changes to the general Community rules relating to medicinal

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1 OJ N° L 147 of 9.6.1975, p. 13
2 OJ N° 22 of 9.2.1965, p. 369/65
3 OJ N° L 15 of 17.1.1987, p. 38
4 OJ N° L 317 of 6.11.1981, p. 1

products. These changes are intended in particular to follow up the Resolution of the European Parliament of 13 June 1986 on the Export of Pharmaceutical Products to the Third World (Banotti Resolution) and the Council Conclusions of 15 May 1987 on improvement in the use of proprietary medicinal products by consumers[5].

These proposals have been drafted in extremely close collaboration with national experts, using the Committee for Proprietary Medicinal Products, and in particular its working party on the quality of medicines, and the ad hoc biotechnology/pharmacy working party. There have also been detailed consultations with the pharmaceutical industry, and with groups representative of the manufacturers of the particular products concerned; radiopharmaceuticals, vaccines, allergens etc. For the proposal on products derived from human blood, an ad hoc meeting of national experts was convened. In addition, the services of the Commission met with various interested groups to discuss different aspects of the package.

The Commission is aware that these proposals do not entirely cover the mandate conferred upon it by the Council. Work on a proposal to bring homeopathic medicinal products within the scope of the Community pharmaceutical directives has met with certain difficulties, arising from the fact that in certain Member States the principles of homeopathy are officially recognised, while in others they are merely tolerated. The Commission therefore intends to continue consultations with interested parties, and will present appropriate proposals on these products as a part of the general proposals for a definitive system for the free movement of medicinal products within the Community, which are scheduled for 1989. In addition, because of the complexity of the legislative provisions involved, and the limited resources available within the Commission, it has not been possible to bring forward proposals to cover veterinary vaccines and veterinary radiopharmaceuticals at the present time. Nevertheless, in cooperation with the Committee for Veterinary Medicinal Products, the Commission has begun a survey of the relevant national provisions, and it intends to bring forward appropriate proposals in 1988, as part of a general review of the Directives relating to veterinary medicinal products[6].

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5 OJ N° C 178 of 7.7.87, p. 2

6 Directives 81/851/EEC and 81/852/EEC of 28 September 1981, OJ N° L 317 of 6.11.1981, p. 1 and p. 16 respectively

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2. THE GENERAL PROPOSAL TO AMEND DIRECTIVES 65/65/EEC, 75/318/EEC and 75/319/EEC

This proposal has four major objectives: to extend the scope of the Directives to cover non-proprietary medicinal products; to improve the information available to consumers about medicinal products; to lay down certain provisions governing the export of medicinal products; and to improve the guarantees of the quality of all medicinal products manufactured within the Community, irrespective of their intended destination. In addition, this proposal contains a series of incidental amendments to the basic Directives which result from the extension of the Directives to cover radiopharmaceuticals, immunological products and products derived from human blood.

2.1. Non-proprietary medicinal products

At the present time, the Community pharmaceutical Directives only apply to proprietary medicinal products, that is "ready-prepared medicinal products placed on the market under a special name and in a special pack". However, in recent years, increasing interest has been given to so-called 'generic' pharmaceuticals, which are copies of established products and are marketed under the international non-proprietary name, either with or without a logo or trade name representing their own manufacturer. In many cases, for commercial reasons, these products are marketed with a special name or in a special pack, and are thus covered by the Community Directives. However, in other cases, doubts may arise. In order to resolve any ambiguities in the present situation, the Commission is proposing that the scope of the directives be extended to cover all industrially produced ready-made medicinal products which are placed on the market in a pharmaceutical form which may be used without further processing. This change will fill any gap which may exist in the current provisions and will enable the manufacturers of the products concerned to benefit from a wider Community market. It will also provide substantial guarantees for patients that these products are manufactured in accordance with the same strict requirements as other categories of medicinal products. As a consequence of this change, and in order to avoid confusion, the Commission is proposing that henceforth Community pharmaceutical legislation should simply refer to 'medicinal products" rather than "proprietary medicinal products'.

2.2. Information for patients

Article 6 of Directive 75/319/EEC has already harmonised the basic information which should be contained in patient information leaflets. However, it is up to the Member States to decide whether or not a leaflet should be included with the packaging of a medicinal product. In its conclusions of 15 May 1987, the Council unanimously requested the Commission to begin studying the possibility of making more systematic the use, and more legible and intelligible the content of patient information leaflets accompanying medicinal products, in particular 'over the counter products', the purpose being to encourage the secure and appropriate use of medicinal products and to satisfy the consumer's wish to be properly informed. In addition, the Commission and the Member States were requested to exchange their experience and consult widely with interested circles, and the Commission was requested to prepare a report for the Council, accompanied, if appropriate, by suitable proposals.

At the present time, there are substantial variations in the practice of Member States in making information available to patients about medicinal products. In certain Member States, patients are provided with information leaflets as a matter of course, while in others leaflets are provided only rarely. However, a number of Member States are reviewing their policies on this matter. For its part, the Commission intends to begin a series of studies on the problems of presenting information for patients with a view to presenting appropriate proposals to the Council in 1990.

Many of the problems associated with the introduction of patient information leaflets result from the difficulties inherent in presenting complex medical and scientific information in a manner which is comprehensible to patients and is not unduly alarmist. These problems are particularly difficult to resolve in the case of the more potent medicines which are only available on medical prescription. However, in the case of those relatively simple medicinal products which are intended to be purchased directly by the consumer without a medical prescription and which are used for the relief of minor self-limiting ailments, these difficulties are less apparent. Indeed, in the latter case, it would appear that clear and comprehensive information is the indispensable corollary of responsible self-medication. The Commission is therefore proposing that the inclusion of a patient information leaflet, established in accordance with Article 6 of Directive 75/319/EEC, should be obligatory in the packaging of medicinal

products which may be obtained without a medical prescription unless all the information required by that Article can be included on the packaging of the product, in which case the leaflet would be redundant.

2.3. Exports of medicinal products

Following the Resolution of the European Parliament of 13 June 1986 on the export of pharmaceutical products to the third world, the Commission undertook a series of consultations with Member States in order to determine how best to respond to the concerns of the Parliament. In addition, the Commission has necessarily had to take into consideration the need to ensure that any proposals were administratively feasible and limited as to their territorial effect.

In accordance with current Community pharmaceutical legislation, all manufacturers of medicinal products must be in possession of a manufacturing authorization. To avoid any possible ambiguity on this point, the Commission is proposing that Article 16 of Directive 75/319/EEC should explicitly state that this manufacturing authorization is required even though all the products manufactured are intended for export. Thus, the existing provisions of Community legislation, and the new requirements discussed in section 2.4. below will apply. At the request either of the exporting manufacturer or the authorities of the recipient country, the Member State concerned will issue a certificate in accordance with the arrangements agreed by the World Health Organisation that the manufacturer is authorised to manufacture medicinal products. In addition, the Member States will annex to the certificate the approved summary of the characteristics of the product. In accordance with Articles 4a and 4b of Directive 65/65/EEC as amended by Directive 83/570/EEC[7], these summaries must be established by Member States for all medicinal products authorised for use on their territories by May 1990 at the latest, well before the date the proposal is scheduled to come into effect. This summary will enable the competent authorities in the recipient country to verify rapidly the authorised conditions of use for a product in the exporting country. Conversely, the absence of a summary will immediately alert the authorities of the recipient country to the fact that the medicine is not authorised for use in the exporting Member State, and they will be able to draw the appropriate conclusions in the light of the explanations given by the company and the prevailing conditions in the recipient country.

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7 OJ N° L 332 of 28.11.1983, p. 1

At the present time, the Member States are obliged by Article 33 of Directive 75/319/EEC to notify the Committee for Proprietary Medicinal Products of any decision to suspend or withdraw a medicinal product. In the future, the Commission is proposing that these notifications should also be made available to WHO for the information of third countries. However, relatively few decisions to suspend or withdraw marketing authorisations are made by the competent authorities. In many cases, the firm concerned unilaterally withdraws the product from the market in advance of possible regulatory action. In such cases, the regulatory authorities of other countries may not be aware that the product has been withdrawn from the market. To remedy this situation, the Commission is proposing that any firm which unilaterally withdraws a product from the market should be obliged to notify the competent authority of the Member State concerned, who would then be obliged to inform the CPMP, and in appropriate cases, the WHO.

2.4. Obligations on manufacturers

At the present time, authorization to manufacture medicinal products is granted by the competent authorities of the Member State in which a manufacturer is established, who are responsible for ensuring that the manufacturer satisfies the legal requirements laid down. The Commission is proposing to supplement these provisions by introducing into the Directives a specific requirement for manufacturers to comply with the principles of good manufacturing practice for medicinal products. The detailed requirements of good manufacturing practice would be laid down in a specific Directive to be adopted by the so-called regulatory committee procedure, with the agreement of a qualified majority of the Member States. In fact, work on the drafting of this Directive is already at an advanced stage, and it is envisaged that it would be completed in time to enable the specific Directive to come into force at the same time as the framework proposal.

2.5. Incidental Provisions

The proposal also contains certain provisions of an incidental nature which result from the extension of the scope of the Directives. First, it is thought necessary to introduce a definition of the word "therapeutic" into Directive 65/65/EEC to make it clear that the concepts of "therapeutic effects" or "therapeutic results" cover not only the use of a medicinal product for the prevention or treatment of disease but also its use for other medicinal purposes, such as diagnosis. Secondly, the requirements

concerning the labelling of medicinal products, leaflets and approved product summaries are being amended to provide that in appropriate cases information should be given on the safe disposal of the product. This is particularly important in the case of radio-active medicinal products and certain biologically active products, but the problem may also arise in other cases.

3. THE THREE PROPOSALS TO EXTEND THE DIRECTIVES TO RADIOPHARMACEUTICALS, IMMUNOLOGICAL PRODUCTS AND MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD

3.1. The General Approach

The three proposals to extend the pharmaceutical Directives to cover radiopharmaceuticals, immunological products and medicinal products derived from human blood are based upon a common approach. In each case, the proposal sets out a series of definitions of the products concerned and establishes the principle that these products may be placed on the market only after an authorization has been granted by the competent authority of the Member State(s) in which they are to be marketed. In addition, the proposals lay down certain fundamental requirements for each of these categories of products. However, it is envisaged that the Council will delegate to the Commission the power to adopt the detailed changes which are necessary to Council Directive 75/318/EEC relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products to take account of the particular characteristics of these products. In order to implement these changes, the Commission will act in cooperation with the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Proprietary Medicinal Products Sector, created by Directive 87/19/EEC, using the so-called regulatory Committee procedure, which requires the approval of a qualified majority of the Member States for the adoption of the measures by the Commission (Procedure III variant a of Council Decision 87/373/EEC of 13 July 1987[8] laying down the procedures for the exercise of implementing powers conferred on the Commission). Work on the preparation of the detailed changes to the testing requirements is in progress and it is envisaged that this will continue during 1988, in parallel with the discussions on these proposals, so that the changes can be formally adopted immediately after the Council approves the Directives and come into effect at the same time.

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8 OJ N° L 197 of 18.7.1987, p. 33

3.2. Particular requirements for immunological products

The proposal on immunological products covers a variety of products of biological origin, including immune sera, vaccines, toxins and allergens. The provisions of Directives 65/65/EEC and 75/319/EEC will apply in full to these products, although certain changes will need to be made to the detailed testing requirements of Directive 75/318/EEC and certain changes are made to the provisions governing the declaration of the qualitative and quantitative composition of these products to take account of their biological origin. There is however one area where the regulation of immunological products requires a somewhat different approach from that used with other categories of medicinal products.

This relates to the requirements for the manufacture of vaccines. In the case of all immunological products, it is important that manufacturers should be able to attain high levels of batch-to-batch consistency in their manufacturing operations, and the proposal contains specific provisions to this effect. However, in the case of vaccines, this is particularly important, since a failure to attain consistency in the biological activity of the vaccine may reduce or remove the protection it offers against disease. For this reason, several Member States operate batch release systems. Thus, samples from each manufacturing batch of a vaccine must be submitted for testing by a state laboratory and the particular batch may only be placed on the market once the laboratory has authorised its release. The Commission is proposing that Member States should be permitted to continue these arrangements for live vaccines, vaccines used for the primary immunization of infants or vaccines used in public health immunization programmes. A list of the vaccines concerned is included in an annex to the proposal. The proposal also provides for the mutual recognition by other Member States of the first batch release control conducted within the Community thus preventing any unnecessary repetition of the tests within the Community.

3.3. Particular requirements for products derived from human blood

Within the Member States of the Community, human blood for the manufacture of blood products is collected by voluntary donation. The national blood collection services are generally organised on a non-profit-making basis, and because of the special nature of the products involved, the commercial manufacture and marketing of blood products is either prohibited or severely restricted. Each Member State has tended to aim for self-sufficiency in the supply of blood and blood products. The Commission

considers that it would be desirable to replace this objective of national self-sufficiency with the objective of self-sufficiency at the Community level at least for medicinal products derived from human blood.

The proposal applies to medicinal products based on blood constituents which are industrially prepared by public or private establishements, in particular to albumin, coagulating factors and immunoglobulins of human origin. It does not cover whole blood, plasma or blood cells. The proposal establishes the principle that all manufacturers must satisfy the provisions of the general pharmaceutical Directives, in particular as regards manufacturing and marketing authorizations. In addition, the proposal recognises the substantial amount of work which has already been done on blood products by the Council of Europe, in particular through the European Agreement on the Exchange of Therapeutic Substances of Human Origin[9], to which the Community is a party, and its recommendations on the measures to be taken in the selection and testing of donors.

Like vaccines, many blood products are subject in the Member States to compulsory testing on individual batches by a laboratory before the release of the batch is authorised. The objective of such tests is to ensure that the products are free of viral contaminants such as AIDS or hepatitis. The Directive therefore authorises Member States to retain such tests, although there should be no unnecessary repetition of them. The details of the tests which are required to be conducted, either by the manufacturer or the state laboratory, will be specified in the detailed provisions for the testing requirements of these products.

3.4. Particular requirements for radiopharmaceuticals

Radiopharmaceuticals are medicinal products based upon radionuclides (radioactive isotopes) which are mainly used for diagnostic purposes. Because many of the radionuclides in common use have relatively short half-lives, radiopharmaceuticals in their ready to use form are often prepared in a hospital shortly before their administration to the patient. A generator is used to produce a daughter radionuclide which is then combined with a carrier presented in the form of a kit to ensure that the radionuclide is transported to the target organ. In Case 35/85 TISSIER[10], the Court of Justice ruled that both the generator and the kit must be considered as medicinal products, and the proposal therefore envisages that marketing authorization should be required for both. In addition,

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9 OJ N° L 207 of 30.7.1986, p. 1
10 Judgement of 20 March 1986, not yet reported

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marketing authorization is required for radiopharmaceuticals which are industrially produced in their ready-to-use form. However, a marketing authorization is not required for a radiopharmaceutical if it is reconstituted in an approved health care establishment by qualified personnel from authorized generators, precursors or kits in accordance with the manufacturers' instructions.

From the public health point of view, the principle factor which differentiates radiopharmaceuticals from other medicinal products is their radioactivity. The proposal makes special reference to the relevant Euratom regulations on radioprotection. In addition, the proposal contains detailed provisions on the labelling of the different layers of packaging of radiopharmaceuticals in accordance with international standards. In accordance with international practice, the information to be labelled on the vial containing the radioactive isotope is given in code, rather than verbal form. Detailed rules are also laid down concerning the information which must be given to health personnel about the safe use and disposal of the product.

3.5. Transitional and final provisions

In accordance with the provisions of Articles 8A and 8C of the European Economic Community Treaty as amended by the Single European Act, the Commission requests Member States to take the necessary measures to conform to these Directives before 1 January 1991; after that date, all new products must comply with these Directives; regarding products which are already on the market on the date of entry into force, the proposals allow Member States the additional period up to 31 December 1992 in order to review and ensure that these products comply with the Directives. Having taken account of the structure and distribution of affected companies, it does not appear, given the information available to the Commission, that the harmonisation proposed would have an effect on the economies of the countries concerned.

4. CONCLUSIONS

The present package of proposals constitutes a further step toward the realisation of an internal market for the pharmaceutical sector by 1992 with a uniformly high level of protection of public health throughout the Community in accordance with the provisions of Article 100 A 3 of the European Economic Community Treaty as amended by the Single European Act. The following additional proposals remain outstanding:

1988 amendments to the veterinary medicines directives
1989 proposals for a definitive system for the free movement of medicinal products for human use within the Community
1990 information for doctors and patients about medicinal products
1990 conditions of delivery of medicinal products to patients

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PROPOSAL FOR A COUNCIL DIRECTIVE

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 A thereof,

Having regard to the proposal from the Commission[1],

In cooperation with the European Parliament[2],

Having regard to the opinion of the Economic and Social Committee[3],

Whereas the essential aim of any rules governing the production, distribution or use of medicinal products must be to ensure a high level of protection of public health,

Whereas the Directives on the approximation of the laws relating to proprietary medicinal products must be adapted to scientific progress and take account of the experience obtained since their adoption;

Whereas in its conclusions of 15 May 1987 on improvement in the use of proprietary medicinal products by the consumer[4] the Council considered that the system for leaflets accompanying proprietary medicinal products, for human consumption, on the market in the Community should be improved;

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4 OJ N° C 178, 7.7.1987, p. 2

Whereas the guarantees of the quality of medicinal products manufactured within the Community should be maintained by requiring compliance with the principles of good manufacturing practice for medicinal products irrespective of the final destination of the products;

Whereas the Commission should be empowered to define in detail the principles of good manufacturing practice for medicinal products in close cooperation with the Committee for Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers in the Proprietary Medicinal Products Sector;

Whereas having regard to the Resolution of the European Parliament of 13 June 1986 on the export of pharmaceutical products to the Third World, measures should be taken to improve the provision of information for third countries about the conditions of use of medicinal products within the Member States;

Whereas the scope of Directive 65/65/EEC[5] as last amended by Directive 87/21/EEC[6] and Second Directive 75/319/EEC[7] as last amended by Directive 83/570/EEC[8] on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products should be extended to cover other ready-made medicinal products which do not comply with the definition of proprietary medicinal products,

Whereas in the Community directives relating to medicinal products the word "therapeutic" should be understood as covering all the medicinal purposes for which a medicinal product may be administered to human beings or animals, which may be to prevent or treat disease, to make a medical diagnosis or to restore, correct or modify physiological functions,

HAS ADOPTED THIS DIRECTIVE:

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5 OJ No 22, 9.2.1965, p. 369/65
6 OJ No L 15, 17.1.1987, p. 36
7 OJ No L 147, 9.6.1975, p. 13
8 OJ No L 332, 28.11.1983, p. 1

Article 1

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products is hereby amended as follows:

1. In Article 1, the following points 4 and 5 are inserted:

"4 Ready-made medicinal product

Any medicinal product prepared in advance which does not comply with the definition of proprietary medicinal products and which is marketed in a pharmaceutical form which may be used without further industrial processing.

5 Therapeutic

The medicinal purpose for which a medicinal product is administered to human beings or animals, as specified in point 2."

2. Article 2 is amended as follows:

"The provisions of Chapters II to V shall apply to medicinal products for human use intended to be placed on the market in Member States in the form of proprietary medicinal products or ready-made medicinal products to the exclusion of medicinal products which are prepared extemporaneously in an individual pharmacy for individual patients."

3. In the title, preamble and Chapters II to V all references to "proprietary medicinal product" or to "proprietary product" shall be replaced by "medicinal product".

4. In Article 4a, the following point 6.6. is inserted:

"6.6. special precautions for disposal of unused product or waste materials, if appropriate".

5. In Article 13, the following point 9 is inserted:

"9. special precautions for disposal of unused product or waste materials, if any".

6. In Article 14, the following fifth indent is added:

" - manufacturer's batch number".

Article 2

In 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, all references to "proprietary medicinal product" or to "proprietary product" shall be replaced by "medicinal product".

Article 3

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 is hereby amended as follows:

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1. In Article 4, the text of paragraph b is amended as follows:

"(b) may submit the medicinal product, its active principles or other constituent materials for testing by a State laboratory or by a laboratory designated for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with point 7 of Article 4, second paragraph, of Directive 65/65/EEC are satisfactory".

2. In Article 6, the last paragraph is replaced by the following:

"The inclusion of a package leaflet in the packaging of 'over the counter medicinal products' shall be obligatory unless all the information required by this Article can be conveyed on the packaging itself.

For the purposes of this Article, 'over the counter medicinal products' are those medicinal products which are placed on the market with a view to their direct sale to the public, without the need for a medical prescription, for use in the relief of minor illnesses not requiring a medical diagnosis.

In the case of other medicinal products, Member States may require that a leaflet be included with the packaging.

Within two years of the date of the adoption of this Directive, the Commission shall present to the Council a report on the possibility of making more systematic the use, and more legible and intelligible the content, of package leaflets, accompanied if appropriate by suitable proposals."

3. In Article 16, the first paragraph is amended as follows:

"1. Member States shall take all appropriate measures to ensure that the manufacture of medicinal products is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export."

4. The following Article 16a is inserted:

"Article 16a

1. At the request of the manufacturer or the authorities of a recipient country, Member States shall certify that a manufacturer of medicinal products is in possession of the authorization referred to in paragraph 1 of Article 16. When issuing such certificates, Member States shall have regard to the prevailing administrative arrangements of the World Health Organization.

2. The summary of the product characteristics approved by the Member State in accordance with Article 4b of Directive 65/65/EEC shall be annexed to the certificate.

3. When the manufacturer is not in possession of a marketing authorisation in the country of origin, he must provide the authorities responsible for establishing the certificate referred to in paragraph 1 with a declaration explaining why no marketing authorisation has ben obtained."

5. In Article 17, the following paragraph d is inserted:

"(d) demonstrate that he complies with the principles of Good Manufacturing Practices for medicinal products laid down by Community law."

6. The following Article 17a is inserted:

"Article 17a

The principles of good manufacturing practices for medicinal products referred to in Article 17, paragraph d shall be adopted, in the form of a directive addressed to Member States, in accordance with the procedure laid down in Article 2c of Directive 75/318/EEC."

7. In the second paragraph of Article 26, the following subparagraph d is inserted:

"(d) report periodically to the competent authorities on whether the manufacturer complies with the principles of good manufacturing practices for medicinal products laid down by Community law".

8. In Article 30, the following second paragraph is inserted:

"Upon request, Member States shall forthwith communicate the reports referred to in subparagraph d of the second paragraph of Article 26 to the competent authorities of another Member State. If, after considering the reports, the Member State receiving the reports considers that it cannot accept the conclusions reached by the competent authority of the Member State in which the report was established, it shall inform the competent authority concerned of its reasons and may request that a further inspection of the manufacturing establishment be carried out. If the Member States concerned are unable to reach agreement, they shall forthwith inform the Commission."

9. The following paragraphs 2 and 3 are added to Article 33:

"2. The person responsible for the marketing of a medicinal product shall be obliged to notify the Member States forthwith of any action taken by him to suspend the marketing of a product or to withdraw a product from the market, together with the reasons for such action. Member States shall ensure that this information is brought to the attention of the Committee forthwith.

3. Member States shall ensure that appropriate information about actions taken pursuant to paragraphs 1 and 2 which may effect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization with a copy to the Committee."

10. The first paragraph of Article 34 is hereby amended as follows:

"This directive shall apply to medicinal products for human use in the form of proprietary medicinal products or ready-made medicinal products to the exclusion of medicinal products which are prepared extemporaneously in an individual pharmacy for individual patients."

11. With the exception of the first paragraph of Article 34, all references to "proprietary medicinal product" or to "proprietary product" shall be replaced by medicinal product.

Article 4

1. Member States shall take the measures necessary to comply with this directive not later than 1 January 1991. They shall forthwith inform the Commission thereof.

2. Requests for marketing authorization lodged after the time-limit referred to in the first paragraph must comply with the provisions of this Directive.

3. Articles 1, 2 and 3 of this Directive, where relevant, shall be progressively extended to existing medicinal products before 31 December 1992.

Article 5

This Directive is addressed to the Member States.

PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 A thereof,

Having regard to the proposal from the Commission[1],

In cooperation with the European Parliament[2],

Having regard to the opinion of the Economic and Social Committee[3],

Whereas disparities in the provisions laid down by law, regulation or administrative action by Member States may hinder trade in immunological products within the Community,

Whereas the essential aim of any rules governing the production, distribution or use of medicinal products must be to ensure a high level of protection of public health,

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Whereas the provisions laid down by Directive 65/65/EEC[4] as last amended by Directive 87/21/EEC[5] and Second Directive 75/319/EEC[6] as last amended by Directive 83/570/EEC[7] on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, although appropriate, are inadequate for immunological medicinal products consisting of vaccines, toxins or serums and allergens,

Whereas in accordance with Article 5 of Directive 87/22/EEC[8] on the approximation of national provisions relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology, the Commission is required to submit proposals to harmonise, along the lines of Directive 75/319/EEC the conditions for authorizing the manufacture and placing on the market of immunological medicinal products before 22 December 1987;

Whereas, before an authorization to market an immunological product can be granted, the manufacturer must demonstrate his ability to attain batch-to-batch consistency;

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4 OJ No 22, 9.2.1965, p. 369/65
5 OJ No L 15, 17.1.1987, p. 36
6 OJ No L 147, 9.6.1975, p. 13
7 OJ No L 332, 28.11.1983, p. 1
8 OJ No L 15, 17.1.1987, p. 38

Whereas the Commission should be empowered to adopt any necessary changes in the requirements for the testing of proprietary medicinal products set out in the Annex to Directive 75/318/EEC[9] of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, as last amended by Directive 87/19/EEC[10] of 22 December 1986 to take account of the special nature of immunological medicinal products in close cooperation with 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;

HAS ADOPTED THIS DIRECTIVE:

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9 JO No L 147, 9.6.1975, p. 1
10 OJ No L 15, 17.1.1987, p. 31

Article 1

1. In derogation from Article 34 of Directive 75/319/EEC, and subject to the provisions of this Directive, Directives 65/65/EEC and 75/319/EEC shall apply to immunological medicinal products consisting of vaccines, toxins and serums and allergen products for human use.

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

   - "immunological medicinal product" shall mean a product of biological origin which is intended to effect the immune system and which is used in the diagnosis, prevention or treatment of disease. Included are vaccines, toxins and serums and allergens,

   - "allergen product" shall mean any product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergising agent,

   - vaccins, toxins and sera shall have the meaning assigned to them in the Annex of Directive 75/319/EEC.

Article 2

1. The quantitative particulars of an immunological medicinal product shall be expressed by mass or by international units or by units of biological activity or by protein content as appropriate to the product concerned.

2. In Directives 65/65/EEC and 75/319/EEC the expressions "qualitative and quantitative particulars of the constituents" shall also include particulars relating to biological activity or to protein content and "qualitative and quantitative composition" shall include the composition of the product expressed in terms of biological activity or of protein content.

3. Whenever the name of an immunological medicinal product is expressed, the common or scientific name of the active constituents shall also be included.

Article 3

In addition to the information referred to in Article 4a of Directive 65/65/EEC, the summary of product characteristics referred to in point 9 of the second paragraph of Article 4 of Directive 65/65/EEC shall contain the following information in respect of immunological products:

- under point 5.4, information about any special precautions to be taken by persons handling the immunological medicinal product and persons administering it to patients, together with any precautions to be taken by the patient.

Article 4

1. Member States shall ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch-to-batch consistency. To this end the competent authority may submit samples from up to five in total of the bulk and/or finished product batches for testing by a state laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 4 of Directive 75/319/EEC, or after a marketing authorisation has been granted.

2. For the purpose of implementing Article 8 of Directive 65/65/EEC and Article 27 of Directive 75/319/EEC, Member States may require persons responsible for marketing immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 22 of Directive 75/319/EEC.

3. Where it considers it necessary in the interests of public health, a Member State may require persons responsible for marketing the live vaccines, vaccines used in the primary immunization of infants, or vaccines used in public health immunization programmes, which are listed in the Annex to this Directive to submit to a competent authority samples from each batch of the bulk and/or finished product for examination by a state laboratory or a laboratory designated for that purpose before release onto the market, unless the competent authority of another Member State has previously examined the batch in question and declared it to be in conformity with the approved specification. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples. The Annex to this Directive containing the list of vaccines which may be submitted for examination prior to release may be amended in accordance with the procedure laid down in Article 2c of Directive 75/318/EEC.

Article 5

Any amendments which are necessary in the testing requirements for medicinal products set out in the Annex to Directive 75/318/EEC to take account of the extension of the scope of Directives 65/65/EEC and 75/319/EEC to cover immunological medicinal products shall be adopted in accordance with the procedure laid down in Article 2c of Directive 75/318/EEC. Any such amendments shall come into effect on the same date as this Directive.

Article 6

1. Member States shall take the necessary measures to comply with this Directive not later than 1 January 1991. They shall forthwith inform the Commission thereof.

2. Requests for marketing authorization for products covered by this Directive lodged after the time-limit referred to in the first paragraph must comply with the provisions of this Directive.

3. This Directive shall be progressively extended to the existing immunological medicinal products before 31 December 1992.

Article 7

This Directive is addressed to the Member States.

ANNEX

LIST OF VACCINES REFERRED TO IN ARTICLE 4(3)

Vaccines for human use, presented or used for the prophylaxis of the following diseases:

Cholera
Diphtheria
Hepatitis
Influenza
Measles
Mumps
Pertussis
Polio
Rabies
Rubella
Tetanus
Tuberculosis
Typhoid
Yellow Fever

PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC
on the approximation of provisions laid down by law, regulation
or administrative action relating to proprietary medicinal products
and laying down additional provisions for
medicinal products derived from human blood

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 A thereof,

Having regard to the proposal from the Commission[1],

In cooperation with the European Parliament[2],

Having regard to the opinion of the Economic and Social Committee[3],

Whereas disparities in the provisions laid down by law, regulation or administrative action by Member States may hinder trade in medicinal products derived from human blood within the Community;

Whereas the essential aim of any rules governing the production, distribution or use of medicinal products must be to ensure a high level of protection of public health;

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Whereas the provisions laid down by Directive 65/65/EEC[4] as last amended by Directive 87/21/EEC[5] and Second Directive 75/319/EEC[6] as last amended by Directive 83/570/EEC[7] on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, although appropriate, are inadequate for medicinal products derived from human blood;

Whereas in accordance with Article 5 of Directive 87/22/EEC[8] on the approximation of national provisions relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology, the Commission is required to submit proposals to harmonise, along the lines of Directive 75/319/EEC the conditions for authorizing the manufacture and placing on the market of medicinal products derived from human blood before 22 December 1987;

Whereas the European Community entirely supports the efforts of the Council of Europe to promote voluntary and non-remunerated blood donation to attain self-sufficiency throughout the Community in the supply of blood products, and to ensure the respect of ethical principles in trade of therapeutic substances of human origin;

Whereas the rules designed to guarantee the quality, safety and efficacy of medicinal products derived from human blood must be applied in the same manner to both public and private establishments;

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4 OJ No 22, 9.2.1965, p. 369/65
5 OJ No L 15, 17.1.1987, p. 36
6 OJ No L 147, 9.6.1975, p. 13
7 OJ No L 332, 28.11.1983, p. 1
8 OJ No L 15, 17.1.1987, p. 38

Whereas, before an authorization to market a medicinal product derived from human blood can be granted, the manufacturer must demonstrate his ability to guarantee batch-to-batch consistency and the absence of viral contamination;

Whereas the Commission should be empowered to adopt any necessary changes in the requirements for the testing of proprietary medicinal products set out in the Annex to Directive 75/318/EEC[9] of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, as last amended by Directive 87/19/EEC[10] of 22 December 1986 to take account of the special nature of medicinal products derived from human blood in close cooperation with 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,

HAS ADOPTED THIS DIRECTIVE:

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9 JO No L 147, 9.6.1975, p. 1
10 OJ No L 15, 17.1.1987, p. 31

Article 1

1. In derogation from Article 34 of Directive 75/319/EEC, and subject to the provisions of this Directive, Directives 65/65/EEC and 75/319/EEC shall apply to medicinal products based on blood constituents which are prepared industrially by public or private establishments, hereinafter referred to as "medicinal products derived from human blood"; these medicinal products include, in particular, albumin, coagulating factors and immunoglobulins of human origin.

2. This directive shall not apply to whole blood, to plasma or to blood cells of human origin.

3. Nothing in the present directive shall in any way derogate from Council Decision 86/346/EEC[11] accepting, in the name of the Community, the European Agreement relating to the exchange of therapeutic substances of human origin.

Article 2

1. The quantitative particulars of a medicinal product derived from human blood shall be expressed by mass or by international units or by units of biological activity as appropriate to the product concerned.

2. In Directives 65/65/EEC and 75/319/EEC the expressions "qualitative and quantitative particulars of the constituents" shall include particulars relating to biological activity and "qualitative and quantitative composition" shall include the composition of the product expressed in terms of biological activity.

3. Whenever the name of a medicinal product derived from human blood is expressed, the common or the scientific name of the active constituents shall also be included.

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11 OJ No L 207, 30.7.1986, p. 1

Article 3

In order to prevent the transmission of infectious diseases, the Member States shall take into consideration the measures recommended within the framework of the Council of Europe and the World Health Organisation in particular for the selection and testing of blood donors.

Article 4

1. Member States shall ensure that the manufacturing processes used in the manufacture of medicinal products derived from human blood are properly validated, attain batch-to-batch consistency and guarantee the absence of viral contaminants. To this end the competent authority may submit samples from up to five in total of the bulk and/or finished product batches for testing by a state laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 4 of Directive 75/319/EEC, or after a marketing authorisation has been granted.

2. For the purpose of implementing Article 8 of Directive 65/65/EEC and Article 27 of Directive 75/319/EEC, Member States may require persons responsible for marketing medicinal products derived from human blood to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 22 of Directive 75/319/EEC.

3. Where it considers it necessary in the interests of public health, a Member State may require persons responsible for marketing medicinal products derived from human blood to submit to a competent authority samples from each batch of the bulk and/or finished product for examination by a state laboratory or a laboratory designated for that purpose before release onto the market, unless the competent authority of another Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 5

Any amendments which are necessary in the testing requirements for medicinal products set out in the Annex to Directive 75/318/EEC to take account of the extension of the scope of Directives 65/65/EEC and 75/319/EEC to cover medicinal products derived from human blood shall be adopted in accordance with the procedure laid down in Article 2(c) of Directive 75/318/EEC. Any such amendments shall come into effect on the same date as this Directive.

Article 6

1. Member States shall take the necessary measures to comply with this Directive not later than 1 January 1991. They shall forthwith inform the Commission thereof.

2. Requests for marketing authorization for products covered by this Directive lodged after the time-limit referred to in the first paragraph must comply with the provisions of this Directive.

3. This Directive shall be progressively extended to the existing medicinal products derived from human blood referred to in Article 1, paragraph 1 before 31 December 1992.

Article 7

This Directive is addressed to the Member States.

PROPOSAL FOR A COUNCIL DIRECTIVE

extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for radiopharmaceuticals

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 A thereof,

Having regard to the proposal from the Commission[1],

In cooperation with the European Parliament[2],

Having regard to the opinion of the Economic and Social Committee[3],

Whereas disparities in the provisions currently laid down by law, regulation or administrative action by Member States may hinder trade in radiopharmaceuticals within the Community;

Whereas the essential aim of any rules governing the production, distribution or use of medicinal products must be to ensure a high level of protection of public health;

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Whereas the provisions laid down by Directive 65/65/EEC[4] as last amended by Directive 87/21/EEC[5] and Second Directive 75/319/EEC[6] as last amended by Directive 83/570/EEC[7] on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, although appropriate are inadequate for radiopharmaceuticals;

Whereas in accordance with Article 5 of Directive 87/22/EEC[8] on the approximation of national provisions relating to the placing on the market of high technology medicinal products, particularly those derived from biotechnology, the Commission is required to submit proposals to harmonise, along the lines of Directive 75/319/EEC, the conditions for authorizing the manufacture and placing on the market of radiopharmaceuticals before 22 December 1987;

Whereas in the case of radiopharmaceuticals authorization should be required for industrially prepared radiopharmaceuticals, generators, kits and precursor radiopharmaceuticals; whereas, however, a separate authorization should not be required for radiopharmaceuticals in their finished form which are made up exclusively from authorized kits, generators or precursor radiopharmaceuticals in health care establishments;

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4 OJ No 22, 9.2.1965, p. 369/65
5 OJ No L 15, 17.1.1987, p. 36
6 OJ No L 147, 9.6.1975, p. 13
7 OJ No L 332, 28.11.1983, p. 1
8 OJ No L 15, 17.1.1987, p. 38

Whereas the Commission should be empowered to adopt any necessary changes in the requirements for the testing of proprietary medicinal products set out in the Annex to Directive 75/318/EEC[9] of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, as last amended by Directive 87/19/EEC[10] of 22 December 1986 to take account of the special nature of radiopharmaceuticals in close cooperation with 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;

Whereas any rules governing radiopharmaceuticals must take into account the provisions of Directive 84/466/Euratom[11] of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment; whereas account should also be taken of Directive 80/836/Euratom[12] which amends the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation as last amended by Council Directive 84/467/Euratom[13] of 3 September 1984, the objective of which is to prevent the exposure of workers or patients to excessive or unnecessarily high levels of ionizing radiation, and in particular of Article 5c thereof, which requires prior authorisation for the addition of radioactive substances to medicinal products as well as for the importation of such medicinal products,

HAS ADOPTED THIS DIRECTIVE:

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9 OJ No L 147, 9.6.1975, p. 1
10 OJ No L 15, 17.1.1987, p. 31
11 OJ No L 265, 5.10.1984, p. 1
12 OJ No L 246, 17.9.1980, p. 1
13 OJ No L 265, 5.10.1984, p. 4

Article 1

1. In derogation from Article 34 of Directive 75/319/EEC and subject to the provisions of this Directive, the provisions of Directives 65/65/EEC and 75/319/EEC shall apply to radiopharmaceuticals for human use, excluding radionuclides in the form of sealed sources.

2. For the purposes of this directive, the following definitions shall apply:

   - 'radiopharmaceutical' shall mean any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose,

   - 'generator' shall mean any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be removed by elution and used in a radiopharmaceutical,

   - 'kit' shall mean any industrial preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration,

   - 'precursor radiopharmaceutical' shall mean any other industrially produced radionuclide for the radio-labelling of another substance prior to administration.

3. Nothing in this directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.

Article 2

The authorization referred to in Article 3 of Directive 65/65/EEC shall be required for generators, kits, precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals. However, authorization shall not be required for a radiopharmaceutical in its ready for use form, if the radiopharmaceutical is prepared by an approved person in an approved health care establishment exclusively from authorized generators, kits or precursor radiopharmaceuticals in accordance with the manufacturer's instructions.

Article 3

In addition to the requirements set out in Article 4 of Directive 65/65/EEC, an application for authorization to market a generator shall also contain the following information and particulars:

- a general description of the system together with a detailed description of the components of the system which may effect the composition or quality of the daughter nucleid preparation,

- qualitative and quantitative particulars of the eluate.

Article 4

For radiopharmaceuticals, in addition to the information referred to in Article 4a of Directive 65/65/EEC, the summary of product characteristics referred to in point 9 of the second paragraph of Article 4 of Directive 65/65/EEC shall contain the following additional points 7 and 8:

"7. full details of radiation dosimetry;

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8. Additional detailed instructions for preparation, and where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready to use pharmaceutical will conform with its specifications."

Article 5

The outer carton and the tin of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the following provisions:

a) The label on the shielding shall include the particulars mentioned in Article 13 of Directive 65/65/EEC. In addition, the labelling on the shielding shall explain in full the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules or, for liquids, the number of millilitres in the container;

b) The vial shall be labelled with the following information:

- the name or code of the medicinal product including the name or chemical symbol of the radionuclide
- the batch identification and expiry date
- the international symbol for radioactivity
- the name of the manufacturer
- the amount of radioactivity as specified under a) above

Article 6

1. Member States shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, generators, kits or precursor radiopharmaceuticals. The text of this leaflet shall be established in accordance with the provisions of Article 6 of Directive 75/319/EEC and shall contain all the information referred to therein. In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the product and special precautions for the disposal of the container and its unused contents.

2. Member States shall permit the use of user information leaflets which have been established in more than one of the languages of the Community provided that the information contained in all the language versions of the leaflet is identical.

Article 7

Any amendments which are necessary in the testing requirements for medicinal products set out in the Annex to Directive 75/318/EEC to take account of the extension of the scope of Directives 65/65/EEC and 75/319/EEC to cover radiopharmaceuticals shall be adopted in accordance with the procedure laid down in Article 2 c of Directive 75/318/EEC. Any such amendments shall come into effect on the same date as this Directive.

Article 8

1. Member States shall take the necessary measures to comply with this Directive not later than 1 January 1991. They shall forthwith inform the Commission thereof.

2. Requests for marketing authorization for products covered by this Directive lodged after the time-limit referred to in the first paragraph must comply with the provisions of this Directive.

3. This Directive shall be progressively extended to existing medicinal products covered by this Directive before 31 December 1992.

Article 9

This Directive is addressed to the Member States.

FINANCIAL STATEMENT

RELATING TO THE EXTENSION OF THE COMMUNITY PHARMACEUTICAL DIRECTIVES TO MEDICINAL PRODUCTS NOT YET COVERED

1. BUDGET HEADINGS

N° A 2511 (travelling expenses of members of committees)

N° B 7750 (biological standardization/contract for provision of services with the European Pharmacopoeia)

2. LEGAL BASIS

- Article 100 A of the EEC Treaty
- Mandate from the Council: Article 5 paragraph 2 of Directive 87/22/EEC (O.J. L 15 of 17.01.1987)

3. DESCRIPTION OF THE PROJECT

3.1. General objective

To include within Community law all categories of industrially prepared medicinal products hitherto not covered, as foreseen by the White Paper on the Completion of the Internal Market, timetable annex, p. 17.

3.2. Specific objective

Elaboration of specific standards. Harmonization of the general principles (Council framework directives) and the specific rules (future Commission directives) necessary to guarantee the quality, safety and efficacy of three additional categories of medicinal products for human use:

- immunological products (in particular vaccines)
- radiopharmaceuticals (radio-isotopes)
- blood products of human origin

3.3. Second specific objectives: elaboration of standard reference preparations

Physico-chemical tests are not sufficient to guarantee the quality of biological medicinal products (vaccines, blood derivates etc.). In addition, it is important to guarantee the absence of viral contamination (AIDS, hepatitis B). The elaboration of biological preparations which can serve as reference standards at European, even world-level, is therefore indispensable, both for the national testing laboratories and for the manufacturers of biological medicinal products.

4. JUSTIFICATION OF THE PROJECT

4.1. Justification of the type of project proposed

The very considerable technical specificity of these new categories of medicinal products requires substantial changes to the testing standards applicable to other medicinal products already covered by Community legislation.

The elaboration of international biological reference preparations requires collaborative studies between the major national testing laboratories, then the adoption of a common standard and finally the stockage and distribution of this standard by a reference centre. The European Pharmacopoeia (Council of Europe) is the European institution best suited for this role.

4.2. Interest of the project at Community level

The realisation of the internal market implies that all categories of industrially produced medicinal products must be able to circulate throughout the Community. Three categories covered here are particularly important for public health, but also present problems of standardization which the Member States will be better placed to resolve together rathen than separately. Because of product liability and the risks attached to vaccines (virulence), to blood products (AIDS, hepatitis) or to radiopharmaceuticals (radioactivity), European firms are tending to leave these sectors, which are nevertheless vital for the prevention and treatment of disease.

5. FINANCIAL IMPLICATIONS

a) Additional personnel required for DG III/B/6, from 1989, would be one administrator (A7) and one secretary, to be found by internal redeployment or through normal budgetary process.

b) Appropriations for three new committees from 1989 (vaccines, blood, radiopharmaceuticals) with 4 meetings a year for each of them, thus 12 in total: ± 60 000 ECU per year. The provision of funding will be considered in the context of the overall budget which will be granted by the budgetary authority under the heading 2511.

c) Contract for provision of services with the European Pharmacopoeia to accelerate the standardization of international biological reference preparations, to be found from within budgetary requests already made for 1989, and for subsequent years from the normal annual budgetary process.

The funding is estimated as:

- 300 000 ECU in 1989
- 500 000 ECU in 1990
- 800 000 ECU a year in 1991 and thereafter

STATEMENT OF IMPACT ON SMALL AND MEDIUM-SIZED FIRMS AND EMPLOYMENT

1. ADMINISTRATIVE OBLIGATIONS ARISING FROM THE APPLICATION OF THE LEGISLATION FOR FIRMS

   Systematic obligation to obtain prior approval before manufacturing or marketing immunological medicinal products, medicinal products derived from human blood, radiopharmaceuticals and non-proprietary medicinal products. In many cases such an obligation already exists at national level.

2. ADVANTAGES FOR THE FIRM

   - YES/NO - WHICH access to a Community scale market with greater legal certainty as to the rules to be applied; abolition of repeat batch control testing

3. INCONVENIENCE FOR THE FIRM

   - YES/NO - obligation to submit to increased administrative surveillance

   - CONSEQUENCES

     Marginally increased production costs which should be offset by access to a larger internal market. The administrative controls envisaged are not disproportionate with the requirement to improve the protection of public health in this sector.

4. EFFECT ON EMPLOYMENT

   No direct effects.

5. HAS PRIOR CONCERTATION WITH THE SOCIAL PARTNERS TAKEN PLACE?

   - YES/NO - consultation of pharmaceutical industry

   OPINION OF SOCIAL PARTNERS - generally favourable

6. IS THERE A LESS RESTRICTIVE ALTERNATIVE?

   No.