

## **REGULATION (EEC) No 2309/93**

### **Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products**

*(OJ No L 214 of 24. 8. 1993, p. 1)*

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 235 thereof,

Having regard to the proposal from the Commission <sup>(1)</sup>,

Having regard to the Opinion of the European Parliament <sup>(2)</sup>,

Having regard to the Opinion of the Economic and Social Committee <sup>(3)</sup>,

Whereas Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products particularly those derived from biotechnology <sup>(4)</sup> has established a Community mechanism for concertation, prior to any national decision relating to a high-technology medicinal product, with a view to arriving at uniform decisions throughout the Community; whereas this route should be followed, particularly in order to ensure the smooth functioning of the internal market in the pharmaceutical sector;

Whereas the experience acquired as a result of Directive 87/22/EEC has shown that it is necessary to establish a centralized Community authorization procedure for technologically advanced medicinal products, in particular those derived from biotechnology; whereas this procedure should also be available to persons responsible for placing on the market medicinal products containing new active substances which are intended for use in human beings or in food-producing animals;

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<sup>(1)</sup> OJ No C 330 of 31. 12. 1990, p. 1 and OJ No C 310 of 30. 11. 1991, p. 7.

<sup>(2)</sup> OJ No C 183 of 15. 7. 1991, p. 145.

<sup>(3)</sup> OJ No C 269 of 14. 10. 1991, p. 84.

<sup>(4)</sup> OJ No L 15 of 17. 1. 1987, p. 38.

Whereas in the interest of public health it is necessary that decisions on the authorization of such medicinal products should be based on the objective scientific criteria of the quality, the safety and the efficacy of the medicinal product concerned to the exclusion of economic or other considerations; whereas, however, Member States should exceptionally be able to prohibit the use on their territory of medicinal products for human use which infringe objectively defined concepts of public order or public morality; whereas, moreover, a veterinary medicinal product may not be authorized by the Community if its use would contravene the legal measures laid down by the Community within the framework of the common agricultural policy;

Whereas, in the case of medicinal products for human use, the criteria of quality, safety and efficacy have been extensively harmonized by Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products <sup>(1)</sup>, and the Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products <sup>(2)</sup>, and by Council Directive 75/318/EEC 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 medicinal products <sup>(3)</sup>;

Whereas in the case of veterinary medicinal products, the same results have been achieved by Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products <sup>(4)</sup> and by Council Directive 81/852/EEC of 28 September 1981 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 veterinary medicinal products <sup>(5)</sup>;

Whereas the same criteria must be applied to medicinal products which are to be authorized by the Community;

Whereas only after a single scientific evaluation of the highest possible standard of the quality, safety or efficacy of technologically advanced medicinal products, to be undertaken within the European Agency for the Evaluation of Medicinal Products, should a marketing authorization be granted by the Community by a rapid procedure ensuring close co-operation between the Commission and Member States;

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<sup>(1)</sup> OJ No 22 of 9. 2. 1965, p. 369/65. Directive last amended by Directive 93/39/EEC (OJ No L 214 of 24. 8. 1993, p. 22).

<sup>(2)</sup> OJ No L 147 of 9. 6. 1975, p. 13. Directive last amended by Directive 93/39/EEC (OJ No L 214 of 24. 8. 1993, p. 22).

<sup>(3)</sup> OJ No L 147 of 9. 6. 1975, p. 1. Directive last amended by Commission Directive 93/39/EEC (OJ No L 214 of 24. 8. 1993, p. 22).

<sup>(4)</sup> OJ No L 317 of 6. 11. 1981, p. 1. Directive last amended by Directive 93/40/EEC (OJ No L 214 of 24. 8. 1993, p. 31).

<sup>(5)</sup> OJ No L 317 of 6. 11. 1981, p. 16. Directive last amended by Directive 93/40/EEC (OJ No L 214 of 24. 8. 1993, p. 31).

Whereas Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products <sup>(1)</sup> has provided that in the event of a disagreement between Member States about the quality, safety or efficacy of a medicinal product which is the subject of the decentralized Community authorization procedure, the matter should be resolved by a binding Community decision following a scientific evaluation of the issues involved within a European medicinal product evaluation agency; whereas similar provisions have been laid down in respect of veterinary medicinal products by Council Directive 93/40/EEC of 14 June 1993 amending Directives 81/851/EEC and 81/852/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products <sup>(2)</sup>;

Whereas the Community must be provided with the means to undertake a scientific evaluation of medicinal products which are presented for authorization in accordance with the centralized Community procedures; whereas, furthermore, in order to achieve the effective harmonization of the administrative decisions taken by Member States in relation to individual medicinal products which are presented for authorization in accordance with decentralized procedures, it is necessary to provide the Community with the means of resolving disagreements between Member States about the quality, safety and efficacy of medicinal products;

Whereas it is therefore necessary to establish a European Agency for the Evaluation of Medicinal Products ('the Agency');

Whereas the primary task of the Agency should be to provide scientific advice of the highest possible quality to the Community institutions and the Member States for the exercise of the powers conferred upon them by Community legislation in the field of medicinal products in relation to the authorization and supervision of medicinal products;

Whereas it is necessary to ensure close co-operation between the Agency and scientists working within the Member States;

Whereas, therefore, the exclusive responsibility for preparing the opinions of the Agency on all matters relating to medicinal products for human use should be entrusted to the Committee for Proprietary Medicinal Products created by the Second Council Directive 75/319/EEC; whereas in respect of veterinary medicinal products this responsibility should be entrusted to the Committee for Veterinary Medicinal Products created by Directive 81/851/EEC;

Whereas the establishment of the Agency will make it possible to reinforce the scientific role and independence of these two Committees, in particular through the establishment of a permanent technical and administrative secretariat;

Whereas it is also necessary to make provisions for the supervision of medicinal products which have been authorized by the Community, and in particular for the intensive monitoring of adverse reactions to those medicinal products through Community pharmacovigilance activities in order to ensure the rapid withdrawal from the market of any medicinal product which presents an unacceptable level of risk under normal conditions of use;

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<sup>(1)</sup> OJ No L 214 of 24. 8. 1993, p. 22.

<sup>(2)</sup> OJ No L 214 of 24. 8. 1993, p. 31.

Whereas the Commission, working in close co-operation with the Agency, and after consultation with Member States, should also be entrusted with the task of co-ordinating the discharge of the various supervisory responsibilities of Member States and in particular the provision of information about medicinal products, monitoring the respect of good manufacturing practices, good laboratory practices and good clinical practices;

Whereas the Agency should also be responsible for co-ordinating the activities of the Member States in the field of the monitoring of adverse reactions to medicinal products (pharmacovigilance);

Whereas it is necessary to provide for the orderly introduction of Community procedures for the authorization of medicinal products alongside the national procedures of the Member States which have already been extensively harmonized by Directives 65/65/EEC, 75/319/EEC and 81/851/EEC; whereas it is therefore appropriate in the first instance to limit the obligation to use the new Community procedure to certain medicinal products; whereas the scope of the Community procedures should be reviewed in the light of experience at the latest six years after the entry into force of this Regulation;

Whereas risks to the environment may be associated with medicinal products containing or consisting of genetically modified organisms; whereas therefore it is necessary to provide for an environmental risk assessment of such products similar to that provided for by Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms <sup>(1)</sup>, together with the assessment of the quality, safety and efficacy of the product concerned within a single Community procedure;

Whereas the Treaty does not provide, for the adoption of a uniform system at Community level, as provided for by this Regulation, powers other than those of Article 235,

HAS ADOPTED THIS REGULATION:

## TITLE I

### *Definitions and Scope*

#### *Article 1*

The purpose of this Regulation is to lay down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and to establish a European Agency for the Evaluation of Medicinal Products.

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<sup>(1)</sup> OJ No L 117 of 8. 5. 1990, p. 15.

The provisions of this Regulation shall not affect the powers of the Member States' authorities as regards the price setting of medicinal products or their inclusion in the scope of the national health systems of the Member States' authorities or their inclusion in the scope of the social security schemes on the basis of health, economic and social conditions. For example, the Member States may choose from the marketing authorization those therapeutic indications and pack sizes which will be covered by their social security organizations.

### ***Article 2***

The definitions laid down in Article 1 of Directive 65/65/EEC and those laid down in Article 1 (2) of Directive 81/851/EEC shall apply for the purposes of this Regulation.

The person responsible for placing the medicinal products covered by this Regulation on the market must be established in the Community.

### ***Article 3***

1. No medicinal product referred to in Part A of the Annex may be placed on the market within the Community unless a marketing authorization has been granted by the Community in accordance with the provisions of this Regulation.
2. The person responsible for placing on the market a medicinal product referred to in Part B of the Annex may request that authorization to place the medicinal product on the market be granted by the Community in accordance with the provisions of this Regulation.
3. Before entry into force of this Regulation and after consultation of the Committee for Proprietary Medicinal Products, Parts A and B of the Annex as regards medicinal products for human use shall be re-examined in the light of scientific and technical progress with a view to making any amendments necessary which will be adopted under the procedure laid down in Article 72.
4. Before entry into force of this Regulation and after consultation of the Committee for Veterinary Medicinal Products, Parts A and B of the Annex as regards veterinary medicinal products shall be re-examined in the light of scientific and technical progress with a view to making any amendments necessary which will be adopted under the procedure laid down in Article 72.
5. The procedures referred to in paragraphs 3 and 4 shall continue to apply after entry into force of this Regulation.

### ***Article 4***

1. In order to obtain the authorization referred to in Article 3, the person responsible for placing a medicinal product on the market shall submit an application to the European Agency for the Evaluation of Medicinal Products, hereinafter referred to as 'the Agency', set up under Title IV.
2. The Community shall issue and supervise marketing authorizations for medicinal products for human use in accordance with Title II.
3. The Community shall issue and supervise marketing authorizations for veterinary medicinal products in accordance with Title III.

## TITLE II

### ***Authorization and Supervision of Medicinal Products for Human Use***

#### **CHAPTER 1**

#### **Submission and examination of applications – authorizations – renewal of authorization**

##### ***Article 5***

The Committee for Proprietary Medicinal Products established by Article 8 of Directive 75/319/EEC, in this Title referred to as ‘the Committee’, shall be responsible for formulating the opinion of the Agency on any question concerning the admissibility of the files submitted in accordance with the centralized procedure, the granting, variation, suspension or withdrawal of an authorization to place a medicinal product for human use on the market arising in accordance with the provisions of this Title and pharmacovigilance.

##### ***Article 6***

1. An application for authorization for a medicinal product for human use must be accompanied by the particulars and documents referred to in Articles 4 and 4a of Directive 65/65/EEC, in the Annex to Directive 75/318/EEC and in Article 2 of Directive 75/319/EEC.

2. In the case of a medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2 (1) and (2) of Directive 90/220/EEC, the application must also be accompanied by:

- a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for by Part B of Directive 90/220/EEC;
- the complete technical dossier supplying the information requested in Annexes II and III to Directive 90/220/EEC and the environmental risk assessment resulting from this information; the results of any investigations performed for the purposes of research or development.

Articles 11 to 18 of Directive 90/220/EEC shall not apply to medicinal products for human use containing or consisting of genetically modified organisms.

3. The application must also be accompanied by the fee payable to the Agency for the examination of the application.

4. The Agency shall ensure that the opinion of the Committee is given within 210 days of the receipt of a valid application.

In the case of a medicinal product containing or consisting of genetically modified organisms, the opinion of the Committee shall respect the environmental safety requirements laid down by Directive 90/220/EEC to ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of genetically modified organisms. During the process of evaluating applications for marketing authorizations for products containing or consisting of genetically modified organisms, necessary consultations will be held by the rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 90/220/EEC.

5. The Commission shall, in consultation with the Agency, the Member States and interested parties, draw up detailed guidance on the form in which applications for authorization are to be presented.

### ***Article 7***

In order to prepare its opinion, the Committee:

- a) shall verify that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directives 65/65/EEC, 75/318/EEC and 75/319/EEC, and examine whether the conditions specified in this Regulation for issuing a marketing authorization for the medicinal product are satisfied;
- b) may ask for a State laboratory or a laboratory designated for this purpose to test the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;
- c) may, where appropriate, request the applicant to supplement the particulars accompanying the application within a specific time limit. Where the Committee avails itself of this option, the time limit laid down in Article 6 shall be suspended until such time as the supplementary information requested has been provided. Likewise, this time limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.

### ***Article 8***

1. Upon receipt of a written request from the Committee, a Member State shall forward the information establishing that the manufacturer of a medicinal product or the importer from a third country is able to manufacture the medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 6.

2. Where it considers it necessary in order to complete its examination of an application, the Committee may require the applicant to submit to a specific inspection of the manufacturing site of the medicinal product concerned. The inspection, which shall be completed within the time limit referred to in Article 6, shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may, if need be, be accompanied by a rapporteur or expert appointed by the Committee.

### **Article 9**

1. Where the opinion of the Committee is that:
  - the application does not satisfy the criteria for authorization set out in this Regulation, or
  - the summary of the product characteristics proposed by the applicant in accordance with Article 6 should be amended, or
  - the labelling or package leaflet of the product is not in compliance with Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets <sup>(1)</sup>, or
  - the authorization should be granted subject to the conditions provided for in Article 13 (2),

the Agency shall forthwith inform the applicant. Within 15 days of receipt of the opinion, the applicant may provide written notice to the Agency that he wishes to appeal. In that case he shall forward the detailed grounds for his appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 2.

2. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Commission, the Member States and the applicant together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.

3. In the event of an opinion in favour of granting the relevant authorization to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:

- a) a draft summary of the product characteristics, as referred to in Article 4a of Directive 65/65/EEC;
- b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, having regard to the criteria laid down in Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use <sup>(2)</sup>, without prejudice to the provisions in Article 3 (4) of that Directive;
- c) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Directive 92/27/EEC, without prejudice to the provisions of Article 7 (2) of that Directive;
- d) the assessment report.

### **Article 10**

1. Within 30 days of receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking account of Community law.

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<sup>(1)</sup> OJ No L 113 of 30. 4. 1992, p. 8.

<sup>(2)</sup> OJ No L 113 of 30. 4. 1992, p. 5.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 9 (3) a), b) and c) shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant.

2. A final decision on the application shall be adopted in accordance with the procedure laid down in Article 73.

3. The rules of procedure of the Committee referred to in Article 73 shall be adjusted to take account of the tasks incumbent upon it in accordance with this Regulation.

These adjustments shall involve the following:

- except in cases referred to in the third subparagraph of paragraph 1, the opinion of the Standing Committee shall be obtained in writing;
- each Member State is allowed at least 28 days to forward written observations on the draft decision to the Commission;
- each Member State is able to require in writing that the draft decision be discussed by the Standing Committee, giving its reasons in detail.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure laid down in Article 72.

4. The Agency shall, upon request, inform any person concerned of the final decision.

### ***Article 11***

Without prejudice to other provisions of Community law, the authorization provided for in Article 3 shall be refused if, after verification of the information and particulars submitted in accordance with Article 6, it appears that the quality, the safety or the efficacy of the medicinal product have not been adequately or sufficiently demonstrated by the applicant.

Authorization shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Directive 92/27/EEC.

### ***Article 12***

1. Without prejudice to Article 6 of Directive 65/65/EEC, a marketing authorization which has been granted in accordance with the procedure laid down in this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State in accordance with Article 3 of Directive 65/65/EEC.

The authorized medicinal products shall be entered in the Community Register of Medicinal Products and shall be given a number which must appear on the packaging.

2. The refusal of a Community marketing authorization shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.

3. Notification of marketing authorization shall be published in the Official Journal of the European Communities, quoting in particular the date of authorization and the number in the Community Register.

4. Upon request from any interested person, the Agency shall make available the assessment report of the medicinal product by the Committee for Proprietary Medicinal Products and the reasons for its opinion in favour of granting authorization, after deletion of any information of a commercially confidential nature.

### ***Article 13***

1. Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration by the Agency of a dossier containing up-to-date information on pharmacovigilance.

2. In exceptional circumstances and following consultation with the applicant, an authorization may be granted subject to certain specific obligations, to be reviewed annually by the Agency.

Such exceptional decisions may be adopted only for objective and verifiable reasons and must be based on one of the causes mentioned in Part 4 G of the Annex to Directive 75/318/EEC.

3. Some products may be authorized only for use in hospitals or for prescription by some specialists.

4. Medicinal products which have been authorized by the Community in accordance with the provisions of this Regulation shall benefit from the ten-year period of protection referred to in point 8 of the second paragraph of Article 4 of Directive 65/65/EEC.

### ***Article 14***

The granting of authorization shall not diminish the general civil and criminal liability in the Member States of the manufacturer or, where applicable, of the person responsible for placing the medicinal product on the market.

## CHAPTER 2

### Supervision and sanctions

#### *Article 15*

1. After an authorization has been issued in accordance with this Regulation, the person responsible for placing the medicinal product on the market shall, in respect of the methods of production and control provided for in points 4 and 7 of the second paragraph of Article 4 of Directive 65/65/EEC, take account of technical and scientific progress and make any amendments that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. The aforementioned person must apply for approval for these amendments in accordance with this Regulation.
2. The person responsible for placing the medicinal product on the market shall forthwith inform the Agency, the Commission and the Member States of any new information which might entail the amendment of the particulars and documents referred to in Articles 6 or 9 or in the approved summary of the product characteristics. In particular the aforementioned person shall forthwith inform the Agency, the Commission and the Member States of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is placed on the market and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned.
3. If the person responsible for placing the medicinal product on the market proposes to make any alteration to the information and particulars referred to in Articles 6 and 9, he shall submit an application to the Agency.
4. The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a notification system or administrative procedures concerning minor variations and define precisely the concept of 'a minor variation'.

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure laid down in Article 72.

#### *Article 16*

In the case of medicinal products manufactured within the Community, the supervisory authorities shall be the competent authorities of the Member State or Member States which have granted the manufacturing authorization provided for in Article 16 of Directive 75/319/EEC in respect of the manufacture of the medicinal product concerned.

In the case of medicinal products imported from third countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 22 (1) (b) of Directive 75/319/EEC are carried out unless appropriate arrangements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.

A Member State may request assistance from another Member State or the Agency.

### ***Article 17***

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the person responsible for placing the medicinal product on the market or the manufacturer or importer from third countries satisfies the requirements laid down in Chapter IV of Directive 75/319/EEC and for exercising supervision over such persons in accordance with Chapter V of Directive 75/319/EEC.

2. Where, in accordance with the second paragraph of Article 30 of Directive 75/319/EEC, the Commission is informed of serious differences of opinion between Member States as to whether the person responsible for placing the medicinal product on the market or a manufacturer or importer established within the Community is satisfying the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the aforementioned person, the manufacturer or the importer; the inspector in question may be accompanied by an inspector from a Member State which is not party to the dispute and/or by a rapporteur or expert nominated by the Committee.

3. Subject to any arrangements which may have been concluded between the Community and third countries in accordance with the second subparagraph of Article 16, the Commission may, upon receipt of a reasoned request from a Member State, the Committee for Proprietary Medicinal Products, or on its own initiative, require a manufacturer established in a third country to submit to an inspection. The inspection shall be undertaken by appropriately qualified inspectors from the Member States, who may, if appropriate, be accompanied by a rapporteur or expert nominated by the Committee. The report of the inspectors shall be made available to the Commission, the Member States and the Committee for Proprietary Medicinal Products.

### ***Article 18***

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer from third countries is no longer fulfilling the obligations laid down in Chapter IV of Directive 75/319/EEC, they shall forthwith inform the Committee and the Commission, stating their reasons in detail and indicating the course of action proposed.

The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Chapter V or Va of Directive 75/319/EEC should be applied in respect of the medicinal product concerned or where the Committee for Proprietary Medicinal Products has delivered an opinion to that effect in accordance with Article 20.

2. The Commission shall in consultation with the Agency forthwith examine the reasons advanced by the Member State concerned. It shall request the opinion of the Committee within a time limit which it shall determine having regard to the urgency of the matter. Whenever practicable, the person responsible for placing the medicinal product on the market shall be invited to provide oral or written explanations.

3. The Commission shall prepare a draft of the Decision to be taken which shall be adopted in accordance with Article 10.

However, where a Member State has invoked the provisions of paragraph 4, the time limit provided for in Article 73 shall be reduced to 15 calendar days.

4. Where urgent action is essential to protect human or animal health or the environment, a Member State may suspend the use on its territory of a medicinal product which has been authorized in accordance with this Regulation. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action. The Commission shall immediately consider the reasons given by the Member State in accordance with paragraph 2 and shall initiate the procedure provided for in paragraph 3.
5. A Member State which has adopted the suspensive measures referred to in paragraph 4 may maintain them in force until such time as a definitive decision has been reached in accordance with the procedure laid down in paragraph 3.
6. The Agency shall, upon request, inform any person concerned of the final decision.

## **CHAPTER 3**

### **Pharmacovigilance**

#### ***Article 19***

For the purpose of this Chapter, the definitions given in Article 29b of Directive 75/319/EEC shall apply.

#### ***Article 20***

The Agency, acting in close co-operation with the national pharmacovigilance systems established in accordance with Article 29a of Directive 75/319/EEC, shall receive all relevant information about suspected adverse reactions to medicinal products which have been authorized by the Community in accordance with this Regulation. If necessary the Committee may, in accordance with Article 5, formulate opinions on the measures necessary to ensure the safe and effective use of such medicinal products. These measures shall be adopted in accordance with the procedure laid down in Article 18.

The person responsible for placing the medicinal product on the market and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to medicinal products authorized in accordance with this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

#### ***Article 21***

The person responsible for the placing on the market of a medicinal product authorized by the Community in accordance with the provisions of this Regulation shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

- a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company and to medical representatives, is collected, evaluated and collated so that it may be accessed at a single point within the Community;

- b) the preparation of the reports referred to in Article 22 for the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;
- c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions for the medicinal product concerned.

### ***Article 22***

1. The person responsible for placing the medicinal product on the market shall ensure that all suspected serious adverse reactions occurring within the Community to a medicinal product authorized in accordance with the provisions of this Regulation which are brought to his attention by a health care professional, are recorded and reported immediately to the Member States in whose territory the incident occurred, and in no case later than 15 days following the receipt of the information.

The person responsible for placing the medicinal product on the market shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a third country are reported immediately to Member States and the Agency and in no case later than 15 days following the receipt of the information.

The arrangements for the reporting of suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, shall be adopted in accordance with Article 26.

2. In addition, the person responsible for placing the medicinal product on the market shall be required to maintain detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to him by a health care professional. Unless other requirements have been laid down as a condition of the granting of the marketing authorization by the Community, these records shall be submitted to the Agency and Member States immediately upon request or at least every six months during the first two years following authorization and once a year for the following three years. Thereafter, the records shall be submitted at five-yearly intervals together with the application for renewal of the authorization, or immediately upon request. These records shall be accompanied by a scientific evaluation.

### ***Article 23***

Each Member State shall ensure that all suspected serious adverse reactions occurring within their territory to a medicinal product authorized in accordance with the provisions of this Regulation which are brought to their attention are recorded and reported immediately to the Agency and the person responsible for placing the medicinal product on the market, and in no case later than 15 days following the receipt of the information.

The Agency shall inform the national pharmacovigilance systems.

### ***Article 24***

The Commission in consultation with the Agency, Member States, and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports.

The Agency, in consultation with the Member States and the Commission, shall set up a data-processing network for the rapid transmission of data between the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products marketed in the Community.

### ***Article 25***

The Agency shall collaborate with the World Health Organization on international pharmacovigilance and shall take the necessary steps to submit promptly to the World Health Organization appropriate and adequate information regarding the measures taken in the Community which may have a bearing on public health protection in third countries and shall send a copy thereof to the Commission and the Member States.

### ***Article 26***

Any amendment which may be necessary to update the provisions of this chapter to take account of scientific and technical progress shall be adopted in accordance with the provisions of Article 72.

## **TITLE III**

### ***Authorization and Supervision of Veterinary Medicinal Products***

#### **CHAPTER 1**

#### **Submission and examination of applications – Authorization – Renewal of authorization**

### ***Article 27***

The Committee for Veterinary Medicinal Products established by Article 16 of Directive 81/851/EEC, in this Title referred to as 'the Committee', shall be responsible for formulating the opinion of the Agency on any question concerning the admissibility of the files submitted in accordance with the centralized procedure, the granting, variation, suspension or withdrawal of an authorization to place a veterinary medicinal product on the market arising in accordance with the provisions of this Title and pharmacovigilance.

### ***Article 28***

1. An application for authorization for a veterinary medicinal product must be accompanied by the particulars and documents referred to in Articles 5, 5a and 7 of Directive 81/851/EEC.

2. In the case of a veterinary medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2(1) and (2) of Directive 90/220/EEC, the application must also be accompanied by:

- a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for in Part B of Directive 90/220/EEC;
- the complete technical dossier supplying the information requested in Annexes II and III to Directive 90/220/EEC and the environmental risk assessment resulting from this information; the results of any investigations performed for the purposes of research or development.

Articles 11 to 18 of Directive 90/220/EEC shall not apply to veterinary medicinal products containing or consisting of genetically modified organisms.

3. The application shall also be accompanied by the fee payable to the Agency for the examination of the application.

4. The Agency shall ensure that the opinion of the Committee is given within 210 days of the receipt of a valid application.

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms, the opinion of the committee shall respect the environmental safety requirements laid down by Directive 90/220/EEC to ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release into the environment or placing on the market of genetically modified organisms. During the process of evaluating applications for marketing authorizations for veterinary medicinal products containing or consisting of genetically modified organisms, necessary consultations shall be held by the rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 90/220/EEC.

5. The Commission shall, in consultation with the Agency, the Member States and interested parties, draw up detailed guidance on the form in which applications for authorization are to be presented.

### ***Article 29***

In order to prepare its opinion, the Committee:

- a) shall verify that the particulars and documents submitted in accordance with Article 28 comply with the requirements of Directives 81/851/EEC and 81/852/EEC and examine whether the conditions specified in this Regulation for issuing a marketing authorization are satisfied;
- b) may ask for a State laboratory or a laboratory designated for this purpose to test the veterinary medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;

- c) may request a State laboratory or laboratory designated for this purpose to verify, using samples provided by the applicant, that the analytical detection method proposed by the applicant in accordance with point 8 of the third paragraph of Article 5 of Directive 81/851/EEC is suitable for use in routine checks to reveal the presence of residue levels above the maximum residue level accepted by the Community in accordance with the provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin <sup>(1)</sup>.
- d) may, where appropriate, request the applicant to supplement the particulars accompanying the application within a specific time limit. Where the Committee avails itself of this option, the time limit laid down in Article 28 shall be suspended until such time as the supplementary information requested has been provided. Likewise, this time limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.

### **Article 30**

1. Upon receipt of a written request from the Committee, a Member State shall forward the information establishing that the manufacturer of a veterinary medicinal product or the importer from a third country is able to manufacture the veterinary medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 28.

2. Where it considers it necessary in order to complete its examination of an application, the Committee may require the applicant to submit to a specific inspection of the manufacturing site of the veterinary medicinal product concerned. The inspection, which shall be completed within the time limit referred to in Article 28, shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may, if need be, be accompanied by a rapporteur or expert appointed by the Committee.

### **Article 31**

1. Where the opinion of the Committee is that:
- the application does not satisfy the criteria for authorization set out in this Regulation, or
  - the summary of the product characteristics proposed by the applicant in accordance with Article 28 should be amended, or
  - the labelling or package insert of the product is not in compliance with Directive 81/851/EEC, or
  - the authorization should be granted subject to the conditions provided for in Article 35 (2),

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<sup>(1)</sup> OJ No L 224 of 18. 8. 1990, p. 1. Regulation last amended by Regulation No 2901/93 (OJ No L 264 of 23. 10. 1993, p. 1).

the Agency shall forthwith inform the applicant. Within 15 days of receipt of the opinion, the applicant may provide written notice to the Agency that he wishes to appeal. In that case he shall forward the detailed grounds for his appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the reasons for the conclusion reached on the appeal shall be annexed to the assessment report referred to in paragraph 2.

2. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Commission, the Member States and the applicant together with a report describing the assessment of the veterinary medicinal product by the Committee and stating the reasons for its conclusions.

3. In the event of an opinion in favour of granting the relevant authorization to market the veterinary medicinal product, the following documents shall be annexed to the opinion:

- a) the draft summary of the product characteristics, as referred to in Article 5a of Directive 81/851/EEC; where necessary this will reflect differences in the veterinary conditions pertaining in the Member States;
- b) in the case of a veterinary medicinal product intended for administration to food-producing animals, a statement of the maximum residue level which may be accepted by the Community in accordance with Regulation (EEC) No 2377/90;
- c) details of any conditions or restrictions which should be imposed on the supply or use of the veterinary medicinal product concerned, including the conditions under which the veterinary medicinal product may be made available to users, in accordance with the criteria laid down in Directive 81/851/EEC;
- d) the draft text of the labelling and package insert proposed by the applicant, presented in accordance with Directive 81/851/EEC;
- e) the assessment report.

### ***Article 32***

1. Within 30 days of receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking account of Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 31 (3) a), b), c) and d) shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant.

2. A final decision on the application shall be adopted in accordance with the procedure laid down in Article 73.

3. The rules of procedure of the Committee referred to in Article 73 shall be adjusted to take account of the tasks incumbent upon it in accordance with this Regulation.

These adjustments shall involve the following:

- except in the cases referred to in the third sub-paragraph of paragraph 1, the opinion of the Standing Committee shall be obtained in writing;

- each Member State is allowed at least 28 days to forward written observations on the draft decision to the Commission;
- each Member State is able to require in writing that the draft decision be discussed by the Standing Committee giving its reasons in detail.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure laid down in Article 72.

4. The Agency shall, upon request, inform any person concerned of the final decision.

### ***Article 33***

Without prejudice to other provisions of Community law, the authorization provided for in Article 3 shall be refused if, after verification of the information and particulars submitted in accordance with Article 28, it appears that:

1. the veterinary medicinal product is harmful under the conditions of use stated at the time of the application for authorization, has no therapeutic effect or the applicant has not provided sufficient proof of such effect as regards the species of animal which is to be treated, or its qualitative and quantitative composition is not as stated;
2. the withdrawal period recommended by the applicant is not long enough to ensure that foodstuffs obtained from treated animals do not contain residues which might constitute a health hazard for the consumer or is insufficiently substantiated;
3. the veterinary medicinal product is offered for sale for a use prohibited under other Community provisions.

Authorization shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 28 are incorrect or if the labelling and package inserts proposed by the applicant are not in accordance with Chapter VII of Directive 81/851/EEC.

### ***Article 34***

1. Without prejudice to Article 4 of Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products <sup>(1)</sup>, and laying down additional provisions for immunological veterinary medicinal products, a marketing authorization which has been granted in accordance with the procedure laid down in this Regulation shall apply throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State in accordance with Article 4 of Directive 81/851/EEC.

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<sup>(1)</sup> OJ No L 373 of 31. 12. 1990, p. 26.

The authorized veterinary medicinal products shall be entered in the Community Register of Medicinal Products and shall be given a number which must appear on the packaging.

2. The refusal of a Community marketing authorization shall constitute a prohibition on the placing on the market of the veterinary medicinal product concerned throughout the Community.
3. Notification of marketing authorization shall be published in the Official Journal of the European Communities, quoting in particular the date of authorization and the number in the Community Register.
4. Upon request from any interested person, the Agency shall make available the assessment report of the veterinary medicinal product by the Committee for Veterinary Medicinal Products and the reasons for its opinion in favour of granting authorization, after deletion of any information of a commercially confidential nature.

### ***Article 35***

1. Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration by the Agency of a dossier containing up-to-date information on pharmaco-vigilance.
2. In exceptional circumstances and following consultations with the applicant, authorization may be granted subject to certain specific obligations, to be reviewed annually by the Agency.

Such exceptional decisions may be adopted for objective and verifiable reasons.

3. Veterinary medicinal products which have been authorized by the Community in accordance with the provisions of this Regulation shall benefit from the ten-year period of protection referred to in point 10 of the third paragraph of Article 5 of directive 81/851/EEC.

### ***Article 36***

The granting of authorization shall not diminish the general civil and criminal liability in the Member States of the manufacturer or, where applicable, of the person responsible for placing the veterinary medicinal product on the market.

## CHAPTER 2

### Supervision and sanctions

#### *Article 37*

1. After an authorization has been issued in accordance with this Regulation, the person responsible for placing the veterinary medicinal product on the market shall, in respect of the methods of production and control provided for in points 4 and 9 of the third paragraph of Article 5 of Directive 81/851/EEC, take account of technical and scientific progress and make changes that may be required to enable the veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods. The aforementioned person must apply for approval for these changes in accordance with this Regulation.

Upon a request from the Commission, the person responsible for placing the veterinary medicinal product on the market shall also review the analytical detection methods provided for in point 8 of the third paragraph of Article 5 of Directive 81/851/EEC and propose any changes which may be necessary to take account of technical and scientific progress.

2. The person responsible for placing the veterinary medicinal product on the market shall forthwith inform the Agency, the Commission and the Member States of any new information which might entail the amendment of the particulars and documents referred to in Articles 28 and 31 or in the approved summary of the product characteristics. In particular the aforementioned person shall forthwith inform the Agency, the Commission and the Member States of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the veterinary medicinal product concerned.

3. If the person responsible for placing the veterinary medicinal product on the market proposes to make any alteration to the information and particulars referred to in Articles 28 and 31, he shall submit an application to the agency.

4. The commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

These arrangements shall include a notification system or administrative procedures concerning minor variations and define precisely the concept of 'a minor variation'.

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure laid down in Article 72.

#### *Article 38*

In the case of veterinary medicinal products manufactured within the Community, the supervisory authorities shall be the competent authorities of the Member State or Member States which have granted the manufacturing authorization provided for in Article 24 of Directive 85/851/EEC in respect of the manufacture of the veterinary medicinal product concerned.

In the case of veterinary medicinal products imported from third countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 30 (1) (b) of Directive 81/851/EEC are carried out unless appropriate arrangements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.

A Member State may request assistance from another Member State or the Agency.

### ***Article 39***

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the person responsible for placing the veterinary medicinal product on the market, or manufacturer or importer from third countries satisfies the requirements laid down in Chapter V of Directive 81/851/EEC and for exercising supervision over such persons in accordance with Chapter VI of Directive 81/851/EEC.

2. Where, in accordance with the second paragraph of Article 39 of Directive 81/851/EEC, the Commission is informed of serious differences of opinion between Member States as to whether the person responsible for placing the veterinary medicinal product on the market or a manufacturer or importer established within the Community is satisfying the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the aforementioned person, the manufacturer or the importer; the inspector in question may be accompanied by an inspector from a Member State which is not party to the dispute and/or by a rapporteur or expert nominated by the Committee.

3. Subject to any arrangements which may have been concluded between the Community and third countries in accordance with the second paragraph of Article 38, the Commission may, upon receipt of a reasoned request from a Member State, the Committee for Veterinary Medicinal Products, or on its own initiative, require a manufacturer established in a third country to submit to an inspection. The inspection shall be undertaken by appropriately qualified inspectors from the Member States, who may, if appropriate, be accompanied by a rapporteur or expert nominated by the Committee. The report of the inspectors shall be made available to the Commission, the Member States and the Committee for Veterinary Medicinal Products.

### ***Article 40***

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer from third countries is no longer fulfilling the obligations laid down in Chapter V of Directive 81/851/EEC, they shall forthwith inform the Committee and the Commission, stating their reasons in detail and indicating the course of action proposed.

The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Chapter VI of Directive 81/851/EEC should be applied in respect of the veterinary medicinal product concerned or where the Committee for Veterinary Medicinal Products has delivered an opinion to that effect in accordance with Article 42.

2. The Commission shall in consultation with the Agency forthwith examine the reasons advanced by the Member State concerned. It shall request the opinion of the Committee within a time limit to be determined by the Commission having regard to the urgency of the matter. Whenever practicable, the person responsible for placing the veterinary medicinal product on the market shall be invited to provide oral or written explanations.

3. The Commission shall prepare a draft of the Decision to be taken which shall be adopted in accordance with the procedure laid down in Article 32.

However, where a Member State has invoked the provisions of paragraph 4, the time limit provided for in Article 73 shall be reduced to 15 calendar days.

4. Where urgent action is essential to protect human or animal health or the environment, a Member State may suspend the use on its territory of a veterinary medicinal product which has been authorized in accordance with this Regulation. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action. The Commission shall immediately consider the reasons given by the Member State in accordance with paragraph 2 and shall initiate the procedure provided for in paragraph 3.

5. A Member State which has adopted the suspensive measures referred to in paragraph 4 may maintain them in force until such time as a definitive decision has been reached in accordance with the procedure laid down in paragraph 3.

6. The Agency shall, upon request, inform any person concerned of the final decision.

## **CHAPTER 3**

### **Pharmacovigilance**

#### ***Article 41***

For the purpose of this Chapter, the definitions given in Article 42 of Directive 81/851/EEC shall apply.

#### ***Article 42***

The Agency, acting in close co-operation with the national pharmacovigilance systems established in accordance with Article 42a of Directive 81/851/EEC, shall receive all relevant information about suspected adverse reactions to veterinary medicinal products which have been authorized by the Community in accordance with this Regulation. If necessary the Committee may, in accordance with Article 27, formulate opinions on the measures necessary to ensure the safe and effective use of such veterinary medicinal products. These measures shall be adopted in accordance with the procedure laid down in Article 40.

The person responsible for placing the veterinary medicinal product on the market and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to veterinary medicinal products authorized in accordance with this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

### ***Article 43***

The person responsible for the placing on the market of a veterinary medicinal product authorized by the Community in accordance with the provisions of this Regulation shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be responsible for the following:

- a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company and to its representatives is collected, evaluated and collated so that it may be accessed at a single point within the Community;
- b) the preparation of the reports referred to in Article 44 for the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;
- c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks of a veterinary medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions for the veterinary medicinal product concerned.

### ***Article 44***

1. The person responsible for placing a veterinary medicinal product on the market shall ensure that all suspected serious adverse reactions occurring within the Community to a veterinary medicinal product authorized in accordance with the provisions of this Regulation which are brought to his attention are recorded and reported immediately to the Member States in whose territory the incident occurred, and in no case later than 15 days following the receipt of the information.

The aforementioned person shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a third country, are reported immediately to the Member States and the Agency and in no case later than 15 days following the receipt of the information.

The arrangements for the reporting of suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, shall be adopted in accordance with Article 48.

2. In addition, the person responsible for placing a veterinary medicinal product on the market shall be required to maintain detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to him. Unless other requirements have been laid down as a condition of the granting of the marketing authorization by the Community, these records shall be submitted to the Agency and Member States immediately upon request or at least every six months during the first two years following authorization and once a year for the following three years. Thereafter, the records shall be submitted at five-yearly intervals together with the application for renewal of the authorization, or immediately upon request. These records shall be accompanied by a scientific evaluation.

**Article 45**

Each Member State shall ensure that all suspected serious adverse reactions occurring within their territory to a veterinary medicinal product authorized in accordance with the provisions of this Regulation which are brought to their attention are recorded and reported immediately to the Agency and the person responsible for placing the veterinary medicinal product on the market, and in no case later than 15 days following the receipt of the information.

The Agency shall inform the national pharmacovigilance systems.

**Article 46**

The Commission in consultation with the Agency, Member States, and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports.

The Agency, in consultation with the Member States and the Commission, shall set up a data-processing network for the rapid transmission of data between the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding veterinary medicinal products marketed in the Community.

**Article 47**

The Agency shall co-operate with international organizations concerned with veterinary pharmaco-vigilance.

**Article 48**

Any amendment which may be necessary to update the provisions of this Chapter to take account of scientific and technical progress shall be adopted in accordance with the provisions of Article 72.

## TITLE IV

### *The European Agency for the Evaluation of Medicinal Products*

#### CHAPTER 1

##### Tasks of the Agency

###### **Article 49**

A European Agency for the Evaluation of Medicinal Products is hereby established.

The Agency shall be responsible for co-ordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products.

###### **Article 50**

1. The Agency shall comprise:
  - a) the Committee for Proprietary Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;
  - b) the Committee for Veterinary Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of veterinary medicinal products;
  - c) a Secretariat, which shall provide technical and administrative support for the two Committees and ensure appropriate co-ordination between them;
  - d) an Executive Director, who shall exercise the responsibilities set out in Article 55;
  - e) a Management Board, which shall exercise the responsibilities set out in Articles 56 and 57.
2. The Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products may each establish working parties and expert groups.
3. The Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

###### **Article 51**

In order to promote the protection of human and animal health and of consumers of medicinal products throughout the Community, and in order to promote the completion of the internal market through the adoption of uniform regulatory decisions based on scientific criteria concerning the placing on the market and use of medicinal products, the objectives of the Agency shall be to provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, the safety, and the efficacy of medicinal products for human or veterinary use, which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.

To this end, the Agency shall undertake the following tasks within its Committees:

- a) the co-ordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community marketing authorization procedures;
- b) the transmission of assessment reports, summaries of product characteristics, labels and package leaflets or inserts for these medicinal products;
- c) the co-ordination of the supervision, under practical conditions of use, of medicinal products which have been authorized within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluating and making available through a database information on adverse reactions to the medicinal products in question (pharmacovigilance);
- d) advising on the maximum limits for residues of veterinary medicinal products which may be accepted in foodstuffs of animal origin in accordance with Regulation (EEC) No 2377/90;
- e) co-ordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice and good clinical practice;
- f) upon request, providing technical and scientific support for steps to improve co-operation between the Community, its Member States, international organizations and third countries on scientific and technical issues relating to the evaluation of medicinal products;
- g) recording the status of marketing authorizations for medicinal products granted in accordance with Community procedures;
- h) providing technical assistance for the maintenance of a database on medicinal products which is available for public use;
- i) assisting the Community and Member States in the provision of information to health care professionals and the general public about medicinal products which have been evaluated within the Agency;
- j) where necessary, advising companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products.

### ***Article 52***

1. The Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products shall each consist of two members nominated by each Member State for a term of 3 years which shall be renewable. They shall be chosen by reason of their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent their competent authorities.

The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the Committees, their working parties and expert groups.

Members of each Committee may arrange to be accompanied by experts.

2. In addition to their task of providing objective scientific opinions to the Community and Member States on the questions which are referred to them, the members of each Committee shall ensure that there is appropriate co-ordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorization.

3. The members of the Committees and the experts responsible for evaluating medicinal products shall rely on the scientific assessment and resources available to the national marketing authorization bodies. Each Member State shall monitor the scientific level of the evaluation carried out and supervise the activities of members of the Committees and the experts it nominates, but shall refrain from giving them any instruction which is incompatible with the tasks incumbent upon them.

4. When preparing the opinion, each Committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and may, at the request of those concerned, include the divergent positions with their grounds.

### ***Article 53***

1. Where, in accordance with the provisions of this Regulation, the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products is required to evaluate a medicinal product, the Committee shall appoint one of its members to act as rapporteur for the co-ordination of the evaluation, taking into consideration any proposal from the applicant for the choice of a rapporteur. The Committee may appoint a second member to act as co-rapporteur.

The Committee shall ensure that all its members undertake the role of rapporteur or co-rapporteur.

2. Member States shall transmit to the Agency a list of experts with proven experience in the assessment of medicinal products who would be available to serve on working parties or expert groups of the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products, together with an indication of their qualifications and specific areas of expertise.

This list shall be updated as necessary.

3. The provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and his employer. The person concerned, or his employer, shall be remunerated in accordance with a fixed scale of fees to be included in the financial arrangements established by the Management Board.

4. On a proposal from the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products, the Agency may also avail itself of the services of rapporteurs or experts for the discharge of other specific responsibilities of the Agency.

**Article 54**

1. The membership of the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.
2. Members of the Management Board, Committee members, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which the public may consult.

**Article 55**

1. The Executive Director shall be appointed by the Management Board, on a proposal from the Commission, for a period of five years, which shall be renewable.
2. The Executive Director shall be the legal representative of the Agency. He shall be responsible:
  - for the day-to-day administration of the Agency,
  - for the provision of appropriate technical support for the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, and their working parties and expert groups,
  - for ensuring that the time limits laid down in Community legislation for the adoption of opinions by the Agency are respected,
  - for ensuring appropriate co-ordination between the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products,
  - for the preparation of the statement of revenue and expenditure and the execution of the budget of the Agency,
  - for all staff matters.
3. Each year, the Executive Director shall submit to the Management Board for approval, while making a distinction between the Agency's activities concerning medicinal products for human use and those concerning veterinary medicinal products:
  - a draft report covering the activities of the Agency in the previous year, including information about the number of applications evaluated within the Agency, the time taken for the completion of the evaluation and the medicinal products authorized, rejected or withdrawn,
  - a draft programme of work for the coming year,
  - the draft annual accounts for the previous year,
  - the draft budget for the coming year.
4. The Executive Director shall approve all financial expenditure of the Agency.

**Article 56**

1. The Management Board shall consist of two representatives from each Member State, two representatives of the Commission and two representatives appointed by the European Parliament. One representative shall have specific responsibilities relating to medicinal products for human use and one relating to veterinary medicinal products.

Each representative may arrange to be replaced by an alternate.

2. The term of office of the representatives shall be three years. It shall be renewable.
3. The Management Board shall elect its Chairman for a term of three years and shall adopt its rules of procedure.

Decisions of the Management Board shall be adopted by a majority of two-thirds of its members.

4. The Executive Director shall provide the Secretariat of the Management Board.
5. Before 31 January each year, the Management Board shall adopt the general report on the activities of the Agency for the previous year and its programme of work for the coming year and forward them to the Member States, the Commission, the Council and the European Parliament.

## **CHAPTER 2**

### **Financial provisions**

#### ***Article 57***

1. The revenues of the Agency shall consist of a contribution from the Community, and the fees paid by undertakings for obtaining and maintaining a Community marketing authorization and for other services provided by the Agency.
2. The expenditure of the Agency shall include the staff, administrative, infrastructure and operational expenses and expenses resulting from contracts entered into with third parties.
3. By 15 February each year at the latest, the Director shall draw up a preliminary draft budget covering the operational expenditure and the programme of work anticipated for the following financial year, and shall forward this preliminary draft to the Management Board together with an establishment plan.
4. Revenue and expenditure shall be in balance.
5. The Management Board shall adopt the draft budget and forward it to the Commission which on that basis shall establish the relevant estimates in the preliminary draft general budget of the European Communities, which it shall put before the Council pursuant to Article 203 of the Treaty.
6. The Management Board shall adopt the Agency's final budget before the beginning of the financial year, adjusting it where necessary to the Community subsidy and the Agency's other resources.
7. The Director shall implement the Agency's budget.
8. Monitoring of the commitment and payment of all the Agency's expenditure and of the establishment and recovery of all the Agency's revenue shall be carried out by the financial controller appointed by the Management Board.
9. By 31 March each year at the latest, the Director shall forward to the Commission, the Management Board and the Court of Auditors the accounts for all the Agency's revenue and expenditure in respect of the preceding financial year.

The Court of Auditors shall examine them in accordance with Article 206a of the Treaty.

10. The Management Board shall give a discharge to the Director in respect of the implementation of the budget.

11. After the Court of Auditors has delivered its opinion, the Management Board shall adopt the internal financial provisions specifying, in particular, the detailed rules for establishing and implementing the Agency's budget.

### ***Article 58***

The structure and the amount of the fees referred to in Article 57(1) shall be established by the Council acting under the conditions provided for by the Treaty on a proposal from the Commission, following consultation of organizations representing the interests of the pharmaceutical industry at Community level.

## **CHAPTER 3**

### **General provisions governing the Agency**

#### ***Article 59***

The Agency shall have legal personality. In all Member States it shall benefit from the widest powers granted by law to legal persons. In particular it may acquire and dispose of real property and chattels and institute legal proceedings.

#### ***Article 60***

1. The contractual liability of the Agency shall be governed by the law applicable to the contract in question. The Court of Justice of the European Communities shall have jurisdiction to give judgment pursuant to any arbitration clause contained in a contract concluded by the Agency.

2. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or its servants in the performance of their duties.

The Court of Justice shall have jurisdiction in any dispute relating to compensation for such damages.

3. The personal liability of its servants towards the Agency shall be governed by the relevant conditions applying to the staff of the Agency.

#### ***Article 61***

The Protocol on the Privileges and Immunities of the European Communities shall apply to the Agency.

#### ***Article 62***

The staff of the Agency shall be subject to the rules and regulations applicable to officials and other staff of the European Communities.

In respect of its staff, the Agency shall exercise the powers which have been devolved to the appointing authority.

The Management Board, in agreement with the Commission, shall adopt the necessary implementing provisions.

### ***Article 63***

Members of the Management Board, members of Committees, and officials and other servants of the Agency shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

### ***Article 64***

The Commission may, in agreement with the Management Board and the relevant Committee, invite representatives of international organizations with interests in the harmonization of regulations applicable to medicinal products to participate as observers in the work of the Agency.

### ***Article 65***

The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the health professions.

### ***Article 66***

The Agency shall take up its responsibilities on 1 January 1995.

## **TITLE V**

### ***General and final provisions***

#### ***Article 67***

All decisions to grant, refuse, vary, suspend, withdraw or revoke a marketing authorization which are taken in accordance with this Regulation shall state in detail the reasons on which they are based. Such decisions shall be notified to the party concerned.

#### ***Article 68***

1. An authorization to place on the market a medicinal product coming within the scope of this Regulation shall not be refused, varied, suspended, withdrawn or revoked except on the grounds set out in this Regulation.
2. An authorization to place on the market a medicinal product coming within the scope of this Regulation shall not be granted, refused, varied, suspended, withdrawn or revoked except in accordance with the procedures set out in this Regulation.



### **Article 69**

Without prejudice to Article 68, and without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for the infringement of the provisions of this Regulation. The penalties must be sufficient to promote compliance with those measures.

Member States shall forthwith inform the Commission of the institution of any infringement proceedings.

### **Article 70**

Additives covered by Council Directive 70/524/EEC of 23 November 1970 concerning additives in feedingstuffs (1), where they are intended to be administered to animals in accordance with that Directive, shall not be considered as veterinary medicinal products for purposes of this Regulation.

Within three years of the entry into force of this Regulation the Commission shall produce a report on whether the level of harmonization achieved by this Regulation and by Council Directive 90/167/EEC of 26 March 1990 laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community (2) is equivalent to that provided for in Council Directive 70/524/EEC, accompanied if necessary by the proposals to modify the status of the coccidiostats and other medicinal substances covered by that Directive.

The Council shall decide on the Commission proposal no later than one year after their submission.

### **Article 71**

Within six years of the entry into force of this Regulation, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation, in Chapter III of Directive 75/319/EEC and in Chapter IV of Directive 81/851/EEC.

### **Article 72**

Where the procedure laid down in this Article is to be followed the Commission shall be assisted by:

- the Standing Committee on Medicinal Products for Human Use, in the case of matters relating to medicinal products for human use,
- the Standing Committee on Veterinary Medicinal Products, in the case of matters relating to veterinary medicinal products.

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(1) OJ No L 270 of 14. 12. 1970, p. 1. Directive last amended by Commission Directive 92/64/EEC (OJ No L 221 of 6. 8. 1992, p. 51).

(2) OJ No L 92 of 7. 4. 1990, p. 42.

The representative of the Commission shall submit to the Committee a draft of the measures to be taken. The Committee shall deliver its opinion on the draft within a time-limit which the Chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the Committee shall be weighted in the manner set out in that Article. The Chairman shall not vote.

The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the Committee.

If the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

If on the expiry of a period of three months from the date of referral to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission.

### ***Article 73***

Where the procedure laid down in this Article is to be followed the Commission shall be assisted by:

- the Standing Committee on Medicinal Products for Human Use, in the case of matters relating to medicinal products for human use,
- the Standing Committee on Veterinary Medicinal Products, in the case of matters relating to veterinary medicinal products.

The representative of the Commission shall submit to the Committee a draft of the measures to be taken. The Committee shall deliver its opinion on the draft within a time-limit which the Chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the Committee shall be weighted in the manner set out in that Article. The Chairman shall not vote.

The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the Committee.

If the measures envisaged are not in accordance with the opinion of the Committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

If on the expiry of a period of three months from the date of referral to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission, save where the Council has decided against the said measures by a simple majority.

***Article 74***

This Regulation shall enter into force on the day following the decision taken by the competent authorities on the headquarters of the Agency.

Subject to the first subparagraph Titles I, II, III and V shall enter into force on 1 January 1995.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 22 July 1993.

*For the Council*

*The President*

M. OFFECIERS-VAN DE WIELE

**ANNEX****PART A**

Medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology,
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods.

Veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

**PART B**

Medicinal products developed by other biotechnological processes which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products presented for an entirely new indication which, in the opinion of the agency, is of significant therapeutic interest.

Medicinal products based on radio-isotopes which, in the opinion of the Agency, are of significant therapeutic interest.

New medicinal products derived from human blood or human plasma.

Medicinal products the manufacture of which employs processes which, in the opinion of the Agency, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity.

Medicinal products intended for administration to human beings, containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in a medicinal product intended for human use.

Veterinary medicinal products intended for use in food-producing animals containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in food-producing animals.