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(Acts whose publication is obligatory)

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 and Article 152(4)(b) thereof,

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

Having regard to the Opinion of the European Economic and Social Committee [2],

After consulting the Committee of the Regions,

In accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) Article 71 of Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [4] provides that, within six years of the entry into force of the Regulation, the Commission is to publish a general report on the experience acquired as a result of the operation of the procedures laid down in the Regulation.

(2) In the light of the Commission's report on the experience gained, it has proved necessary to improve the operation of the authorisation procedures for the placing of medicinal products on the market in the Community and to amend certain administrative aspects of the European Agency for the Evaluation of Medicinal Products. In addition, the name of that Agency should be simplified and changed to the European Medicines Agency, (hereinafter referred to as the 'Agency').

(3) It emerges from the conclusions of that report that the amendments to be made to the centralised procedure set up by Regulation (EEC) No 2309/93 consist of corrections to some of the operating procedures and adaptations to take account of the probable development of science and technology and the future enlargement of the European Union. It also emerges from the report that the general principles previously established which govern the centralised procedure should be maintained.

(4) Moreover, since the European Parliament and the Council have adopted Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use [5] and Directive 2001/82/EC of 6 November 2001 on the Community code relating to veterinary medicinal products [6], all the references to the codified Directives in Regulation (EEC) No 2309/93 should be updated.

(5) For the sake of clarity, it is necessary to replace the said Regulation with a new Regulation.

(6) It is appropriate to preserve the Community mechanism set up by the repealed Community legislation for concertation prior to any national decision relating to a high-technology medicinal product.

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(1) OJ C 75 E, 26.3.2002, p. 189 and OJ C . . . (not yet published in the Official Journal).

(2) OJ C 61, 14.3.2003, p. 1.

(3) Opinion of the European Parliament of 23 October 2002 (OJ C 300 E, 11.12.2003, p. 308), Council Common Position of 29 September 2003 (OJ C 297 E, 9.12.2003, p. 1), Position of the European Parliament of 17 December 2003 (not yet published in the Official Journal) and Council Decision of 11 March 2004.

(4) OJ L 214, 24.8.1993, p. 1. Regulation as last amended by Regulation (EC) No 1647/2003 (OJ L 245, 29.9.2003, p. 19).

(5) OJ L 311, 28.11.2001, p. 67. Directive as last amended by Council Directive 2004/27/EC (see p. 34 of this Official Journal).

(6) OJ L 311, 28.11.2001, p. 1. Directive as amended by Council Directive 2004/28/EC (see p. 58 of this Official Journal).

(7) Experience gained since the adoption of 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 [1] has shown that it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation. This is particularly important in the context of the emergence of new therapies, such as gene therapy and associated cell therapies, and xenogenic somatic therapy. This approach should be maintained, particularly with a view to ensuring the effective operation of the internal market in the pharmaceutical sector.

(8) With a view to harmonising the internal market for new medicinal products, this procedure should also be made compulsory for orphan medicinal products and any medicinal product for human use containing an entirely new active substance, i.e. one that has not yet been authorised in the Community, and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes. Four years after the date of entry into force of this Regulation, the procedure should also become compulsory for medicinal products for human use containing a new active substance, and for which the therapeutic indication is for the treatment of autoimmune diseases and other immune dysfunctions and viral diseases. It should be possible to review the provisions in point 3 of the Annex via a simplified decision-making procedure not earlier than four years after the entry into force of this Regulation.

(9) As regards medicinal products for human use, optional access to the centralised procedure should also be provided for in cases where use of a single procedure produces added value for the patient. This procedure should remain optional for medicinal products which, although not belonging to the abovementioned categories, are nevertheless therapeutically innovative. It is also appropriate to allow access to this procedure for medicinal products which, although not innovative, may be of benefit to society or to patients if they are authorised from the outset at Community level, such as certain medicinal products which can be supplied without a medical prescription. This option may be extended to generic medicinal products authorised by the Community, provided that this in no way undermines either the harmonisation achieved when the reference medicinal product was evaluated or the results of that evaluation.

(10) In the field of veterinary medicinal products, administrative measures should be laid down in order to take account of the specific features of this field, particularly those due to the regional distribution of certain diseases. It should be possible to use the centralised procedure for the authorisation of veterinary medicinal products used within the framework of Community provisions regarding prophylactic measures for epizootic diseases. Optional access to the centralised procedure should be maintained for veterinary medicinal products containing a new active substance.

(11) For medicinal products for human use, the period for protection of data relating to pre-clinical tests and clinical trials should be the same as that provided for in Directive 2001/83/EC. For medicinal products for veterinary use, the period for protection of data relating to pre-clinical tests and clinical trials as well as safety and residue tests should be the same as that provided for in Directive 2001/82/EC.

(12) In order to reduce the cost for small and medium-sized enterprises of marketing medicinal products authorised via the centralised procedure, provisions should be adopted to allow for a reduction of fees, deferring the payment of fees, taking over responsibility for translations and offering administrative assistance in respect of these enterprises.

(13) In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able exceptionally to prohibit the use in their territory of medicinal products for human use which infringe objectively defined concepts of public policy and public morality. Moreover, a veterinary medicinal product is not to be authorised by the Community if its use would contravene the rules laid down within the framework of the Common Agricultural Policy or if presented for a use prohibited under other Community provisions, inter alia Directive 96/22/EC [2].

(14) Provision should be made for the quality, safety and efficacy criteria in Directives 2001/83/EC and 2001/82/EC to apply to medicinal products authorised by the Community and it should be possible to assess the risk-benefit balance of all medicinal products when they are placed on the market, at the time of the renewal of the authorisation and at any other time the competent authority deems appropriate.

[1] OJ L 15, 17.1.1987, p. 38. Directive repealed by Directive 93/41/EEC (OJ L 214, 24.8.1993, p. 40).

[2] Council Directive 96/22/EC of 29 April 1996 concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of β-agonists (OJ L 125, 23.5.1996, p. 3).

(15) The Community is required, pursuant to Article 178 of the Treaty, to take account of the development policy aspects of any measure and to promote the creation of conditions fit for human beings worldwide. Pharmaceutical law should continue to ensure that only efficacious, safe and top-quality medicinal products are exported, and the Commission should consider creating further incentives to carry out research into medicinal products against widespread tropical diseases.

(16) There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1] to apply to medicinal products authorised by the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive.

(17) The Community should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the decentralised Community authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with decentralised authorisation procedures, it is necessary to endow the Community with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.

(18) The structure and operation of the various bodies making up the Agency should be designed in such a way as to take into account the need constantly to renew scientific expertise, the need for cooperation between Community and national bodies, the need for adequate involvement of civil society, and the future enlargement of the European Union. The various bodies of the Agency should establish and develop appropriate contacts with the parties concerned, in particular representatives of patients and health-care professionals.

(19) The chief task of the Agency should be to provide Community institutions and Member States with the best possible scientific opinions so as to enable them to exercise the powers regarding the authorisation and supervision of medicinal products conferred on them by Community legislation in the field of medicinal products. Only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards, should marketing authorisation be granted by the Community, and this should be done by means of a rapid procedure ensuring close cooperation between the Commission and Member States.

(20) In order to ensure close cooperation between the Agency and scientists operating in Member States, the composition of the Management Board should be such as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Community system for authorising medicinal products.

(21) The Agency's budget should be composed of fees paid by the private sector and contributions paid out of the Community budget to implement Community policies.

(22) Paragraph 25 of the Interinstitutional Agreement of 6 May 1999 between the European Parliament, the Council and the Commission on budgetary discipline and improvement of budgetary procedure [2] provides for the Financial Perspective to be adjusted in order to cover the new needs resulting from enlargement.

(23) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in a Committee for Medicinal Products for Human Use. As far as veterinary medicinal products are concerned, such responsibility should be vested in a Committee for Medicinal Products for Veterinary Use. As regards orphan medicinal products, the task should fall to the Committee on Orphan Medicinal Products set up under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products [3]. Lastly, as regards herbal medicinal products, this responsibility should be vested in the Committee on Herbal Medicinal Products set up under Directive 2001/83/EC.

(24) The creation of the Agency will make it possible to reinforce the scientific role and independence of the committees, particularly through the setting-up of a permanent technical and administrative secretariat.

[1] OJ L 121, 1.5.2001, p. 34.

[2] OJ C 172, 18.6.1999, p. 1.

[3] OJ L 18, 22.1.2000, p. 1.

(25) The field of activity of the Scientific Committees should be enlarged and their operating methods and composition modernised. Scientific advice for future applicants seeking marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises, should be put in place. The committees should be able to delegate some of their evaluation duties to standing working parties open to experts from the scientific world appointed for this purpose, whilst retaining total responsibility for the scientific opinions issued. The re-examination procedures should be amended to provide a better guarantee for applicants' rights.

(26) The number of members of the Scientific Committees participating in the centralised procedure should be established with a view to ensuring that the committees remain of an efficient size after the enlargement of the European Union.

(27) It is also necessary to reinforce the role of the Scientific Committees in such a way as to enable the Agency to participate actively in international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organisation.

(28) Furthermore, in order to create greater legal certainty it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of medicinal products authorised by the Community, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Community and to specify the sanctions and the procedures for implementing them in the event of failure to observe the provisions of this Regulation and the conditions contained in the authorisations granted under the procedures it establishes.

(29) It is also necessary to take measures for the supervision of medicinal products authorised by the Community, and in particular for the intensive supervision of undesirable effects of these medicinal products within the framework of Community pharmacovigilance activities, so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative risk-benefit balance under normal conditions of use.

(30) In order to enhance the efficiency of market surveillance, the Agency should be responsible for coordinating Member States' pharmacovigilance activities. A number of provisions need to be introduced to put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk-benefit balance of a medicinal product.

(31) It is also appropriate to entrust the Commission, in close cooperation with the Agency and after consultations with the Member States, with the task of coordinating the execution of the various supervisory responsibilities vested in the Member States, and in particular with the tasks of providing information on medicinal products and of checking the observance of good manufacturing, laboratory and clinical practices.

(32) It is necessary to provide for the coordinated implementation of Community procedures for the authorisation of medicinal products, and of the national procedures of Member States which have already been harmonised to a considerable degree by Directives 2001/83/EC and 2001/82/EC. It is appropriate that the operation of the procedures laid down by this Regulation be re-examined by the Commission every ten years on the basis of experience gained.

(33) In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions. In the field of medicinal products for human use, a common approach should also be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation.

(34) Member States have developed an evaluation of the comparative efficacy of medicinal products aimed at positioning a new medicinal product with respect to those that already exist in the same therapeutic class. Similarly, the Council, in its Conclusions on medicinal products and public health [1], adopted on 29 June 2000, emphasised the importance of identifying medicinal products that presented an added therapeutic value. However this evaluation should not be conducted in the context of the marketing authorisation, for which it is agreed that the fundamental criteria should be retained. It is useful in this respect to allow for the possibility of gathering information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product.

[1] OJ C 218, 31.7.2000, p. 10.

(35) In line with the current provisions of Directives 2001/83/EC and 2001/82/EC, the term of validity of a Community marketing authorisation should be limited initially to a period of five years, upon the expiry of which it should be renewed. Thereafter the marketing authorisation should normally be of unlimited validity. Furthermore, any authorisation not used for three consecutive years, that is to say, one which has not led to the placing on the market of a medicinal product in the Community during that period, should be considered invalid, in order, in particular, to avoid the administrative burden of maintaining such authorisations. However, this rule should be subject to exemptions when these are justified on public health grounds.

(36) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms [1], to be conducted in parallel with the evaluation, under a single Community procedure, of the quality, safety and efficacy of the product concerned.

(37) The measures necessary for the implementation of this Regulation should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [2].

(38) The provisions of Regulation (EC) No 1647/2003 [3] amending Regulation (EC) No 2309/93 as regards the budgetary and financial rules applicable to the Agency and access to the Agency's documents should be fully incorporated into this Regulation,

HAVE ADOPTED THIS REGULATION:

TITLE I

DEFINITIONS AND SCOPE

Article 1

The purpose of this Regulation is to lay down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and to establish a European Medicines Agency (hereinafter referred to as 'the Agency').

The provisions of this Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. In particular, Member States shall be free to choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Article 2

The definitions laid down in Article 1 of Directive 2001/83/EC and those laid down in Article 1 of Directive 2001/82/EC shall apply for the purposes of this Regulation.

The holder of a marketing authorisation for medicinal products covered by this Regulation must be established in the Community. The holder shall be responsible for the placing on the market of those medicinal products, whether he does it himself or via one or more persons designated to that effect

Article 3

1. No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.

2. Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

(a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or

(b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level.

Immunological veterinary medicinal products for the treatment of animal diseases that are subject to Community prophylactic measures may also be granted such authorisation.

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[1] OJ L 106, 17.4.2001, p. 1. Directive as last amended by Regulation (EC) No 1830/2003 of the European Parliament and of the Council (OJ L 268, 18.10.2003, p. 24).
[2] OJ L 184, 17.7.1999, p. 23.
[3] OJ L 245, 29.9.2003, p. 19.

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