



COMMISSION OF THE EUROPEAN COMMUNITIES

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2001/0252 (COD)

Modified proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

**laying down Community procedures for the authorisation and supervision and
pharmacovigilance of medicinal products for human and veterinary use and establishing
a European Agency for the Evaluation of Medicinal Products**

(presented by the Commission pursuant to
Article 250 (2) of the EC Treaty)

Modified proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Community procedures for the authorisation and supervision and pharmacovigilance of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

(Text with EEA relevance)

1. BACKGROUND

Transmission of the proposal to the Council and to the European Parliament

- COM(2001) 404 final – 2001/0252 (COD) -

by virtue of article 175, paragraph 1 of the Treaty: 26 November 2001

Opinion of the European Economic and Social Committee: 18 September 2002

Opinion of the European Parliament – first reading: 23 October 2002

2. OBJECTIVE OF THE COMMISSION PROPOSAL

Regulation 2309/93 provides for the possibility of an evaluation of the Community procedures for the authorisation and the supervision of medicinal products which entered into force in 1995. In view of the experience gained during 1995 and 2000 and the analysis performed by the Commission in its report ‘on the operation of the Community procedures for the marketing authorisation of medicinal products (COM(2001) 606 final of 23.10.2001)’ it appeared necessary to amend Regulation 2309/93 and Directives 2001/83/EC and 2001/82/EC laying down the Community codes in relation to medicinal products for human and veterinary use.

In general, four major objectives appear to be particularly relevant.

- (1) to assure a high level of public health protection, notably by making safe, innovative products available to patients as quickly as possible, and by an increased supervision of the market through the strengthening of inspection procedures and of pharmacovigilance;
- (2) to complete the single market for pharmaceutical products taking into account the stakes of globalisation and to establish a regulatory and legislative framework that favours the competitiveness of European industry;
- (3) to respond to the challenges of the future enlargement of the European Union;
- (4) to rationalise and simplify the system as well as to improve its overall coherence and visibility and the transparency of its procedures.

Finally with respect to veterinary medicines, the proposals aim specifically to take into account the problem of the availability of medicinal products for veterinary use.

3. OPINION OF THE COMMISSION ON THE AMENDMENTS ADOPTED BY THE PARLIAMENT

3.1. Amendments accepted by the Commission: 12, 14, 16, 28, 30, 32, 33, 36, 37, 40, 41, 61, 69, 72, 75, 77, 78, 84, 90, 95, 98, 99, 101 (in part), 102, 103, 104, 106, 107 (in part), 108 (in part), 110 (in part), 111, 112, 114, 115, 116, 117, 120, 123, 124, 125, 126, 127, 128 (in part), 130 and 135.

The Commission can accept the following amendments with the wording proposed by the European Parliament. Certain provisions, other than those targeted by the amendments, have been brought into line with the new wording, where necessary. This concerns, in particular, Article 13, paragraph 3; Article 32, paragraph 1, subparagraph 1; Article 32, paragraph 2, subparagraph 2a; Article 34, paragraph 2; Article 35, paragraph 3 and Article 44, paragraph 3a.

- Amendment 12 aimed at introducing a new recital concerning the financial aspects of the agency in view of enlargement:

“Recital 17 a

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 ⁽¹⁾ provides that the Financial Perspective will be adjusted on order to cover the new needs resulting from enlargement

⁽¹⁾ OJ C172 18.6.1999, p.1

- Amendment 14 aimed at including a negative benefit/risk analysis as a reason for withdrawing a medicinal product from the market:

“Recital 24:

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 benefit/ risk balance** under normal conditions of use.

- Amendment 16 aimed at modifying the name of the Agency in certain linguistic versions :

“Article 1, first paragraph:

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 **Medicinal Products** Agency (hereinafter referred to as ‘the Agency’).

- Amendments 28 and 69 aimed at strengthening the inspection of the manufacturing sites of the applicant for medicinal products for human and veterinary use:

“Article 8, paragraph 2, subparagraph 1:

2. Where it considers it necessary in order to complete its examination of an application, the Committee for Human Medicinal Products may require the applicant to submit to a specific

*inspection of the manufacturing site of the medicinal product concerned. **Such inspections may be carried out unannounced.***

“Article 30, paragraph 2, subparagraph 1:

*1. Where it considers it necessary in order to complete its examination of the application, the Committee for Veterinary Medicinal Products may require the applicant to submit to a specific inspection of the manufacturing site of the veterinary medicinal product concerned. **Such inspections may be made unannounced.**”*

– Amendments 30, 32, 33 and 72 aimed at shortening the time limit for the decision-making process:

“Article 9, paragraph 3:

*3. Within **15** days of its adoption, the Agency shall send the final opinion of the Committee for Human Medicinal Products to the Commission, to the Member States and to the applicant. The opinion shall be accompanied by a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.*

Article 10, paragraph 1, subparagraph 1:

*1. Within **15** days of receipt of the opinion referred to in Article 5, paragraph 2, the Commission shall prepare a draft of the decision to be taken in respect of the application.*

Article 10, paragraph 2, subparagraph 2 a:

The Commission decision shall adopt its final decision within 15 days after the end of the procedures referred to in Articles 77, paragraph 3 and 77, paragraph 4.

Article 31, paragraph 3:

*3. Within **15** days of its adoption, the Agency shall send the final opinion of the Committee for Human Medicinal Products to the Commission, to the Member States and to the applicant, together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.*

Article 32, paragraph 1, subparagraph 1:

*1. Within **15** days of receipt of the opinion referred to in Article 27, paragraph 2, the Commission shall prepare a draft of the decision to be taken in respect of the application.*

Article 32, paragraph 2, subparagraph 2 a:

The Commission decision shall adopt its final decision within 15 days after the end of the procedures referred to in Articles 77, paragraph 3 and 77, paragraph 4.”

Amendments 36 and 75 aimed at publishing information concerning the refusals or negative opinions for applications for marketing authorisation:

“Article 11, paragraph 2 a:

2a. Information about all refusals and the reasons for them shall be made publicly accessible.

Article 33, paragraph 2 a:

2a. Information about all refusals and the reasons for them shall be made publicly accessible.”

- Amendment 37 aimed at completing the details of the notifications of marketing authorisations published in the Official Journal:

“Article 12, paragraph 2:

*2. Notifications of marketing authorisations shall be published in the Official Journal of the European Communities, quoting in particular the date of authorisation, the registration number in the Community Register, **the INN (international non-proprietary name) of the active substance of the medicinal product, the pharmaceutical form and the ACT code.***

“Article 34, paragraph 2:

*2. Notifications of marketing authorisations shall be published in the Official Journal of the European Communities, quoting in particular the date of authorisation, the registration number in the Community Register, **the INN (international non-proprietary name) of the active substance of the medicinal product, the pharmaceutical form and the ACT code.***

Amendments 40 and 77 aimed at altering the period of validity of the marketing authorisation in the case where this has not been followed by the placing on the market of the medicinal product. The same provision is introduced in the case of previously authorised medicinal products which have not been on the market for a certain period:

“Article 13, paragraph 2:

*2. Any authorisation which is not followed by the actual placing of the medicinal product for human use authorised on the Community market within **three** years of authorisation shall cease to be valid.*

Article 13, paragraphe 3:

3. When a previously marketed medicinal product for human use has not been marketed for three consecutive years, the authorisation granted for this medicinal product shall cease to be valid.

Article 35, paragraph 2:

*2. Any authorisation which is not followed by the actual placing of the medicinal product for human use authorised on the Community market within **three** years of authorisation shall cease to be valid.*

Article 35, paragraph 3

3. When a previously marketed medicinal product for human use has not been marketed for three consecutive years, the authorisation granted for this medicinal product shall cease to be valid.

- Amendments 41 and 78 aimed at introducing a derogation from the rule that a marketing authorisation is valid for three years:

“Article 13, paragraph 3 a:

2 a. In exceptional circumstances and on public health grounds the competent authority may grant a derogation from paragraphs 2 and 3. Such a derogation must be duly justified.

“Article 35, paragraph 3 a:

2 a. In exceptional circumstances and on public health or animal health grounds the competent authority may grant a derogation from paragraphs 2 and 3. Such a derogation must be duly justified.

– Amendment 61 aimed at preventing the marketing authorisation holder from providing pharmacovigilance information without the consent of the Agency:

“Article 22, paragraph 3 a:

3a. The holder of a marketing authorisation shall not be authorised to communicate information concerning pharmacovigilance issues to the general public without the consent of the Agency.

Article 44, paragraph 3 a:

3a. The holder of a marketing authorisation shall not be authorised to communicate information concerning pharmacovigilance issues to the general public without the consent of the Agency.”

– Amendments 84, 102, 103, 104, 106 and 114 aimed at modifying the method of nominating and of working of the Committees of the Agency and 101, 107 and 108, in part, except for the reference to the Committee for Herbal Medicinal Products (the method of nominating and the work of the committee, along the lines of what is set out for the Committee on Orphan Medicinal Products in the specific Regulation, is set out in the proposal for the Directive concerning medicinal products, currently undergoing its first reading in the European Parliament and the Council):

– *“Article 50, paragraph 2:*

2. The Committees referred to in points (a) to (d) of paragraph 1 may each establish standing and temporary working parties. The Committees referred to paragraph 1(a) and (b) shall set up panels in order to secure, in connection with the evaluation of medicinal products, the benefit of expertise focused in particular on a specific type of medicinal product or treatment. The Committees referred to paragraph 1(a) to (d) shall lay down in their rules of procedures the precise arrangements for consulting the panels and delegating certain tasks to them. They shall also determine the arrangements for nominating members of the working parties and the panels on the basis of the lists of experts referred to in the second subparagraph of Article 55(2).

Article 54, paragraph 1, subparagraphs 1 and 2:

With a view to the appointment of the members of the Committee for Human Medicinal Products, the Committee on Herbal Medicinal Products and the Committee for Veterinary Medicinal Products, each Member State shall propose, for each committee, five persons selected on the basis of their role and their experience in the evaluation of human or veterinary medicinal products.

On the basis of those proposals the Executive Director shall appoint one member per Member State, taking into account the need for the committee to be multidisciplinary in nature. These members shall maintain relevant contacts with the national competent authorities.

The members appointed on a proposal from the Member States shall propose to the Executive Director (with a view to securing their appointment) five additional members for each committee, chosen on the basis of their specific scientific competence. The members of each committee shall be appointed for a three-year period which shall be renewable.

Wherever possible, the committees shall seek to establish contacts, on an advisory basis, with patients associations, professionals working in the sector, etc.

Article 54, paragraph 1, subparagraph 4:

The Executive Director of the Agency or his/her representative and representatives of the Commission shall be entitled to attend all the meetings of the Committees and all the meetings convened by the Agency or its committees.

Article 54, paragraph 5:

5. Each Committee shall establish its own rules of procedure. These rules shall in particular lay down:

(a) the procedures for appointing and replacing the Chairman,

(b) the procedures for consulting and delegating certain tasks to working parties,

(c) consultation, in connection with the evaluation procedures for medicinal products, of the panels referred to in the second subparagraph of Article 50, paragraph 2, subparagraph 2.

(d) the establishment of a procedure for the urgent adoption of opinions, particularly in relation to the provisions on market surveillance and pharmacovigilance laid down in this Regulation.

They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 55, paragraph 1, subparagraph 1 a and 1 b:

When the panels referred to in the second subparagraph of Article 50 paragraph 2, subparagraph 2 are consulted, the Committee shall forward to them the evaluation report(s) drawn up by the rapporteur or the co-rapporteur. The opinion issued by the panel shall be forwarded to the chairman of the relevant Committee in such a way as to ensure that the deadlines laid down in Article 6, paragraph 3 and Article 28, paragraph 3 are met.

The substance of the opinion shall be included in the final evaluation report published pursuant to Article 12, paragraph 3 and Article 34, paragraph 3.

Article 55, paragraph 1, subparagraph 2:

*If there is an appeal against one of its opinions, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. This appeal procedure may deal only with the points relating to the initial opinion provisionally identified by the applicant and may only be based on scientific data available at the time the Committee adopted the initial opinion. **Consultation of a panel may be requested in connection with such an appeal***

Article 55, paragraph 2, subparagraph 1:

*Member States shall transmit to the Agency the names of national 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 Human Medicinal Products or the Committee for Veterinary Medicinal Products, **and also on panels**, together with an indication of their qualifications and specific areas of expertise.*

Article 57, paragraph 2, subparagraph 1:

*2. The Executive Director shall be the legal representative of the Agency. He/she shall be responsible **for appointing the members of the scientific committees, pursuant to Article 54, paragraph 1 or other provisions of Community law.***

- Amendment 90 aimed at modifying the functions of the Agency, concerning inspections of compliance with good practices:

“Article 51, paragraph 1, point g):

*(g) coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice **and the verification of compliance with pharmacovigilance obligations;***

- Amendment 95, aimed at specifying the contents of the database on medicinal products:

“Article 51, paragraph 2:

*2. The database provided for in point (j) of paragraph 1 shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapters IV (Title III) of Directive 2001/83/EC and Directive 2001/82/EC respectively. The database shall subsequently be extended to include **any medicinal product marketed in the European Union.***

- Amendments 98 and 99 aimed at publishing documents prepared in the event of a disagreement between the Agency and a scientific committee:

“Article 53, paragraphs 3 and 4:

3. Where there is a fundamental disagreement over scientific points and the body concerned is a Community agency or a scientific committee, the Agency and the body concerned shall work together either to solve the disagreement or to submit a joint document

*to the Commission clarifying the scientific points of disagreement. **This document shall be published immediately after its adoption***

4. *Except where otherwise provided for in this Regulation, in Directive 2001/83/EC or in Directive 2001/82/EC, where there is a fundamental disagreement over scientific points and the body concerned is a body in a Member State, the agency and the national body concerned shall work together either to solve the disagreement or to prepare a joint document clarifying the scientific points of disagreement. **This document shall be published immediately after its adoption***”

- Amendments 110 (second and third part), 111 and 112 aimed at specifying the contents of the code of conduct of the Agency as well as publishing and making accessible on request the declarations of interest of the Members of the boards and committees of the Agency:

“Article 56, paragraph 2, subparagraph 1, 1a and 2:

*Members of the Management Board, members of the Advisory Board, members of the Committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, **and they shall make an annual declaration of their financial interests**. All indirect interests which could relate to the pharmaceutical industry shall be entered in a register held by the Agency which is accessible to the public, **on request, at the Agency's offices**.*

The Agency's code of conduct shall provide for the implementation of this article with particular reference to the acceptance of gifts.

*Members of the Management Board, members of the Advisory Board, members of the Committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the points on the agenda. **These declarations shall be available to the public.***”

- Amendment 115 aimed at covering the activities of the Committee on Herbal Medicinal Products in the context of the responsibilities of the executive director:

“Article 57, paragraph 3, subparagraph 1:

*Each year, the Executive Director shall submit the following to the Management Board for approval, while making a distinction between the Agency's activities concerning medicinal products for human use, **herbal medicinal products** and those concerning veterinary medicinal products:*”

- Amendments 116 and 117 aimed at modifying the composition of the Management Board:

“Article 58, paragraphs 1 and 2

1. *The Management Board shall consist of **15 members appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission which includes considerably more names of candidates than there are members to be appointed, together with one representative of the Commission. Two of the members shall come from industrial associations, one from patients' organisations, one from doctors' organisations, and one shall represent social security schemes. The list***

drawn up by the Commission shall be forwarded to the European Parliament, together with the relevant documentation. As soon as possible, and within three months of notification, the European Parliament may submit its views for consideration to the Council, which shall then appoint the Management Board. Appointment of the members of the Management Board shall be carried out in such a way as to guarantee the highest level of competence, a broad range of relevant expert knowledge and, with respect to these criteria, the widest possible geographical spread in the Union.

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 once.***"

– Amendments 120, 123, 124, 125 and 126 aimed at reviewing the provisions relative to the finances of the Agency:

"Article 60, paragraph 1:

*1. The revenues of the Agency shall consist of **contributions** from the Community and the fees paid by undertakings for obtaining and managing a marketing authorisation and for other services provided by the Agency. **The budgetary authority will re-examine when necessary the level of the contributions on the basis of an evaluation of needs and the level of fees.***

"Article 60, paragraph 3:

*3. By 15 February of each year at the latest, the Director shall draw up a preliminary draft **estimate** covering the operational expenditure and the **draft** programme of work anticipated for the following financial year, and shall forward this preliminary draft, **including** an establishment plan, to the Management Board.*

"Article 60, paragraph 6:

*6. The Management Board shall adopt the Agency's **final work programme** and final budget before the beginning of the financial year, adjusting it where necessary to the Community subsidy and the Agency's other resources. **Any modification of the establishment plan and of the budget shall be notified to the budgetary authority under the form of a rectifying budget.***

"Article 60, paragraph 9:

*9. By 31 March of 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 248 of the Treaty **and shall publish an annual report on the Agency's activities.***

"Article 60, paragraph 10:

*10. On a recommendation **from the Council, the European Parliament** shall give a discharge to the Director in respect of the implementation of the **Agency's budget.**"*

– Amendment 127 aimed at making the Community rules relative to the fight against fraud applicable to the activities of the Agency:

“Article 60 a:

1. **In order to combat fraud, corruption and other unlawful activities the provisions of Regulation (EC) No 1073/1999 of the European Parliament and of the Council of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF)(*) shall apply without restriction.**

2. ***The Agency shall accede to the Interinstitutional Agreement of 25 May 1999 concerning internal investigations by the European Anti-Fraud Office (OLAF) and shall issue, without delay, the appropriate provisions applicable to all the employees of the Agency.***”

(*) OJ L 136,31.5.1999, p.1”

– Amendment 128 (in part) aimed at replacing the term “amount” by “level” of fees:

“Article 61:

*The structure and the **level** of the fees referred to in Article 60(1) shall be established by the Council acting under the conditions provided for by the Treaty on a proposal from the Commission, following the latter’s consultation of organisations representing the interests of the pharmaceutical industry at Community level.*”

– Amendment 130 aimed at extending the possibility of helping small and medium-sized pharmaceutical firms at the time of submission of marketing authorisation applications or for applications relating to diseases with a regional distribution:

“Article 69:

*The Management Board shall, in the case of veterinary medicinal products which have limited markets, or in the case of **human and** veterinary medicinal products intended for diseases with a regional distribution, adopt the necessary administrative measures to provide help to **small and medium-sized** pharmaceutical companies at the time of submission of their applications. These administrative measures shall include, in particular, taking over the responsibility for translations by the Agency.*”

– Amendment 135 aimed at making public, at the request, of the Agency the names of marketing authorisation holders subject to financial penalties by the Commission:

“Article 74, paragraph 3:

3. *At the Agency's request, the Commission may impose financial penalties on the holders of marketing authorisations granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down by the Commission in accordance with the procedure **provided for** in Article 77, paragraph 2.*

The Commission shall publish the names of the holders of the marketing authorisations involved and the amounts of and reasons for the financial penalties imposed.”

3.2. Amendments accepted in part or in principle by the Commission : 1, 4, 13, 15, 18, 20, 22, 23, 24, 25 (second part), 31, 34, 38, 43, 44, 47, 49 (first sentence), 50, 51, 52, 53, 54, 59, 60, 62, 63, 64, 66, 68, 73, 76, 79, 80, 81, 82, 86, 87, 88, 89, 91 (last sentence), 93 (except the last sentence), 96, 100, 105 (second part), 109, 113, 118, 121, 129, 131 (without the references to Regulation (EC) N° 1049/2001), 134, 140, 141, 153, 155, 163, 165 and 166.

Certain provisions other than those targeted by the amendments accepted in principle by the Commission have been brought into line with the amendments introduced by the European Parliament. These concern, in particular, Article 28, paragraph 1, subparagraph 1; Article 34, paragraph 3, subparagraph 2; Article 35, paragraph 4; Article 40, paragraph 4a; Article 42, subparagraph 3; Article 43a; Article 44, paragraph 3, subparagraph 2; Article 46, subparagraph 1 and 3a; and Article 48a.

- The Commission can accept amendments 1 and 13 aimed at providing particular support to small and medium-sized enterprises by reason of the extension of the scope of the centralised procedure to all medicinal products containing a new active substance. These measures are aimed at reducing the costs associated with the request for authorisation submitted to the Agency and to facilitate the requests for scientific advice. Rewording is necessary to indicate the possibility of a specific but not dispensatory system for these companies and to indicate specifically, but not exclusively, the possibility for small and medium-sized enterprises to request scientific advice :

“Recital 8:

*With a view to harmonising the internal market for new medicinal products, this procedure should also be made compulsory for any medicinal product which is intended to be administered to humans or animals and contains an entirely new active substance, that is, one that has not yet been authorised in the Community. **Provision should be made in this context for a derogation for small and medium-sized enterprises so that the cost of marketing the medicinal products developed by these enterprises can be kept within reasonable bounds.***

Recital 20:

*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 for the development of advice for companies – **in particular, small and medium sized enterprise** – should be put in place. The committees should be able to delegate some of their evaluation duties to standing working parties, open to recognised experts from the scientific world appointed for this purpose, whilst retaining total responsibility for the scientific opinions issued. The appeal procedures should be amended to provide a better guarantee for applicants’ rights.”*

- Similarly, the Commission accepts the principle of amendment 129 aimed at introducing an arrangement to provide for a reduction in the fees payable by small and medium-sized enterprises. A rewording is necessary, however, to avoid in the body of the Regulation a reference to an example or precedent so as to determine the procedure by which the Commission will adopt the measures to implement such an arrangement. Therefore, a *new subparagraph* is introduced in *article 61* and worded as follows:

“Article 61, subparagraph 1 a:

Applications related to medicinal products submitted by small and medium size companies, established in the Community, shall benefit from a fee reduction and/or a delayed payment of the fee, as for orphan drugs, according to provisions which will be adopted by the Commission”.

- The Commission can accept in principle amendments 4 (first part) and 100 aimed at making a reference to the principle of comparative efficacy; it is however useful when referring to such a principle to acknowledge its development by the Member States and the importance of analysing the methods used by the Member States. It is important also to emphasise that this evaluation should not be considered as a necessary criterion for the application or for the authorisation of medicinal products. In effect only the criteria of the quality, safety and efficacy of the particular medicinal product should be used in the evaluation of medicinal products. Recital 11 should not be modified; a new *recital 28 a* is introduced and worded as follows:

“The 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, 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 to gather information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product.”

A new article is also introduced to provide for the possibility for the Agency, at the request of the Commission, to collect information from the competent authorities of the Member States in charge of performing evaluations of efficacy compared to that of already authorised medicinal products. A new *article 53 a* is introduced and worded as follows:

“At the request of the Commission, the Agency will collect information on the methods used by the competent authorities in the Member States to determine the therapeutic progress contributed by each new medicinal product.”

- The Commission can accept the principle contained in the second part of amendment 4 concerning the application of the ethical requirements of Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products authorised by the Community as well as the application of these same requirements to clinical trials conducted outside the Community on medicinal products destined to be authorised by the Community. A new *recital 12 a* is therefore introduced and is worded as follows:

“There is also a need to provide for the ethical requirements of Directive 2001/20/EC of the European Parliament and 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 (*) 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 will be verified that these trials were conducted respecting the principles of

good clinical practice and the ethical requirements equivalent to the provisions of this Directive.

(*) OJ L 121 of 1.5.2001, p. 34”

- In the same context of Directive 2001/20/EC on clinical trials, the Commission also accepts the principle of amendment 96, aimed at providing that the database on medicinal products established by *article 51, paragraph 1, point j)* contains information relating to clinical trials. However, the addition of such a provision does not appear to be necessary; the Directive on clinical trials already provides for a specific database for clinical trials conducted with a view to the authorisation of medicinal products for human use.
- The Commission accepts the principle contained in amendments 15 and 47 concerning Directive 89/105/EEC relating to national procedures for the pricing and reimbursement of medicinal products and the conduct of a specific study on its implementation. In this context the Commission intends to present a report on the implementation of this Directive by the Member States. To preserve the Commission’s right of initiative, a recital and an explicit provision for this intention does not seem necessary in a text that is aimed only at the procedure of authorisation and supervision of medicinal products.
- The Commission accepts the principle contained in amendments 18 and 22 concerning the naming of generic medicinal products of reference products authorised through the centralised procedure. The international non-proprietary name and its translation into the different languages of the Member States, even if these differ, are considered as equivalent in all the Member States. *Article 3, paragraph 3, point c)* is worded as follows:

“c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made. For the purposes of this provision, all the linguistic versions of the international non-proprietary name are considered to be the same.”

- The Commission accepts the principle of amendment 20 concerning the use of the evaluation of the benefit risk analysis in the context of the authorisation of a medicinal product. The principle is already set out in the general provisions of Directive 2001/83/EC on the Community code for medicinal products for human use to which the Regulation, which is the object of the present proposal, refers. A specific provision, therefore, is not necessary.
- The Commission accepts the principle of amendments 23 and 68 aimed at making an explicit reference to the competence of the Committees on Medicinal Products for Human and Veterinary Use to give opinions in the case of arbitration between the Member States in the context of the mutual recognition procedure. Directives 2001/83/EC and 2001/82/EC on the Community codes for medicinal products for human and veterinary use define explicitly the competences of these committees in the context of these procedures. Specific provisions in the Regulation, which is the object of the present proposal, are therefore not necessary.
- Regarding the first part of amendment 24 and the second part of amendment 25 aimed at certain requirements set out in Directive 2001/20/EC on clinical trials, the Commission accepts the principle and refers to the new recital 12 *a*, introduced as a result of amendment 4, second part. An explicit reference to the implementation of this Directive is therefore not necessary. It is not necessary either in relation to specific trials in children;

this Directive already contains specific provisions that apply to studies conducted in children with respect to the second part of amendment 24, the Commission accepts this but proposes a new wording which delineates more precisely the scope of the derogation from the principle of one single name for medicinal products authorised by the Community. *Article 6, paragraph 1, subparagraph 1* for medicinal products for human use and *article 28, paragraph 1, subparagraph 1* for medicinal products for veterinary use are worded as follows:

“*Article 6, paragraph 1, subparagraph 1:*

*Each application for authorisation for a medicinal product for human use shall specifically include all the information and documents referred to in Articles 8(3), 10a and 11 of Directive 2001/83/EC, and Annex I thereto. The information and documents are to take account of the Community nature of the authorisation requested, and **except in exceptional cases relating to the application of the law on trade marks**, use a single name for the medicinal product.*

“*Article 28, paragraph 1, subparagraph 1:*

*Each application for authorisation for a medicinal product for veterinary use shall specifically include all the information and documents referred to in Articles 12, paragraph 3, 13a and 14 of Directive 2001/82/EC, and Annex I thereto. The information and documents are to take account of the Community nature of the authorisation requested, and **except in exceptional cases relating to the application of the law on trade marks**, use a single name for the medicinal product.*

- The Commission accepts the principle of amendments 31 and 73 aimed at permitting in the opinions of the committees of the Agency, the inclusion of the conditions relating to the use of certain medicinal products so as to guarantee their safe and effective use. A new *point b) a* is added to *article 9, paragraph 4* with respect to medicinal products for human use and a new *point c) a* to *article 31, paragraph 4* with respect to medicinal products for veterinary use. They are worded as follows:

“*Article 9, paragraph 4*

b a) details of any conditions or restrictions which should be imposed so as to guarantee the safe and effective use of the medicinal product, in particular mechanisms for controlling and monitoring its use and administration.

Article 31, paragraph 4

c a) details of any conditions or restrictions which should be imposed so as to guarantee the safe and effective use of the medicinal product, in particular mechanisms for controlling and monitoring its use and administration.”

- The Commission accepts the principle of amendment 34 aimed at including an accelerated procedure for medicinal products used in certain treatments with a view to making them available to patients more quickly. This procedure is already foreseen in *article 13, paragraph 6* of the draft Regulation; the additional reference in *article 10* is, therefore, not necessary.
- The Commission accepts the principle of amendments 38 and 76. They aim at introducing the notion of a register of assessment reports for medicinal products. The Commission,

however, considers that this register is not necessary since the assessment reports shall be made available to the general public. With respect to the requirement aimed at providing the separate reasons for each authorised indication, this is already the practice in the opinions of the committees of the Agency. An explicit provision is, therefore, not necessary. *Article 12, paragraph 3* and *article 34, paragraph 3* are reworded as follows:

“*Article 12, paragraph 3:*

*The Agency shall **immediately** publish the assessment report on the medicinal product for human use drawn up by the Committee for Human Medicinal Products, and the reasons for its opinion, after deletion of any information of a commercially confidential nature.*

Article 34, paragraph 3

*The Agency shall **immediately** publish the assessment report on the medicinal products for veterinary use drawn up by the Committee for Veterinary Medicinal Products, and the reasons for its opinion, after deletion of any information of a commercially confidential nature”.*

- The Commission accepts the principle of amendments 43, 51, 53, 79, 81, the first part of amendment 87, the last part of amendment 109 and part of amendment 131 aimed at introducing specific provisions for the publication amongst other things of the opinions of the committee of the Agency concerning conditional authorisations, assessment reports, summaries of product characteristics, labels and package leaflets as well as information related to suspected adverse effects of medicinal products authorised by the Community and urgent decisions aimed at suspending the use of a medicinal product, by reference to the implementation of Regulation 1049/2001 relating to public access to documents of the European Parliament, Council and the Commission. However, the application of the provisions set out in this Regulation to the documents of the Agency is already the object of a separate proposal to modify Regulation 2309/93. This proposal, currently under discussion in the European Parliament aims to make the provisions of Regulation 1049/2001 obligatory “for documents held by the Agency”.
- The Commission accepts the principle of amendment 44 aimed at clarifying the provisions concerning the authorisation of certain medicinal products under exceptional circumstances. *Article 13, paragraph 5* for medicinal products for human use and *article 35, paragraph 4* for medicinal products for veterinary use have been reworded as follows:

“*Article 13, paragraph 5:*

*In exceptional circumstances and following consultation with the applicant, authorisation **may be granted subject to a requirement to introduce specific procedures, in particular concerning the safety of the medicinal product, for notifying the relevant authorities of any incident related to its use and for any action taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in annex I to Directive 2001/83/EC. The maintenance of the authorisation is bound to the annual reassessment of these requirements.***

Article 35, paragraph 4:

*In exceptional circumstances, and following consultation with the applicant, authorisation **may be granted subject to a requirement to introduce specific procedures, in particular concerning product safety, for notifying the relevant authorities of any incident related to***

its use and for any action taken. Such authorisation may be granted only for objective, verifiable reasons. The maintenance of the authorisation is bound to the annual reassessment of these requirements.”

- The Commission accepts in part the principle of amendment 49 aimed at introducing the responsibility of the applicant for the accuracy of the documents and the data submitted. However, the second part of the amendment which is aimed at setting out the procedure to be followed by the Agency in the case of incorrect data should not appear in the Regulation. It could be set out in the framework of the internal rules of the Agency. *Article 15 a* is worded as follows:

“The applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.”

The Commission accepts the principle of amendment 50 aimed at assuring the provision of information to health-care professionals by means of networks provided by professional associations, amongst other things. A new *paragraph 4 a, Article 18*, for medicinal products for human use and a new *paragraph 4 a, Article 40*, for medicinal products for veterinary use are worded as follows:

“Article 18, paragraph 4 a:

In this case, the Member State shall assure that health-care professionals are rapidly informed of its action and the reasons for the action. The network provided by the professional associations shall be fully used to this effect. The Member States shall inform the Commission and the Agency of the procedures put in place for this purpose

Article 40, paragraph 4 a:

In this case, the Member State shall assure that health-care professionals are rapidly informed of its action and the reasons for the action. The network provided by the professional associations shall be fully used to this effect. The Member States shall inform the Commission and the Agency of the procedures put in place for this purpose. ”

- The Commission accepts the principle of amendments 52, 80 and 121 aimed at providing public funding commensurate with the pharmacovigilance activities carried out by the Agency. This provision, however, should figure in the chapter in the proposed Regulation which concerns the finances of the Agency. A new paragraph, therefore, should be included in Article 60 of the proposed Regulation; it is reworded as follows:

“Article 60, paragraph 1 a:

In order to ensure full independence, the activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance should receive guaranteed and adequate funding.”

- The Commission accepts the principle of amendment 54 concerning the role of patients in the communication of adverse effects. However, a rewording is necessary to limit the number receiving these communications; in effect it does not seem appropriate that patients should transmit this information directly to marketing authorisation holders, without the intervention of a health-care professional or a competent authority who could manage or filter such information. *Articles 20, subparagraph 3* and *42, subparagraph 3* is therefore reworded as follows:

Article 20, subparagraph 3

*“The holder of the marketing authorisation and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to the medicinal products for human use authorised under this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation. **Patients shall be encouraged to communicate any adverse reaction to their health-care professionals or to the competent authorities for pharmacovigilance.***

Article 42, subparagraph 3

*“The holder of the marketing authorisation and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to the medicinal products for veterinary use authorised under this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation. **Animal owners and breeders shall be encouraged to communicate any adverse reaction to health-care professionals or to the competent authorities for pharmacovigilance.**”*

- The Commission accepts the principle of amendments 59 and 60 aimed at clarifying the time-lines for the submission of the first updated period in safety report and the contents of these reports. Rewording is necessary, however, to indicate the Community context of the medicinal products to which the Regulation applies. Therefore, *article 22, paragraph 3, subparagraph two* for medicinal products for human use and *article 44, paragraph 3, subparagraph two* for medicinal products for veterinary use are worded as follows:

“Article 22, paragraph 3, subparagraphs 2 and 3:

*Unless other requirements have been laid down as a condition of granting of the marketing authorisation by the Community, these records shall be submitted in the form of an updated periodical report on safety, to the Agency and Member States immediately upon request or at least every six months during the first two years **following the initial placing on the market in the Community**, and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately on request.*

*These reports shall be accompanied by a scientific evaluation, **notably a benefit-risk analysis of the medicinal product.***

Article 44, paragraph 3, subparagraphs 2 and 3:

*Unless other requirements have been laid down as a condition of the marketing authorisation by the Community, these records shall be submitted in the form of an updated periodical report on safety, to the Agency and Member States immediately upon request or at least every six months during the first two years **following the initial placing on the market in the Community**, and once a year for the following two years. Thereafter the reports shall be submitted at three-yearly intervals, or immediately on request.*

*These reports shall be accompanied by a scientific evaluation, **notably a benefit-risk analysis of the medicinal product.**”*

The Commission accepts the principle of amendment 62 aimed at specifying the contents of the guidance developed for the collection, verification and presentation of adverse reaction reports. A rewording is necessary, however, so as not to place constraints on the contents of

such guidance. *Article 24, subparagraph 1* for medicinal products for human use and *article 46, subparagraph 1* for medicinal products for veterinary use are worded as follows:

“Article 24, subparagraph 1:

*The Commission, in consultation with the Agency, the Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports. **This guidance shall contain, in particular for the benefit of health-care professionals, rules concerning the transmission of information on adverse reactions.***

Article 46, subparagraph 1:

*The Commission, in consultation with the Agency, the Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse reaction reports. **This guidance shall contain, in particular for the benefit of health-care professionals, rules governing the transmission of information on adverse reactions.**”*

- The Commission accepts the principle of amendments 63 and 88 concerning the dissemination of pharmacovigilance information by means of the access of all interested parties to the database containing this information. *Article 51, paragraph 1, point d)* is worded as follows:

*“d) ensuring the dissemination of information on adverse reactions to medicinal products authorised in the Community by means of a database permanently accessible to all Member States; **health-care professionals, companies and the public shall have appropriate levels of access to these databases; with personal data protection being guaranteed;**”*

The Commission accepts the principle of amendment 64 aimed at providing a specific provision for data collected during the two years following the initial placing on the market. *A new subparagraph* is introduced into *article 24, subparagraph 3* for medicinal products for human use and *into article 46, subparagraph 3* for medicinal products for veterinary use, with a rewording which makes such a collection of data possible but not obligatory.

“Article 24, subparagraph 3 a:

For a period of two years following the initial placing on the market in the Community, the Agency may request that specific pharmacovigilance data be collected from targeted groups of patients. These data shall be evaluated by the Agency.

Article 46, subparagraph 3 a:

***For a period of two years following the initial placing on the market in the Community, the Agency may request that specific pharmacovigilance data be collected under targeted conditions. These data will be evaluated by the Agency.**”*

- The Commission accepts the principle of amendment 66 aimed at providing for strengthened coordination between the national pharmacovigilance systems and the Agency. However, the detailed organisation of national pharmacovigilance systems is a matter for the competence of each Member State; a rewording of the provision is therefore necessary. *Article 25 a*, for medicinal products for human use and *article 47 a* for medicinal products for veterinary use are worded as follows:

“Article 25 a:

The Agency and the national public pharmacovigilance systems shall be organised and operate as a coherent and interactive pharmacovigilance system through which the monitoring of the occurrence of adverse reactions takes place continuously. The Agency shall coordinate the national pharmacovigilance systems, which shall operate in accordance with the criteria of transparency and objectivity.

Article 47 a:

The Agency and the national public pharmacovigilance systems shall be organised and operate as a coherent and interactive pharmacovigilance system through which the monitoring of the occurrence of adverse reactions takes place continuously. The Agency shall coordinate the national pharmacovigilance systems, which shall operate in accordance with the criteria of transparency and objectivity.”

- The Commission accepts the principle of amendment 82 aimed at providing a particular provision in the context of medicinal products for veterinary use, regarding the obligations of the qualified person responsible for pharmacovigilance. In particular this person should also inform the competent authorities, amongst other things, of the presence of residues. *Article 43, point d)* is therefore reworded as follows:

“d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a veterinary medicinal product, particularly information concerning post marketing studies, **as well as information regarding residues of medicinal products.**”

- The Commission accepts the principle of amendment 86 aimed at providing that the Agency shall contain minority views, if these have been expressed. This provision is already set out in *article 54, paragraph 4* of the proposed *Regulation* which specifies that “*the opinion shall consist of the position of the majority of the Members and their divergent positions, with their grounds*”. A new position is, therefore, not necessary.
- The Commission accepts the principle of the second part of amendment 87 aimed at providing for the labels and package leaflets or inserts to be written in a manner that is comprehensive to the public, and checked as being scientifically accurate, in cooperation with industry, patient association and health-care professionals. However, these provisions clearly appear in title V of Directive 2001/83/EC on the Community code relating to medicinal products for human use as well as in title V of Directive 2001/82/EC on the Community code relating to medicinal products for veterinary use. These titles also apply to medicinal products authorised by the centralised procedure that is set out in the proposed Regulation.
- With respect to the functions of the Agency set out in *article 51, paragraph 1* of the proposed Regulation, the Commission accepts the principle of amendments 89 and partially those of amendments 91 and 93. Amendment 89 aims to establish the function of assisting the Member States in the communication of pharmacovigilance information. A rewording is necessary so as not to refer to the Commission; in effect, in the area of pharmacovigilance, for medicinal products authorised through the centralised procedure, the Agency is directly competent for the handling of such information. A new *point d) a)* is introduced and worded as follows:

“Article 51, paragraph 1

d) a) assisting the Member States in the rapid communication of information concerning pharmacovigilance to health-care professionals.”

The last part of amendment 91 aims to establish that the information held in the database accessible to the general public shall be worded in an appropriate and comprehensible manner. *Point j)* is therefore reworded as follows:

“Article 51, paragraph 1

j) creating a database on medicinal products to be accessible to the general public and giving technical assistance for its maintenance; the information provided to the public shall be worded in an appropriate and comprehensive manner;”

The Commission accepts amendment 93, except the last part, with the goal of strengthening the competences of the Agency in relation to the fight against bioterrorism. The last part is not acceptable; in effect, it is not up to the Agency to determine shortcomings in research and strategies to combat biological warfare. *A new point n) a)* should be introduced, therefore, and worded as follows:

“Article 51, paragraph 1

n) a) compilation of scientific information concerning pathogenic agents which might be used in biological warfare, and assessment of the stocks of vaccines and medicinal products currently available to treat them;”

- The Commission partially accepts the principle of amendment 105 aimed at providing for contacts between the rapporteurs and patient organisations in relation to the preparation of the evaluation. *Article 55, paragraph 1, first subparagraph* is therefore reworded to provide for the possibility of such a consultation should the rapporteur deem it necessary: *“where, in accordance with the provisions of this Regulation, the Committee for Human Medicinal Products or the Committee for Veterinary Medicinal Products is required to evaluate a medicinal product, it shall appoint one of its members to act as rapporteur for the coordination of the evaluation. The committee concerned may appoint a second member to act as co-rapporteur. The rapporteur may establish contact with the representatives of patient organisations relevant to the indication of the medicinal product concerned.”*
- The Commission accepts the principle of amendment 109 (first part) aimed at providing an obligation for all members of the committees and boards of the Agency, as well as the rapporteurs and experts, to declare their conflicts of interest at each meeting. However, this provision is already set out in *article 56, paragraph 2, second subparagraph* of the proposed *Regulation*. A specific provision is therefore not necessary.
- The Commission accepts the principle of amendment 113 aimed at setting out the procedure for nominating the Executive Director of the Agency. A rewording is necessary to provide for the proposal of the Commission at the time of a removal of an Executive Director from his post by the Management Board. *Article 57, paragraph 1* is therefore reworded as follows:

“The Executive Director shall be appointed by the Management Board for a period of five years, on the basis of a list of candidates proposed by the Commission following a call for

expressions of interest published in the Official Journal of the European Communities and elsewhere. Before appointment, the candidate nominated by the Management Board shall be invited forthwith to make a statement to the European Parliament and to answer any questions put by its Members. The mandate may be renewed once. At the proposal of the Commission, the Executive Director may be removed from the post by a majority vote of the Members of the Management Board.

- The Commission accepts the principle of amendment 118 aimed at providing for the attendance of the chairmen of the scientific committees at the meetings of the Management Board. A rewording is necessary, however, to include such attendance as an option, which reflects current practice, and to remove the reference to the absence of the right to vote; in effect, the chairmen would not be members of the Management Board and therefore would not have the right to vote. *Article 58, paragraph 3* is therefore reworded as follows:

“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. The chairman of the scientific committees may be invited to the meetings of the Management Board.”

- The Commission accepts in part the principle of amendment 131 aimed at introducing a provision for the publication of the rules and internal procedures of the Agency, its committees and its working groups. A new *subparagraph* is therefore introduced into *article 70* and reworded as follows:

“Article 70, second subparagraph :

The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the internet.”

This amendment also provides for the introduction of provisions concerning the way in which the assessment reports are written as well as the contents of the reports. A rewording is necessary, however, aimed firstly at introducing these provisions in the chapters concerning the authorisation and evaluation of medicinal products for human and veterinary use and secondly to limit, in view of the public access, the requirement for the assessment report to contain a summary which includes, in particular the conditions of use of the medicinal product. A new *subparagraph* is introduced therefore into *article 12, paragraph 3, and 34, paragraph 3* reworded as follows:

“Article 12, paragraph 3, subparagraph 2

The European Public Assessment Reports (EPARs) shall include a summary written in a manner that is accessible to the public. This summary shall contain in particular a section relating to the conditions of use of the medicinal product.

Article 34, paragraph 3, subparagraph 2

The European Public Assessment Reports (EPARs) shall include a summary written in a manner that is accessible to the public. This summary shall contain in particular a section relating to the conditions of use of the medicinal product.

- The Commission accepts the principle of amendment 134 aimed at including in the framework of provisions relative to compassionate use a requirement for continued access of a patient to a medicinal product after its authorisation, during the period between

authorisation and placing on the market. However, a rewording is necessary to clarify the wording of the provision. *A new paragraph 7 bis* is introduced to *article 73* and worded as follows:

“Article 73, paragraph 7 a:

Where a compassionate use programme is set up, the manufacturer shall ensure that the patients who benefit from the medicinal product made available in this context shall continue to have access to the medicinal product once authorised, during the time between the authorisation and the placing on the market.”

- The Commission accepts the principle of amendment 140 which aims to clarify the notion of the responsibility for placing a medicinal product on the market. It recognises the possibility of effecting the placing on the market by the marketing authorisation holder himself or by his representative. A rewording is necessary to clarify that the notion of responsibility lies only with the holder of the authorisation.

Article 2, subparagraph 2 is therefore worded as follows :

“Article 2, subparagraph 2

The holder of a marketing authorisation for the medicinal products covered by this Regulation should be established in the Community. He is responsible for the placing on the market of the medicinal product whether this is done in practice by himself or by one or other persons designated to this effect”.

- The Commission accepts the principle of amendment 141 which aims to provide a requirement on the part of the holder of the marketing authorisation to inform the competent authorities of any suspension of the marketing of the medicinal product. The provision should be reworded, however, to use the term “suspension” and not “ban or withdrawal” and to include a time limit within which the information should be provided. A new *article 21 a* and a new *article 43 a* are introduced and worded as follows :

“Article 21a

The holder of a marketing authorisation shall also inform the agency of any possible suspension, temporary or permanent, of the marketing of the product. This notification shall take place, unless there are exceptional circumstances, at least two months before the interruption in the marketing

Article 43 a

The holder of a marketing authorisation shall also inform the agency of any possible suspension, temporary or permanent, of the marketing of the product. This notification shall take place, unless there are exceptional circumstances, at least two months before the interruption in the marketing”

- The Commission accepts amendments 153 and 155 which aim to include a requirement on the part of the Agency with respect to the competent authorities of the Member States at the time of the withdrawal of applications for marketing authorisation for medicinal products for human and veterinary use before the opinion of the competent scientific committee has been given. Rewording is necessary to provide a requirement for the applicant to communicate the reasons for such a withdrawal and a greater obligation to

inform on the part of the Agency. A new *Article 10a* and a new *Article 32a* are therefore introduced and worded as follows :

“Article 10a :

If an applicant withdraws an application for marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate his reasons and the Agency shall publish this information.

Article 32a :

If an applicant withdraws an application for marketing authorisation previously submitted to the Agency before an opinion has been given on the application, the applicant shall communicate his reasons and the Agency shall publish this information.

- The Commission accepts the principle of amendments 163, 165 and 166 aimed at changing the period of validity of the marketing authorisation. In effect the European Parliament proposes to amend the Commission’s proposal which aims to remove the requirement to renew the authorisation after 5 years. The European Parliament proposes to introduce a requirement to renew the authorisation five years after the first marketing authorisation. After this first renewal, the authorisation will be considered as valid for an unlimited period. *Recital 29* and *Article 13 paragraph 1* for medicinal products for human use and *Article 35 paragraph 1* for medicinal products for veterinary use are therefore amended as proposed by the European Parliament. A rewording is necessary, however, to specify better the context of the first evaluation as well as to avoid adding time limits for such a procedure.

“Recital 29 :

*In line with the current provisions of Directives 2001/83/EC and 2001/82/EC the term of validity of a Community marketing authorisation **for new medicinal products** should be **limited initially to five years. After this first renewal, the marketing authorisation shall be considered as valid for an unlimited period.***

*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 linked to maintaining such authorisations.*

Article 13, paragraph 1 :

*Without prejudice to paragraphs 2 and 3, **the marketing authorisation shall be valid for five years.***

This authorisation may be renewed after five years on the basis of a reassessment of benefit compared to risk. On the occasion of the five year renewal of the marketing authorisation, the authorisation holder shall submit a consolidated dossier on the quality, safety and efficacy of the medicinal product with all the variations introduced during the five years of validity.

The application for renewal shall be submitted to the Agency at least six months prior to the date of expiry of the authorisation.

After this renewal, the marketing authorisation shall be valid for an unlimited duration.

Article 35, paragraph 1 :

Without prejudice to paragraphs 2 and 3, the marketing authorisation shall be valid for five years.

This authorisation may be renewed after five years on the basis of a reassessment of benefit compared to risk. On the occasion of the five year renewal of the marketing authorisation, the authorisation holder shall submit a consolidated dossier on the quality, safety and efficacy of the medicinal product with all the variations introduced during the five years of validity.

The application for renewal shall be submitted to the Agency at least six months prior to the date of expiry of the authorisation.

After this renewal, the marketing authorisation shall be valid for an unlimited duration”.

3.3. Amendments not accepted by the Commission: 2, 3, 5, 6, 7, 8, 10, 21, 25 (first part), 26, 27, 29, 39, 42, 45, 46, 48, 49 (except the first sentence), 56, 57, 58, 65, 67, 70, 71, 83, 85, 91 (except the last sentence), 92, 93, (last sentence), 94, 97, 101 (the reference to the Committee on Herbal Medicinal Products), 105 (first part), 107 (first part), 108 (the reference to the Committee on Herbal Medicinal Products), 110 (the first part), 119, 122, 128 (last part), 132, 133, 145, 147, 148, 152, 157 (first part), 162, 173, 174 and 175.

- The Commission does not accept amendment 2 aimed at explicitly *citing* herbal medicinal products as medicinal products that may be of particular benefit to patients and consequently could benefit, on an optional basis, from access to an authorisation through the centralised procedure. Although not excluding this possibility, the Commission does not consider it necessary to mention this explicitly in a recital; *in effect, in effect, the characteristics of these medicinal products through their “traditional” nature will mean that the possibility foreseen in article 3, paragraph 2 of the proposed regulation will not apply to this type of medicinal products in particular.*
- The Commission does not accept amendment 3 aimed at foreseeing an obligation for the Commission to prepare a proposal for a specific regulation establishing a policy for orphan medicinal products for veterinary use. This recital does not reflect any provision for the proposed regulation. In addition, it would oblige the Commission to propose a regulation within a precise time limit which would go against the Commission’s right of initiative. The position of the Commission regarding the basic question is contained in the Commission Communication of 5 December 2000 (COM(2002)806 final) concerning the availability of veterinary medicinal products.
- The Commission does not accept amendments 5, 6, 10 and 83 aimed at introducing into the recitals, on the one hand a reference to the provisions of Directive 2001/20/EC on clinical trials and on the other hand obligations concerning paediatric indications as well as a provision obliging the scientific committee to consult experts in paediatrics. Concerning the reference to the provisions of Directive 2001/20/EC on clinical trials, this has already been taken up within the context of amendments 4 and 96, which the Commission has accepted in principle. The issues concerning medicinal products for paediatric use will be taken up in the future legislative proposal that will be aimed specifically at the questions relating to these medicinal products.
- The Commission does not accept amendments 7, 8 and 26 aimed at introducing two recitals concerning medicines destined for export and incentives for research on medicinal

products against tropical diseases. Another provision is also aimed at introducing an obligation to verify at the time of the request for marketing authorisation whether the medicinal product may also be suitable for the treatment of tropical diseases. The proposed regulation is aimed uniquely, with the exception of article 52 concerning cooperation with the World Health Organisation, at medicinal products to be placed on the market in the Community. In addition it would not be justifiable to require research on use in the treatment of possible tropical diseases for all medicinal products without distinction. The consequence of such an obligation would be an increase in the requirements for marketing authorisation and delay the availability of medicinal products to patients.

- The Commission does not accept amendment 21 aimed at introducing an exception to one of the three conditions allowing the optional application of national authorisation procedures to generics of medical products that have been authorised through the centralised procedure. The condition in question is the one concerning the conformity in all respects of the summary of product characteristics of the generic medicinal product with that of the reference medicinal product. The exception would aim to exclude from this condition certain parts of the summary of product characteristics, which would still be covered by patent law at the time the generic medicinal product was marketed. The Commission considers, however, that the competent authorities in charge of the authorisation of generic medicinal products do not have the competence to take into consideration during their evaluation criteria other than the criteria of quality, safety and efficacy.
- The Commission does not accept the first part of amendment 25 aimed at introducing an *obligation/option* to include with the request for authorisation a comparison with existing medicinal products authorised for the same indications. The comparative efficacy of a medicinal product cannot be considered as a criterion for authorisation. Only those elements necessary to demonstrate the quality, efficacy and safety of each individual product can be required at the time of the request for marketing authorisation.
- The Commission does not accept amendment 27 aimed at introducing an obligation for State laboratories or laboratories designated by the Member State for the testing of medicinal products not to have a direct interest in the final authorisation of the medicinal product. This obligation is neither justified nor necessary; in effect State laboratories have no interest, direct or indirect, in the authorisation of medicinal products. In this context for each Member State they exercise an activity of surveillance or control in the name of the competent authority of each Member State.
- The Commission does not accept amendments 29 and 70 aimed at making obligatory the possibility of a rapporteur or expert appointed by the committees of the Agency to accompany the inspectors from the Member States. This must remain a possibility; it would be disproportionate to make this systematic for each inspection carried out.
- The Commission does not accept amendment 39 aimed at adding to the body of data that the marketing authorisation holder must provide to the Agency, data relating to adverse reactions to the product concerned. The transmission of these data is already foreseen in the specific framework of the rules relating to pharmacovigilance.
- The Commission does not accept amendment 42, 56 and 58 aimed at obliging the package leaflet of all new medicinal products authorised by the Agency to include the phrase ‘newly authorised medicinal product’ as well as an invitation to patients to report any adverse effects and an obligation to the marketing authorisation holder to handle any

information reported directly by the patient. However, and as formulated in amendment 54 which the Commission has accepted in principle, *patients cannot be invited to communicate adverse effects directly to the marketing authorisation holders without an intervention or a filter of the health professionals or the competent authorities.*

- The Commission does not accept amendment 45 aimed at setting out a procedure to be followed by the scientific committee of the Agency following the submission of a request for the application of the accelerated procedure. The Commission considers that the details of such a procedure should be decided in the context of the adoption of the internal rules of procedure of the relevant committee.
- The Commission does not accept amendment 46 aimed at removing the period of 10 years data protection proposed in the context of medicinal products authorised according to the centralised procedure and at proposing that this period should automatically be the period applicable in the context of medicinal products authorised according to national procedures. The Commission considers that the period of data protection for medicinal products authorised through the centralised procedure is particular to that procedure; in effect, by virtue of its scope it applies to more innovative medicines or medicines which have been manufactured using a procedure of biotechnology. For this reason, the period currently foreseen by Regulation 2309/93 should not be modified nor depend on the final outcome of the period of data protection which will be decided for medicines authorised in the Member States.
- The Commission does not accept amendment 48 aimed at introducing a reference to Community law in the context of the provisions relating to the adaptation to technical progress of methods of manufacture and control. The Commission considers that this reference is not legally necessary.
- The Commission does not accept amendment 49, apart from the first sentence which concerns the responsibility for the data submitted, aimed at providing for a procedure to be applied by the Agency when the data submitted by the applicant or the authorisation holder are incorrect. The Commission considers that the question of the procedure to be followed in such a case is already set out in article 11, paragraph 2 of the proposed regulation.
- The Commission does not accept amendment 57 aimed at removing the possibility, in exceptional cases, to communicate adverse effects by a means other than electronic reporting. It is necessary to maintain this reference for the cases where transmission by the electronic route prove to be technically impossible.
- The Commission does not accept amendment 65 aimed at providing an obligation for the agency to publish an annual report on reported adverse effects as well as to indicate areas of further research requirements. As the reports on the adverse effects of individual products are not compiled on an annual basis, it does not seem appropriate to provide for such an obligation. In addition, the Agency does not have the competence to define research policy at the Community level.
- The Commission does not accept amendment 67 aimed at providing for an obligation for authorisation holders to contribute to the costs incurred by the pharmacovigilance activities developed by the Agency. On the other hand, the Commission has accepted in principle amendments 52, 80 and 121 which aim to guarantee that the pharmacovigilance activities will benefit from an adequate and guaranteed financing.

- The Commission does not accept amendment 71, nor amendment 107, first part, aimed at providing for the possibility that the grounds for appeal against the opinions of the committees of the Agency could be based on new data that were not available at the time of *the first opinion*. The Commission considers that the appeal should only be possible on the basis of data which has already been evaluated. In effect, if new data were to appear, these should be the subject of a completely new evaluation.
- The Commission does not accept amendment 85, nor the reference to the committee for herbal medicinal products contained in amendments 101, 105, and 108 aimed at defining the competences, the rules of nomination of the members as well as the way of working of this committee. These provisions figure in the proposed directive on medicinal products, which is currently the subject of a first reading before the Council and Parliament. In effect, the competences of this committee, its composition and its way of working, in line with the provisions for the committee on orphan medicinal products in the specific regulation, should be established in the framework of the new directive.
- The Commission does not accept the first, second and third parts of amendment 91 aimed, in the context of the data base on authorised medicinal products, at assuring the independence with respect to pharmaceutical companies, at permitting a comparison between different medicines and at including a specific section on medicines authorised for paediatric use. As far as the first part is concerned, it cannot be excluded that pharmaceutical firms do not contribute financially to the development of this data base; with regard to the second part the data base will contain necessary and *particular* information for each medicinal product on the basis of which a comparison *could be possible*; finally, as far as the third part is concerned, the future legislative proposal specifically medicines for children will contain the necessary elements for the development of a data base.
- The Commission does not accept the last part of amendment 93 aimed at giving to the Agency, within the framework of activities against bioterrorism, the competence to evaluate the deficiencies in research in this area and the strategies to combat biological warfare. This concerns a competence which should belong to policy-making bodies and not to a scientific agency.
- The Commission does not accept amendment 94 aimed at providing for the participation of the Agency in the implementation of specific measures relative to the capacity-building in developing countries, particularly through initial and further training courses for employees of the authorisation and inspection authorities in such countries. The provisions of the proposed regulation are only aimed at the authorisation, supervision and pharmacovigilance of authorised medicines; such a provision would not fall within the scope of the proposal.
- The Commission does not accept amendment 97 aimed at extending the cooperation with the World Health Organisation to a cooperation also with the International Office of Epizootics. The establishment of such a procedure in the sector of veterinary medicinal products has not been the subject of a specific request on the part of the Office concerned. Such a procedure requires a collaboration and engagement on the part of the international organisation which so far has not been discussed.
- The Commission does not accept the first part of amendment 110 aimed at providing requirements for the personnel of the Agency relating to financial interests or other interests concerning the pharmaceutical industry. This provision is not necessary as these

personnel are already subject to the rules of the statute applicable to officials or other agents working for the European institutions.

- The Commission does not accept amendment 119 aimed at providing for, within the composition of the Advisory Board, representatives of interested parties or other organisations other than the competent authorities of the Member States. As the objective of such an Advisory Board is to bring together the competent authorities of the Member States and in particular considering amendment 116 which the Commission has accepted on the composition of the Management Board, it is not considered appropriate to provide for representatives of other interested parties within the Advisory Board in addition. Moreover, the functions of this board are not decision making and are supposed to allow the positions of the competent authorities of the Member States to be heard.
- The Commission does not accept amendment 122 aimed at providing for the commitment on the part of the budgetary authority to assure the adequate financial resources for all new competences or tasks that are transferred to the Agency. A similar provision has already been accepted by the Commission in the context of amendment 120.
- The Commission does not accept the last part of amendment 128 aimed at providing for the possibility for the Management Board to adjust the level of the fees each year in line with the rate of inflation. The fees regulation, Council Regulation (EC) No 297/95 of 10 February 1995, sets out that a modification of the level of the fees should be adopted by the Commission through a comitology procedure. An amendment of the regulation is necessary for each modification of the fees.
- In the context of the provision concerning compassionate use the Commission does not accept amendments 132 and 133 aimed firstly at providing that the entirety of title II, chapter 3 on pharmacovigilance applies to medicines made available in the name of compassionate use, and secondly at requiring the manufacturer to finance the medicinal products. The reference to the entirety of the chapter on pharmacovigilance can not be applied to medicines for compassionate use as they are not yet authorised. The essential provisions of this chapter which should be applied are already taken up in the original proposal of the Commission. With respect to financing, the public authorities' decision to finance compassionate treatments cannot be excluded.
- The Commission does not accept amendment 145 aimed at removing the requirement that only a single authorisation may be granted to a particular applicant for a specific medicinal product. The reason for and the objective of the centralised procedure are to have one medicinal product, one authorisation, one name valid throughout the Community. The Commission proposal, however, provides for certain exceptional cases where, for reasons of public health linked to the availability of a medicinal product the same medicinal product could be the object of several authorisations. These cases will remain limited and should be considered as exceptional.
- The Commission does not accept amendments 147 and 148 aimed at introducing the question of the difference between the sexes as an obligatory criteria to take into consideration during the evaluation of a medicinal product. In any event, this question comes under the procedure of scientific evaluation and a differentiated approach according to the application. The reference in the body of the legislation is not necessary.
- The Commission does not accept amendment 152 aimed at introducing a recital that considers that the central tasks of the Agency should be financed through the community

budget. The fees should serve to pay for the services carried out for industry; the community contribution should serve to finance the tasks of a public nature required of the Agency by the legislators, whether they are central or not.

- The Commission does not accept the first part of amendment 157 aimed at including in the database on authorised medicinal products the data concerning pharmacovigilance. Specific databases for pharmacovigilance and for clinical trials are already provided for in Community legislation.
- The Commission does not accept amendment 162 aimed at defining patient representative groups as well as specifying their composition and way of working. This question will be taken up during the adoption of the public health programme which, amongst other things, will establish the legal basis for the financing and Community support for these groups.
- The Commission does not accept amendment 173 aimed at specifying that the legislation applicable to medicinal products involves matters relating to public health. This consideration already figures in a number of recitals in the Commission proposal and is the basis of a number of provisions of this proposal.
- The Commission does not accept amendment 174 aimed at introducing an obligation to publish evaluation reports including the elements which could be considered to be commercially confidential. It seems appropriate for legal reasons to preserve without derogation the exemption of certain commercially confidential elements of the evaluation report from any publishing requirements.
- The Commission does not accept amendment 175 aimed at providing that the duration of the evaluation could not be less than 90 days. The detail of the different stages of the scientific evaluation procedure should be left to the internal rules of procedure of the different scientific committees. It is not appropriate to include them in the regulation.

4. MODIFIED PROPOSAL

In keeping with Article 250, paragraph 2, of the EC treaty, the Commission has modified its proposal along the lines indicated below.