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REPORT FROM THE COMMISSION

**on the experience acquired as a result of the operation of the procedures
for granting marketing authorisations for medicinal products laid down
in Regulation (EEC) N° 2309/93, in chapter III of directive 75/319/EEC
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**Report on the basis of
Article 71 of Regulation (EEC) No 2309/93**

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I. INTRODUCTION

Medicinal products are goods covered by the internal market principle of **free movement of goods**, as has been confirmed by the Court of Justice on several occasions. Consequently, Article 28 EC forbids all quantitative restrictions on imports and all measures having equivalent effects between Member States. However, Article 30 EC allows prohibitions or restrictions on imports, exports or goods in transit justified on certain grounds, including the **protection of health and life of humans and animals**. On the basis of these provisions, the Member States have enacted and maintained specific legislation on medicinal products for human and veterinary use, thus restricting the free movement of these products in the internal market.

In order to remove these obstacles to the internal market in pharmaceuticals while at the same time ensuring a high level of public health protection, the Community has **gradually developed a harmonised legislative framework for medicinal products**. The first major step was the adoption of Council Directive 65/65/EEC⁴ of 26 January 1965 stipulating, inter alia, that a medicinal product may only be placed on the market in the European Union after a marketing authorisation has been granted. By now, this Directive has been amended several times. Step by step, the framework was extended and refined by a great number of legal acts, including, with regard to medicinal products for human and veterinary use:

- Directive 75/318/EEC on the particulars and documents accompanying an application for marketing authorisation⁵,
- Directive 75/319/EEC containing important substantial and procedural provisions,

¹ Council Regulation (EEC) n° 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, OJ L 214, 24.8.1993, p. 1.

² Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ L 147, 9.6.1975, p. 13.

³ Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products, OJ L 317, 6.11.1981, p. 1.

⁴ Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ B 22, 9.2.1965, p. 369.

⁵ Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, OJ L 147, 9.6.1975, p. 1.

- Directive 89/105/EEC on issues of prices and reimbursement⁶,
- Directive 89/342/EEC on immunological medicinal products⁷,
- Directive 89/343/EEC on radiopharmaceuticals⁸,
- Directive 89/381/EEC on medicinal products derived from human blood or human plasma⁹,
- Directive 91/356/EEC on good manufacturing practice¹⁰,
- Directive 92/25/EEC on the wholesale distribution¹¹,
- Directive 92/26/EEC on the classification for the supply of medicinal products¹²,
- Directive 92/27/EEC on the labelling and on package leaflets¹³,
- Directive 92/28/EEC on the advertising of medicinal products¹⁴,
- Directive 92/73/EEC on homeopathic medicinal products¹⁵,
- Directive 81/851/EEC relating to veterinary medicinal products,
- Directive 81/852/EEC on the particulars and documents accompanying an application for marketing authorisation for veterinary medicinal products¹⁶,

⁶ Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8.

⁷ Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directive 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens, OJ L 142, 25.5.1989, p. 14.

⁸ Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals, OJ L 142, 25.5.1989, p. 16.

⁹ Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma, OJ L 181, 28.6.1989, p. 44.

¹⁰ Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use, OJ L 193, 17.7.1991, p. 30.

¹¹ Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use, OJ L 113, 30.4.1992, p. 1.

¹² Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use, OJ L 113, 30.4.1992, p. 5.

¹³ Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets, OJ L 113, 30.4.1992, p. 8.

¹⁴ Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use, OJ L 113, 30.4.1992, p. 13.

¹⁵ Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products, OJ L 297, 13.10.1992, p. 8.

¹⁶ Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of testing of veterinary medicinal products, OJ L 317, 6.11.1981, p. 16.

- Directive 90/677/EEC on the extension of the Community provisions on veterinary medicinal products to include immunological products¹⁷,
- Directive 91/412/EEC on good manufacturing practice for veterinary medicinal products¹⁸,
- Directive 92/74/EEC on homeopathic veterinary medicinal products¹⁹,
- Regulation (EEC) n° 2377/90 on maximum residue limits for veterinary medicinal products in foodstuffs of animal origin²⁰.

Despite this legislation, the progress in terms of completing the single market in pharmaceuticals was not satisfactory. In the beginning of the 1990s, it was therefore decided to fundamentally improve the authorisation procedures. A **new system** was established with the adoption of Regulation (CEE) n° 2309/93²¹ as well as a number of Directives²² amending the existing legislative framework. This new system entered into force in 1995 and is based on **two separate procedures** for the granting of marketing authorisation for a medicinal product:

- The **centralised procedure**²³ leads to a single marketing authorisation valid throughout the whole Community. It is granted in the form of a Commission decision, which is based on a scientific evaluation by the committees created within the European Agency for the Evaluation of Medicinal Products (EMA)²⁴. This procedure is mandatory for certain medicinal products developed by means of biotechnological processes. Over and above that, the procedure is optional for certain other categories of medicinal products, inter alia those presented for an entirely new indication constituting a significant innovation, new medicinal products derived from human blood or human plasma or those containing a new active substance which had

¹⁷ Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products, OJ L 373, 31.12.1990, p. 26.

¹⁸ Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products, OJ L 228, 17.8.1991, p. 70.

¹⁹ Council Directive 92/74/EEC of 22 September 1992 widening the scope of Directive 81/851/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to veterinary medicinal products and laying down additional provisions on homeopathic veterinary medicinal products, OJ L 297, 13.10.1992, p. 12.

²⁰ Council Regulation (EEC) n° 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin, OJ L 224, 18.8.1990, p. 1.

²¹ 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, OJ L 214, 24.8.1993, p. 1

²² Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products, OJ L 214, 24.8.1993, p. 22; Council Directive 93/40/EEC of 14 June 1993 amending Directives 81/851/EEC and 81/852/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products, OJ L 214, 24.8.1993, p. 31; Council Directive 93/41/EEC of 14 June 1993 repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high- technology medicinal products, particularly those derived from biotechnology, OJ L 214, 24.8.1993, p. 40.

²³ For the different phases of this procedure see flow chart no 1 in the annex.

²⁴ Established by Article 49 paragraph 1 of Regulation 2309/93.

not been authorised by the 1st January 1995 by any Member State for use in a medicinal product.

- For those medicinal products, not eligible for the centralised procedure or where the applicant chooses not to follow the centralised procedure, the new system provides for a **mutual recognition procedure**²⁵. Where eligible, this procedure has to be used by the applicant whenever an application for marketing authorisation for a medicinal product concerns two or more Member States. Within this procedure, the competent authority of one Member State, the so-called Reference Member State, carries out the scientific evaluation. The other Member States concerned by an application for the same product shall recognise the evaluation of the Reference Member State. A Concerned Member State may however raise objections where it considers that there are grounds for supposing that the authorisation of the medicinal product may present a risk to public health. In this case, all the Member States concerned by the application shall use their best endeavours to reach an agreement on the issue. If they fail, the matter is referred to the EMEA where an arbitration procedure is followed. The arbitration leads to a Commission decision addressed to the Member States concerned by the matter, which have to implement the necessary provisions.

The Commission adopted two Communications, 94/C82/04²⁶ and 98/C2016²⁷ with a view to better specifying the scope of both procedures and to interpret the provisions dealing with procedural aspects.

When establishing this new system, it seemed appropriate to make sure that it could be evaluated in due course. **Article 71 of Regulation 2309/93** therefore obliged the Commission to report on the experience acquired as a result of the operation of the two authorisation procedures within six years of the entry into force of the Regulation. An obligation to review the newly established legislative framework was not laid down, intentionally leaving open the possibility of follow-up based on the results of the evaluation.

During the preparation of this report it appeared necessary to extend the evaluation and the reflections on necessary legislative amendments not only to the authorisation procedures, as envisaged in Article 71 of Regulation 2309/93, but also to other aspects of the pharmaceutical legislation. The main reasons to consider other aspects of the pharmaceutical legislation are based on the development of science and technology, certain positions taken by the European Parliament (reports) and/or by the Council (conclusions or resolutions), and more generally the evolution of the European society. The **scope of the report** has **consequently been extended** to the whole regulatory system established by the pharmaceutical legislation.

²⁵ For the different phases of this procedure see flow chart no 2 in the annex.

²⁶ JO C 82, 19.3.1994, p. 4.

²⁷ JO C 229, 22.7.1998, p. 4.

II. THE NEW AUTHORISATION PROCEDURES – EVALUATION AND REVIEW PROPOSALS

As already mentioned, Article 71 of Regulation (EEC) n° 2309/93 provides for the obligation for the Commission to publish a general report on the overall functioning of the system. In particular the objective of this report is to evaluate the experience acquired as a result of the operation of the centralised and the mutual recognition authorisation procedures laid down in this Regulation, in Chapter III of Directive 75/319/EEC (medicinal products for human use) and in Chapter IV of Directive 81/851/EEC (medicinal products for veterinary use) after six years of operation.

II.1. Experience with the system since 1995

In order to gain a comprehensive and objective picture of the experience with these procedures made by all parties concerned such as the national authorities, industry, patients and health professionals, the Commission asked an independent consultant to systematically investigate the general experiences. This approach aimed to guarantee a better basis for an appropriate and unbiased report on the overall functioning of the new marketing authorisation procedures.

II.1.1. Evaluation by external consultants

In 1999, the Commission concluded a contract with **CMS Cameron McKenna and Andersen Consulting** for the evaluation of the operation of the two authorisation procedures²⁸. The task was to review the regulatory processes and the telematics systems in place and to analyse the extent to which the results achieved over the period from 1995 to 1999 have met the objectives set out in the legislation.

Between February and August 2000, **extensive consultations and interviews** were held by the consultants. Questionnaires and interviews covered the regulatory authorities responsible for authorising medicines for human and veterinary use. A series of interviews were carried out within the EMEA to get an insight into detailed operation of the centralised procedure and the role of the EMEA. The chairmen of the CPMP²⁹, CVMP³⁰, MRFG³¹ and VMRFG³² were interviewed in order to review practical issues, which have arisen from the operation in the new systems. The marketing authorisation holders who had used the centralised procedure were invited to participate by completing a detailed questionnaire concerning their most recent experience of using the system and by taking part in follow up interviews on issues raised in the questionnaire. According to the same methodology a large sample of marketing authorisation holders who had used the mutual recognition procedure was selected for questionnaires and interviews. Group discussions were conducted with all major pharmaceutical associations upon a range of issues arising from the two procedures. Ministries in the Member States, responsible for health, social affairs, finance and agriculture were sent written questionnaires, seeking their opinions upon issues such as evaluation of the safety of medicinal products and access to market. A selective number of regulatory authorities responsible for authorising medicines in candidate countries were also approached. Ministries in candidate countries responsible for health, social affairs, finance and agriculture could also give an opinion upon issues such as evaluation of safety and access to market.

²⁸ Contract PSR/99/502316.

²⁹ CPMP: Committee for Proprietary Medicinal Products.

³⁰ CVMP: Committee for Veterinary Medicinal Products.

³¹ MRFG: Mutual Recognition Facilitation Group.

³² VMRFG: Veterinary Mutual Recognition Facilitation Group.

Professional associations responsible for the regulation of doctors, dentists, pharmacists and veterinary practitioners were sent written questionnaires, seeking the comments of those prescribing, dispensing or administering medicinal products on issues such as transparency, the assessment of safety and the availability of medicines. Patient associations were invited to participate in two ways. National consumer organisations, together with associations representing a broad spectrum of disease areas and countries of establishment were sent written questionnaires, asking for their views on issues such as the authorisation and the availability of new medicines. In addition, the questionnaire was placed on the website of the Commission service responsible for the pharmaceutical legislation³³ to provide the interested associations with the opportunity to send in their contributions.

The **final report**, referred to hereafter as Cameron McKenna Andersen report, was published in October 2000. It is available on the website cited above³⁴. For details on the evaluation done by the external consultants and their findings, reference is made to this report.

II.1.2 Further information and statistics

In addition to the analysis of Cameron McKenna/Andersen, the Commission organised and participated in various workshops and public hearings on the evaluation of the existing legislation and possible legislative amendments. These workshops and hearings involved the participation of Member States representatives, European associations in the area of pharmaceuticals as well as other interested parties. All oral and written remarks of Member States as well as industry, health professionals, consumers and patients have been carefully considered.

When evaluating the overall development and success of the existing procedures and their development, **further facts and statistics** have to be taken into consideration. Unless otherwise indicated, these figures relate to the period between 1995 and 2001:

a) Statistics relating to the EMEA

To contribute to the protection and promotion of public and animal health, the EMEA has to mobilise scientific resources from throughout the European Union to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health professionals. It is also important to develop efficient and transparent procedures to allow timely access by patients to innovative medicines through a single marketing authorisation, as well as to control the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues of veterinary medicines in food of animal origin.

To manage these tasks, the EMEA has continuously expanded. This is reflected in the significant increase in the budget, from 6 813 085 ECU in 1994 to 62 152 000 € in 2001³⁵ and also in the increasing EU subsidies to the EMEA budget³⁶. The amount of these subsidies has changed over the years. Starting with a subsidy of 6 800 000 ECU in 1994 there are, since the year 2000, in addition to the general annual subsidy, special contributions from EEA-EFTA states and a special one voted by the EU budgetary authority for orphan medicinal products. The general subsidy for the year 2001 amounts to 14 000 000 €, the special orphan subsidy

³³ <http://pharmacos.eudra.org>.

³⁴ Under the address <http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2000/nov/reportmk.pdf>.

³⁵ See table 1 on “EMEA budget evolution” in the annex.

³⁶ See table 2 on “EU contribution to EMEA budget” in the annex.

amounts to 1 300 000 €. The EEA-EFTA state contribution amounts to 250 000 €. In general, the relative part of the EU contributions to the EMEA budget has decreased continuously over the years³⁷. Whereas in 1996 (starting up phase), the percentage was about 47 %, it had decreased to less than 23 % in 2001.

In line with the significant expansion of activities the staff of the EMEA has continuously increased³⁸. All the staff working at the EMEA have the status of temporary agents under the EU staff regulations. There are no permanent officials, but some additional interim staff and national experts. The number of people in post rose from 50 (as of 31.12.1995 with 17 externals) to 194 (as of 31.12.2000 with 3 national experts and 13 externals).

b) Statistics on the two procedures³⁹

- Apart from the medicinal products for which it is mandatory (Part A of the Annex to Regulation (EEC) n° 2309/93), the **centralised procedure** has been extensively used for medicinal products for which it is optional (Part B of the same Annex).

For medicinal products for human use, from 1995 to 2000 inclusive, 97 applications were filed under Part A and 182 applications under Part B for a total of 279 applications⁴⁰. For medicinal products for veterinary use, from 1995 to 2000 inclusive, 18 applications were filed under Part A and 21 applications under Part B for a total of 39 applications⁴¹. After the granting of a marketing authorisation, the applicant can apply for extensions or variations of the marketing authorisation already granted. The figures contained in table 5 and 6 of the annex give a complete picture on the applications, variations and extensions, withdrawals by the applicants before the end of the procedure and opinions given by the CPMP and CVMP.

For medicinal products for human use, from 1995 to May 2001, 171 have been authorised, 2 have been suspended and 12 revoked⁴². Some revocations are made upon request of the marketing authorisation holder but suspensions or revocations are generally linked to pharmacovigilance issues. For the centralised procedure, as well as for the mutual recognition procedure, the number of variation applications is increasing dramatically. In the centralised procedure, from 1995 to 2000, 816 type I variations (minor variations) and 385 variations type II (major variations) have been processed.

³⁷ See table 3 on “Percentage of EU contributions to EMEA budget” in the annex.

³⁸ See table 4 on “Staff evolution (number of posts)” in the annex.

³⁹ Regarding veterinary medicinal products, the figures show that the evolution of the new system points to an initial reluctance on the part of the pharmaceutical companies to get acquainted with and use the centralised and mutual recognition procedures. The small size of the market of veterinary medicinal products has also to be taken into consideration.

⁴⁰ See table 5 on “Centralised procedures (human medicinal products)” in the annex.

⁴¹ See table 6 on “Centralised procedures (veterinary medicinal products)” in the annex.

⁴² See table 7 on “Centralised procedure: Figures on Marketing Authorisations granted by the European Commission (status in 5/2001)” in the annex.

For medicinal products for veterinary use, from 1995 to May 2001, 26 have been authorised and 1 has been suspended⁴³. No authorisations have been revoked. For these products, it has to be indicated that relatively few variations to the marketing authorisations have been processed (57 type I and 6 type II). The number of extensions to marketing authorisations was 9 and one abridged application has been authorised after informed consent from the original marketing authorisation holder.

- The **mutual recognition procedure**, as far as medicinal products for human use are concerned, has been used for medicinal products like generics, extensions of marketing authorisations already granted, medicinal products having followed the "concertation procedure" which was in place before the entry into force of the centralised procedure as well as for medicinal products containing new active substances.

From 1995 to 2000, 988 procedures have been finalised⁴⁴.

Concerning most particularly medicinal products containing new active substances and taking into account only those for which the centralised procedure is optional, since 1995 until 2000, 113 applications were made through the centralised procedure and 73 through the mutual recognition procedure⁴⁵.

For the mutual recognition procedure, as well as in the centralised procedure, the number of variation applications is increasing dramatically. In the mutual recognition procedure, 2 183 type I variations and 1 096 type II variations have been processed⁴⁶.

Concerning medicinal products for veterinary use, the number of mutual recognition procedures has increased significantly since the 1st January 1998 when the mutual recognition procedure became compulsory for the majority of the different types of pharmaceutical products⁴⁷. Whereas in 1996 and in 1997 there were only 13, respectively 16 mutual recognition procedures concluded, the number rose to 31 in 1999 and 32 in 2000⁴⁸. It is difficult to discern any specific trend, although the majority of the products in the mutual recognition procedure are not innovative. The centralised procedure and the mutual recognition procedure were both used to a similar extent for authorisation of innovative products, excluding biotechnological products (List A) subject to a compulsory assessment in the centralised procedure. Concerning most particularly medicinal products containing new active substances for which the centralised procedure is optional, from 1995 to 2000, 20 applications were made through the centralised procedure and 14 followed the mutual recognition procedure⁴⁹.

⁴³ See table 7 on "Centralised procedure: Figures on Marketing Authorisations granted by the European Commission (status in 5/2001)" in the annex.

⁴⁴ See table 9 on "Mutual recognition procedure (human medicinal products)" in the annex.

⁴⁵ See table 11 on "Applications for human medicinal products with new active substances submitted under the centralised procedure and the mutual recognition procedure since 1995" in the annex.

⁴⁶ See table 9 on "Mutual recognition procedure (human medicinal products)" in the annex.

⁴⁷ Article 8a of Directive 81/851/EEC, as modified by Council Directive 93/40/EEC of 14 June 1993 amending Directives 81/851/EEC and 81/852/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products, OJ L 214, 24.8.1993, p. 31.

⁴⁸ See table 10 on "Mutual recognition procedures (veterinary medicinal products since 1996) in the annex.

⁴⁹ See table 12 on "Applications for veterinary medicinal products with new active substances submitted under the centralised and the mutual recognition procedure since 1995" in the annex.

Where mutual recognition cannot be achieved or where there is a lack of harmonisation between decisions taken by the Member states for a particular medicinal product or where the interests of the Community are involved, referrals to the EMEA can be made. For medicinal products for human use, from 1995 to May 2001, 21 referral procedures have been completed concerning 33 medicinal products⁵⁰. For medicinal products for veterinary use, from 1995 to May 2001, 3 referral procedures have been processed⁵¹.

II.2. Assessment and review proposals

II.2.1 General remarks

- In assessing the overall success of the two authorisation procedures, the answers received during the various consultations made by the external consultant as well as by the Commission depend on a number of objective and subjective factors, including the differing perceptions and interests. Indeed, very often widely differing views were expressed on a concrete issue, making it impossible to determine a consensus or even to identify a more general tendency. The views of regulators and industry are frequently different and relatively polarised. The views of different regulators often vary as noticeably as the views of different companies. On several key issues, such as the adjustments that need to be made to the mutual recognition and centralised procedures, there is less consistency in the views expressed by regulators (particularly in relation to long-term strategy for regulation) than in the views of industry.
- Stemming from the findings of the assessment, this part of the report indicates also the lines to be taken when amending the existing pharmaceutical legislation. In doing so, the report will describe the **general approach** to be followed where changes are needed, but it will not refer to individual and concrete provisions, which will be elaborated in the explanatory memorandum of the relevant legislative proposals.
- As a way of general consideration on the future legislative proposals described below, the review of the pharmaceutical legislation has to pursue a set of four major objectives:
 - To ensure a high level of **public health protection** for the European citizen, in particular by allowing rapid access to innovative and safe products and by tight market surveillance, based on reinforced procedures of control and pharmacovigilance. With regard to veterinary medicinal products, the level of protection of animal health should be improved in particular by increasing the number of medicinal products available.
 - To further complete the **internal market** in pharmaceuticals and to establish a regulatory framework favourable to the **competitiveness** of European pharmaceutical industry, while taking into consideration aspects of **globalisation**.
 - To meet the challenges of an **enlargement** of the European Union.

⁵⁰ See table 8 on “Community referral procedures” in the annex.

⁵¹ See table 8 on “Community referral procedures” in the annex.

- To rationalise and to simplify, as far as possible, the system and to improve its global coherence, its visibility and the **transparency** of the procedures.

These corresponding and intrinsically linked goals can be realised optimally only if the review achieves a **sound overall equilibrium** between all of them. This requires a Community system that is dynamic, consistent, and efficient and provides for a proper balance between the centralised and decentralised systems. In general, the evaluation of the existing authorisation procedures has proven that the system in place since 1995 works well and has contributed to achieving a high level of public health protection as well as progressing the internal market in pharmaceuticals in Europe. As a consequence, there is **no need to fundamentally change the current system** with its dual structure.

The following indications on how to further improve the regulatory framework of pharmaceuticals in Europe can therefore be limited to **optimisation and amendment of the present procedures**, while keeping their general structure. Unless otherwise specified, the following observations apply both to human and to veterinary medicines.

II.2.2 Overall results

When the new system was designed in the early 1990s, the basic assumption was that the **same fundamental objectives** would **apply to both procedures**, namely to ensure a high level of public health protection *and* to contribute to the completion of the internal market in medicinal products. The success of the two procedures has to be measured against these goals.

With regard to the first objective, the evaluation by the external consultant in line with the views of the Commission allows the conclusion that **both systems have succeeded in ensuring a high level of public health protection** and, in particular in the human sector, an increase availability of innovative medicinal products. Both systems have provided a high degree of quality, safety and efficacy for medicinal products made available for human beings and animals. The requirements with regard to the three fundamental criteria of medicinal products laid down in the existing legislation ensured a high level of public health protection.

However, the **degree** to which the two procedures have contributed to the **completion of the internal market in pharmaceuticals differs considerably**. It is unanimously recognised the positive impact on the free movement of pharmaceuticals of the centralised procedure. This procedure has worked efficiently and the concept of a Community authorisation did not meet significant problems in practice. On the contrary, the mutual recognition procedure did not function as expected, as explained in detail below. The idea of a mutual recognition of scientific evaluation of one Member State by the competent authorities of the other Member States has been realised only to a certain extent.

A positive effect of both procedures has been that the **availability** of new medicines has increased over the last five years, in particular in the sector of medicinal products for human use. Criticism however focused on the length of time between an application and the final marketing authorisation, which was claimed to be excessive in some cases. Further concern related to situations where a medicinal product was authorised but not effectively put on the market or, after a certain time on the market, was withdrawn. Problems also occurred with regard to veterinary medicinal products where it is feared that the availability of medicinal products for food producing animals decreases as a result of the introduction of the requirements to establish maximum residue limits.

An overall assessment of the two authorisation procedures in terms of **cost-benefit** is difficult. The procedures have not yet produced real dividends in terms of cost efficiencies through economies of scale. Still, there is a need to reduce the administrative burden where this does not have public health implications. Similarly, there is a certain perception that the renewals of marketing authorisation are less and less based in practice on a scientific re-evaluation, but appear to be a simple administrative procedure. This situation causes financial burdens to the marketing authorisation holders and is resource consuming for the competent authorities without adding to the protection of public health. In terms of cost efficiencies, it also has to be considered that national authorities are under significant resource pressure and that the funding of the decentralised system, and indirectly of the centralised system, by national authorities is an increasing cause for concern in some Member States.

There is a strong demand, supported both by national authorities and marketing authorisation holders, for **greater transparency** of the authorisation procedures. To improve the current situation, a Community level initiative is generally preferable to divergent solutions in each individual Member State.

Certain criticism was also made to the system on the handling of **generic medicinal products**. The current legislative obligation for the applicant of the generic medicines to use the same procedure taken by the reference medicinal product, together with the provisions relating to the data exclusivity protection period, amounts to significant obstacles for generic medicines.

On the whole, it should be noted that the **principal structure of the system** operating since 1995 is **well-balanced, sound and has produced satisfactory effects**. The system could contribute towards ensuring a high level of public health protection, supporting the development of European pharmaceutical industry, and – to a different extent – to further harmonising the internal market of pharmaceuticals. As a consequence, there is a widespread consensus that both procedures have their specific merits and contributions to the fundamental objectives of the pharmaceutical system and for this reason should be kept in parallel, even if improved in individual aspects.

II.2.3. Centralised procedure

- **Scope**

According to the results of the Cameron McKenna Andersen report, there is a **general opinion** within marketing authorisation holders and Member States that the centralised system is capable of working well with a high level of satisfaction. There also is general recognition of the very considerable contribution made by the EMEA to the successful launch of the system. The EMEA is viewed as well managed and having discharged effectively all the functions allotted to it by legislation.

The procedure has proven its **effectiveness for biotechnology** medicinal products, and made biotechnology processes fully acceptable in the pharmaceutical sector. The scientific innovation on which new kinds of medicinal products using complex techniques are based (e.g. gene therapy) makes European evaluation, based on pooling the best scientific skills from national agencies, even more necessary.

The Community-level evaluation requires a high level of expertise. By using both the national resources provided by Member States and the necessary external experience (i.e. a network of approximately 2 300 experts), the EMEA ensures that the quality of the scientific evaluation is fully satisfactory.

Nevertheless, the Commission considers that, in order to boost competitiveness by helping innovative companies and to cope with foreseeable future evolution in terms of innovation and technical progress, the scientific profile of the EMEA should be reinforced by providing additional scientific support and by specifying and expanding some of its tasks. In order to achieve this, an increased and flexible scientific expertise is needed – which could be developed either in the framework of scientific specialised expert ad hoc groups and in-house advisory structures or by establishing communication channels with experts from the scientific community outside the Agency.

A significant number of companies and Member State authorities are in favour of the centralised system being **opened up to a broader range of products**. This is a good indicator of the general level of confidence in the principles underlying the system and the advantages that it can bring.

The Commission considers, in the light of **scientific developments during the last 6 years**, that the list of products for which the centralised procure is mandatory does not correspond to the needs of the market for medicinal products and to the need for a unique scientific assessment. The decentralised procedure is not adequate for authorisation of medicinal products containing new active substances, taking into consideration the high costs for their development as well as the effects on society when those products are only placed on the market of a limited number of Member States. This last fact (lack of homogeneity of the Community market) will probably become even more a cause for concern after the enlargement of the European Union. This observation applies also to the products included in list B of the Annex, which is considered inadequate and rather narrow, especially in the case of other innovative products and of generic medicinal products.

1. **List A of the Annex to Regulation 2309/93 should be maintained and it should still be mandatory for the products referred to in it to be authorised through the centralised procedure.**
2. The centralised procedure should become **mandatory for all new active substances, i.e. any substance, which has not been part of an authorised medicinal product in any of the Member States.**
3. The centralised procedure should be open, on an optional basis, to any other product provided for which the applicant shows that the product constitutes a **significant innovation or that there is a Community interest, for patients and from animal health point of view, in respect of the granting of an authorisation under this procedure.** Along these same lines, an authorisation under this procedure should also be possible for **immunological veterinary products** subject to Community prophylactic measures.
4. This procedure should be optional in the case of **generic medicinal products** of centrally authorised reference products.

- **Authorisation procedure**

The **development of new technologies** is viewed as posing new challenges that justify a review of the assessment procedures of the CPMP. Some further flexibility is needed to provide solutions in two situations, which are currently not covered by the regulation. On the one hand, the cases where the availability of a given product is indispensable for reasons of public health. On the other hand, the fact that very often certain patients could obtain and have at their disposal certain medicines, which are not covered by an authorisation (compassionate use). Both situations can have negative consequences on public health if no guidance is provided at Community level regarding the conditions of use, or on public confidence if patient needs in the various Member States are not addressed in a fair and equitable way.

The Commission agrees that the assessment procedure is, in some cases, not rapid enough. In the case of innovative products, slow developments in the procedure might neutralise the beneficial effects that the placing of the market of innovative products might have on society. It also recognises the need to accelerate the part of the procedure dealing with the final decision process.

1. The different steps for the **authorisation procedure should remain basically the same** for both human and veterinary medicinal products.
2. The **authorisation procedure should be accelerated**. This could be achieved by shortening some deadlines in the different steps of the procedure.
3. Along the same lines **accelerated assessment procedures** (fast track procedures) should be foreseen for medicinal products of major interest from the point of view of public health and therapeutic innovation.
4. In some cases, **conditional authorisation**, to be re-evaluated on a yearly basis should be made possible; the possibility of an authorisation **under exceptional circumstances** will be maintained under the conditions already described in the existing legislation.
5. Regarding **compassionate use** of medicinal products for human use according to which patients may have at their disposal certain medicines, before authorisation is granted, the EMEA should be able to adopt recommendations to be applied by Member States within their own administrative framework. These recommendations would aim mainly at establishing the conditions for this compassionate use to be put into practice

There is also margin for improvement as far as **transparency** is concerned, in both respects, regarding information on the product characteristics and the assessment reports on the medicinal products, as well as the reasons and the documentation on which a decision on granting or refusing an authorisation is based. Greater transparency would make the procedure more easily accessible and easier to understand for all interested parties and would facilitate an even smoother and more rapid handling of marketing authorisation applications.

Transparency rules should be improved regarding the dissemination by the Agency of the documents on which the authorisation decision is based by publishing the assessment reports, the opinions delivered by the committees and the conclusions reached in case of appeal. A general transparency requirement could be added in order to ensure that any interested person may have access to the summary of product characteristics, the assessment report on the medicinal products and the parts of the file and documents which are not of confidential nature.

Another factor which, under the current circumstances, creates an important administrative burden for marketing authorisation holders and adds to the workload of the Agency is the **renewal requirement for marketing authorisations every five years**. It is not perceived as the appropriate way of assessing that the medicinal product effectively meets the requirements for its authorisation. It is more appropriate to substitute reinforced surveillance system to a continuous five-year administrative renewal. **Pharmacovigilance and supervision requirements** should be strengthened in order to respond to the need to guarantee the objective of public health protection in that context. The duties of the marketing authorisation holders should also be reinforced. Their obligation to record and report to the Member States should not remain limited to all suspected serious adverse reactions but be expanded to any other suspected serious adverse reactions of which they may reasonably be expected to be aware.

The marketing authorisation procedure does not allow precise administrative control on whether effective use of marketing authorisations is made, especially in those cases where a product, covered by an authorisation, is no longer on the market. In fact, there is no obligation for marketing authorisation holders to inform the agency of the date when a product is placed on the market.

1. The limits regarding the **validity of the authorisation** should be abolished; authorisations should be valid for unlimited duration.
2. The marketing authorisation holder would have to make **effective use of the marketing authorisation**, otherwise, if the product is not placed on the community market after a certain period, the authorisation should cease to be valid.
3. The frequency for submission of periodic safety reports, in the context of pharmacovigilance, should be reviewed – records should be submitted at **shorter yearly intervals** (maximum three years) than the current five-year intervals.
4. The obligation to inform the Agency on **the dates of actual marketing of the medicinal product in the Member states** or if the product ceases to be marketed should be introduced.

- **Decision making process within the centralised procedure**

One of the most criticised areas of the centralised procedure is the decision-making process that follows the scientific evaluation by the EMEA. The **time length** of this administrative phase does not appear to be justified, in particular with regard to the general intention to streamline and shorten the whole evaluation and authorisation process. To improve and speed up the decision making process it is important to improve the rules in order to allow a faster conclusion of the post-evaluation phase. However, apart from some internal improvements, the time frames set out in Regulation (EEC) n° 2309/93 should be re-evaluated and if possible be reduced.

Adaptations have to be included in the text of the regulation to ensure conformity with the provisions of the new Council **Decision 1999/468/EC**⁵².

1. Member States will have a deadline of **15 days** to react to the Commission proposal.
2. The regulatory procedure should be replaced by references to Articles 3 and 5 of Decision 1999/468/EC, which provide for the **consultation and management procedures**.

The regulatory procedure should be only used in the context of technical modifications to the legislation, in particular in the case of adaptation to scientific and technical progress of the directive (basically the Annexes).

- **EMEA**

1. Structure of the EMEA

The number of **scientific committees** of the EMEA does not reflect the current bodies providing for the scientific assessment within the EMEA. Moreover, the **composition** of these scientific committees needs to be reviewed in the light of the enlargement perspective for example by reducing the number of representatives from two to one.

The **Management Board**, in its present form, needs to be reviewed to take into account the future enlargement of the European Union. The new composition will also need to be in line with the last proposals adopted by the Commission for the creation of the European Food Authority as well as the two Agencies on Maritime and Air Safety. It has also to provide sufficient guarantees that the interests of the civil society and industry are represented. The current structure of the Management Board is not adequate in the context of modern management and decision making theories to ensure representation of all interested parties.

On the same lines, and with the purpose of completing the whole coherence of the administrative system of the EMEA, it seems appropriate to regroup all the national **Heads of Agencies** in the form of an Advisory Board, which could give advice to the Commission and to the executive director of the EMEA.

The Commission understands that the EMEA should be competent to give appropriate and systematic **scientific advice** to companies aiming to actively participate in the innovation process. This is the case in particular for small and medium companies developing biotechnological or innovative products for which scientific advice is crucial for the correct and complete preparation of the scientific dossier.

⁵² Council Decision 1999/468/EC of 28 June 1999 laying down the procedure for the exercise of implementing powers conferred on the Commission, OJ L 184, 17.7.1999, p. 23.

1. The structure of the EMEA needs to be completed in order to include the **Committee for Orphan Medicinal Products**, set up under Regulation (EC) n° 141/2000⁵³ and the **Committee for Herbal Medicinal Products**, which will be set up by a new Directive on traditional herbal medicinal products to be proposed soon.
2. An **Advisory Board**, composed of representatives of the national competent authorities, which would have a consultative function with respect to the EMEA and the Commission activities regarding authorisation procedures for pharmaceuticals, will be created.
3. Increased flexibility should be introduced as regards the different **expert groups** that can be created by the scientific committees and that form part of the EMEA. The possibility of creating working parties and expert groups should be completed by procedures for delegating certain tasks to these working parties. Also the creation of administrative structures and specialised groups, with the participation, where necessary, of experts in specific scientific fields, allowing for instance the development of scientific advice procedures for the companies, should be envisaged. The possibility of using experts even from outside the EU should not be excluded provided that guarantees regarding selection, independence and qualifications are met.
4. The structure of the **Management Board** should also be reviewed to take into consideration the future enlargement of the EU, the need for an adequate representation of the civil society (patients, industry) and the proposed structure for the new Agencies (Food Authority, Maritime Safety Agency and Air Safety Agency).

2. Tasks of the EMEA

The scope of activities of the EMEA should be widened by inclusion of tasks, which go beyond the evaluation of medicinal products in the context of the marketing authorisation. This role as a **scientific adviser** will allow the Commission to request the EMEA scientific advice on any issue regarding the authorisation of medicinal products.

Co-operation with the **World Health Organisation** should be reinforced for the assessment of certain medicinal products intended exclusively for the markets of third countries.

On the basis of the Commission's experience in the field of **parallel distribution**, numerous complaints as well as cases before the European Court of Justice, provide enough evidence that action needs to be taken in that respect in order to prevent problems and ensure coherence in the application of Community legislation.

Additional sanctions to the ones already included in the legislation, for instance **financial sanctions**, to be imposed directly by the EMEA on the holders of market authorisation if they fail to observe certain obligations laid down in connection with the authorisations, should be considered. At this stage, the implication of the EMEA in imposing sanctions is not sufficient. No financial sanctions are foreseen even if experience shows that most effective dissuasion is achieved by applying financial penalties.

⁵³ European Parliament and Council Regulation (EC) n° 141/2000 of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

1. The EMEA should contribute more actively in the framework of **dialogues on international harmonisation**.
2. The possibility should be considered of giving the EMEA the task of ensuring that the conditions laid down in Community legislation on medicinal products and in the marketing authorisation are observed in the case of **parallel distribution** of medicinal products authorised under the centralised procedure.
3. The committees forming part of the EMEA should play an increased role by assisting the Executive Director of the EMEA and the Commission in drawing up, at their request, **any opinions on scientific matters concerning medicinal products**.
4. A greater competence of the Commission when imposing **sanctions** is needed; the competence to impose financial sanctions should be considered.

II.2.4. Mutual recognition procedure

- **General assessment of the procedure**

There is a **clear acceptance and support** for the mutual recognition procedure. The available experience is limited, since the mutual recognition procedure was obligatory only from 1998 onwards. But even with this limited knowledge it is possible to conclude that the mutual recognition procedure has contributed to a certain extent to the completion of the internal market in pharmaceuticals while safeguarding a high level of public health protection.

The mutual recognition procedure with its possibility to include only a limited number of Member States in the procedure, offers a **flexibility** that is important for those medicinal products intended only for a restricted part of the European market, especially in the veterinary sector. Many pharmaceutical companies, particularly the small- and medium-sized enterprises, confirmed that the mutual recognition procedure meets their commercial needs more effectively than the centralised system, since they do not have the resources to operate on the entire European market. However, this has to be put in perspective with legitimate patient needs to have medicinal products available in the different Member States.

Currently, there is a certain concern about the **duration of the authorisation procedure**, which seems too long in general. However, the main problem with this procedure is that, in practice the Member States **too often do not recognise** the marketing authorisation and the scientific evaluation carried out by another Member State. Instead of relying on the evaluation done by the Reference Member State, the competent authorities of the Concerned Member States often make their own evaluation. This lack of true mutual recognition is confirmed by the findings of the Cameron McKenna Andersen report.

Further problems are created by the current provisions concerning objections that may be raised by the Concerned Member States to challenge the evaluation done by the Reference Member State. The existing provisions allow such objections where the Concerned Member State considers that there are grounds for supposing that the authorisation of the medicinal product may present a **risk to public health**. This notion has not been defined in the legislative provisions, thus leaving it open to a broad interpretation by the national authorities. As a consequence, the notion of “risk to public health” is invoked in a number of situations where it does not appear to be consistent with the idea of mutual recognition.

Once objections of public health have been raised, it often proves to be quite **difficult to reach an agreement** between the dissenting Member States. The difficulties in reaching a common solution were often linked to the fact that the Reference Member State, on the basis of its scientific evaluation, had already granted a marketing authorisation. From an administrative and political point of view, it is more difficult to put into question a national scientific evaluation when decisions have already been taken on the basis of this evaluation.

The informal groups on mutual recognition (**MRFG and VMRFG**)⁵⁴ that have been established to improve the operation of the mutual recognition procedure have worked with remarkable success. They have contributed to the general improvement of the procedure and in particular to the creation of a framework for the Member States to reach agreement on the action to be taken in respect of applications where objections on public health grounds have been raised. However, being informal groups with no legal basis, there has been some concern about the legal effect of the groups' work.

Finally, problems relate to the **arbitration** procedure, as confirmed by the Cameron McKenna Andersen report. The intricacies of the mutual recognition procedure described above continued to persist in the arbitration phase and, in particular the problem of how to deal with a common interpretation of "risk to public health". Further points, which made the arbitration procedure particularly unattractive for the applicants, were the considerable duration of the arbitration phase and the fact that during this phase the product could not be marketed in the other Concerned Member States, even if they had been ready to grant the authorisation.

As a consequence, the applicant very often chose to **withdraw** the application from the Member State, which had raised the objections. During the three years of the transitional period from 1995 to 1997, when the mutual recognition procedure was not yet obligatory, 112 out of 249 new applications for human medicines that had been finalised through the mutual recognition procedure, were finalised with at least one withdrawal, which is equal to 46 %. In the years between 1998 and 2000, the figures were 223 out of 616 new applications, which represents 36 %⁵⁵. Despite this slight decrease, both figures show that there is a significant problem. As a comparison, the numbers of arbitration procedures were extremely small. In 1997, there were only two arbitration procedures, one relating to a new application, one to a type II-variation. In 1998, there was one arbitration procedure for a new application and four arbitration procedures for type II-variations⁵⁶.

The Commission as well as a certain number of national authorities is concerned by this relation between withdrawals and arbitration procedures. By withdrawing the application from a Member State that has raised the objections, the applicant **prevents a thorough evaluation of the objection raised** and, accordingly, a Community-wide solution. Even if the notion of "risk to public health" might sometimes have been invoked without a substantial justification, some of the objections raised indeed justified a Community re-examination of the scientific evaluation of the product.

⁵⁴ See footnotes 31 and 32.

⁵⁵ Figures based on the MRFG report "Analysis of Withdrawals in the Mutual Recognition Procedure" of 23.1.2001.

⁵⁶ Figures based on the respective annual report of the MRFG. No figures on referrals for 1999 and 2000 are available.

1. First of all, concerning the **duration of the national authorisation procedure**, the current deadline of 210 days should be reduced to 150 days of which 120 days will cover the assessment report. By adding the duration of the mutual recognition procedure, the total number of days will be comparable with the deadline of 210 days for the centralised procedure.
2. As regards the procedure itself, different modalities should be foreseen depending on whether or not the medicinal product is already authorised in a Member State. Where the medicinal product is already authorised, the mutual recognition phase has to be based on the existing authorisation. Where the medicinal product is not yet authorised, the Member States concerned with an application should **agree on the scientific evaluation report before any authorisation is given**.
3. It is necessary to better specify the concept of **risk for public health**, as referred to in the legislation, in order to prevent the mutual recognition procedure from being stopped.
4. In order to facilitate the smooth running of the procedure, it seems appropriate to give a formal and legal status to **the existing MRFG/VMRFG**. Their responsibilities should concern in particular the part of the procedure dealing with the objections based on the concept of risk for public health.
5. During the **arbitration** phase, which involves the EMEA, it appears necessary to ensure that the objections related to the serious risk for public health are evaluated properly and that necessary follow-up measures are taken, independently of the application withdrawal. In order to further harmonise the level of public health protection resulting from the arbitration procedures, it seems desirable to extend the Commission decision to *all* Member States. To meet the significant dissatisfaction with the length of the arbitration procedure, the time limits should be re-evaluated and, where possible, shortened.

- **Pharmacovigilance and supervision**

Taking into consideration the fundamental objective of the achievement of the highest level of public health protection, the legislative framework for the follow-up of **pharmacovigilance** measures has not been totally satisfactory *from a Community perspective even though this has not caused an issue from a public health point of view*. The current provisions on pharmacovigilance allow Member States, in case of urgency, to suspend a marketing authorisation in their territories, without ensuring the necessary follow-up at Community level.

The existing pharmaceutical legislation contains provisions on the control of quality and on good manufacturing practices, which only cover the finished product, and not the **active substances used as starting materials** for medicinal products. Experience has shown that this limited approach is not always adequate because the quality of a finished medicinal product is linked to the complete process from manufacturing of the starting materials until the final manufacturing of the product.

1. To further improve and harmonise the level of safety of medicinal products, new provisions should be established to make sure that **urgent action** taken by one Member State is thoroughly evaluated on a European level and that, where necessary, appropriate measures are taken by *all* Member States.
2. The Commission should be empowered to lay down detailed guidelines on the manufacturing of **active substances used as starting materials** for medicinal products and to establish the obligation to use only those active substances as starting materials that have been manufactured in compliance with these guidelines.
3. The system of **inspections** should also cover the control, under specific conditions, of active substances used as starting materials.

II.2.5. Specific issues

Apart from the points outlined above, the evaluation of the system for authorisation of medicinal products also points to a need for changes to the existing legislation on the following specific issues:

- **Definition of medicinal products**

The current definition of a medicinal product for the purposes of the pharmaceutical legislation is worded in a way that could not cover certain new or future forms of medical treatment, in particular those related to gene therapy and cell therapy. There is a clear need for a regulatory framework, both predictable and sustainable, for these new therapies. For reasons of coherence and effectiveness, it appears best to include these treatments in the existing framework rather than to establish a separate set of rules.

The definition of medicinal product (definition “by function”) should be modified to include **new therapies**.

- **Generic medicinal products**

The experience of the past shows that certain problems have occurred with regard to generic medicinal products. Whereas the incentives to develop innovative medicines should be maintained and if possible improved, future legislation must at the same time lay down clear rules for generic medicines that fulfil an equally important role within the health care system. The legislation should provide for an **optimal balance between innovative medicinal products and generic medicines**.

The possibility of preventing a generic medicinal product from been **authorised** by withdrawing the original product from the market should be excluded by appropriate wording of the relevant provisions.

To avoid the scientific tests required to prepare a generic application being carried out outside the Community for purely legal reasons, without having substantial influence on the access to the market, it might be appropriate to introduce a provision allowing such kinds of activity during the **period of patent protection** applied to the original product.

On the other hand, the different levels of **data protection** for centrally and nationally authorised medicinal products seems difficult to justify. Harmonisation of the time periods, and the linkage between data protection for nationally authorised medicines and corresponding patent protection, should therefore be re-considered. The experience in the field of human medicinal products shows that there should be some kind of incentive to further improve existing medicinal products, in particular to develop new and important therapeutic indications. Such an incentive could be an additional data protection period.

1. **Data protection periods** should be harmonised with the period provided for the centralised authorised products.
2. An **extension of one year of data protection** period could be allowed if a medicinal product, covered by the normal data protection period, has developed a new therapeutic indication with an important benefit for patients within the first 8 years of protection.
3. The term **generic medicinal product** should be introduced and defined in the legislation.
4. The possibility **to prepare and to file a generic application** during the period of patent protection applied to the reference medicinal product should be introduced.

- **Advertising of medicinal products for human use**

There is a growing interest and knowledge among the general public for information on medicinal products. In particular patients suffering from long-term diseases are looking for information about possible treatments, using world-wide communication tools and especially the Internet. Against this background, it seems appropriate to abandon the strict prohibition of advertising of prescription-only medicines. However, with regard to the negative effects of an abusive advertising, any new possibilities to disseminate information to the general public should be subject to sufficient control mechanisms. These should include, apart from the control by public authorities, a self-regulatory procedure under the surveillance of the same authorities. When establishing such new possibilities of information, it should be considered to limit them in a first experimental phase to certain therapeutic indications or diseases. After sufficient experience has been gained on the effects in the different dimensions and the procedures of control, it could be envisaged to further expand the scope of such provisions.

1. **Specific information on request** of patients or groups of patients should be authorised for medicinal products subject to medical prescription.
2. As a first stage, and in order to evaluate the effects of such a measure, this information would be allowed only for the **treatment of three long-term/chronic diseases**.
3. Industry would need to adopt **principles of good conduct as well as self-regulatory control** procedures, which will be agreed with the competent authorities.
4. After a certain period, the implementation of these provisions should be **evaluated and if necessary adapted**.

- **Homeopathic medicinal products**

Since their entry into force, Directives 92/73/EEC and 92/74/EEC on homeopathic medicinal products for human/veterinary use have achieved only a limited level of harmonisation. A detailed analysis of their functioning is contained in the Commission Report to the European Parliament and Council on the application of Directives 92/73/EEC and 92/74/EEC⁵⁷. To further improve the availability of these medicinal products and to move on in completing the internal market for these medicines, it appears necessary to amend the relevant legislation. In the area of veterinary medicine, homeopathic medicinal products intended for food producing animals should also be eligible for the simplified registration procedure, in particular due to their increasing use in organic farming.

1. The option for establishing a **simplified registration procedure** for certain homeopathic medicinal products should be changed into an obligation.
2. As far as possible, simplified registrations granted by one Member State should be **recognised throughout the Community**.

II.3. Specific provisions concerning veterinary medicinal products and their availability

The **reduction of the available veterinary medicinal products** for food producing animals is an increasing problem⁵⁸. The review of the pharmaceutical legislation provides the opportunity to address partly this issue.

The pharmaceutical legislation should provide **incentives** to enhance the interest of pharmaceutical firms in certain market segments by making the investments required prior to the marketing more attractive.

An incentive not to focus only on the species that represent the most economically interesting market should be granted. Considering the specific treatment needed for bees and fish and the small market that these species represent, specific incentives should also be granted for veterinary medicinal products for these species.

In addition, the **use of existing medicinal products by practitioners** should be facilitated. In particular, in the absence of an authorised medicinal product for a specie and/or indication concerned on their territory, Member States should allow the use by a veterinarian, in a food producing animal, of a medicinal product available else-where in the Community under conditions that will not endanger the protection of consumers and that will ensure information to the owners and/or health professionals in their own language.

⁵⁷ COM(1997) 362 final of 14.7.1997.

⁵⁸ See Commission Communication of 5.12.2000, COM(2000) 806 final.

In addition, the active substances which enter in the composition of a veterinary medicinal product must be subject to toxicological and residue safety evaluation in order to set **Maximum Residue Limits (MRLs) according to Regulation 2377/90**. The establishment of MRLs is one factor, which has led the reduction of available medicines for food producing animals. Therefore, the link between the two procedures would benefit from a clarification, and the Commission intends to propose a review of this Regulation in the near future, to take into consideration, among other issues, the issue of extrapolation from one species to another.

1. Specific provisions for veterinary medicinal products on the **data protection period** could be set up.
2. The 10 years **data protection period could be extended** depending on the number of animal species for which a firm would get a marketing authorisation (one year per additional food producing species, up to a maximum of 13 years for 4 species or more). This extension of the data protection period would only be valid if the granting or extension of the marketing authorisation to several food-producing species is done within 3 years after the first marketing authorisation.
3. The provisions defining the conditions for using medicinal products for food-producing species ("**cascade**" **provision**), which are not authorised in a certain Member State, should be revised.

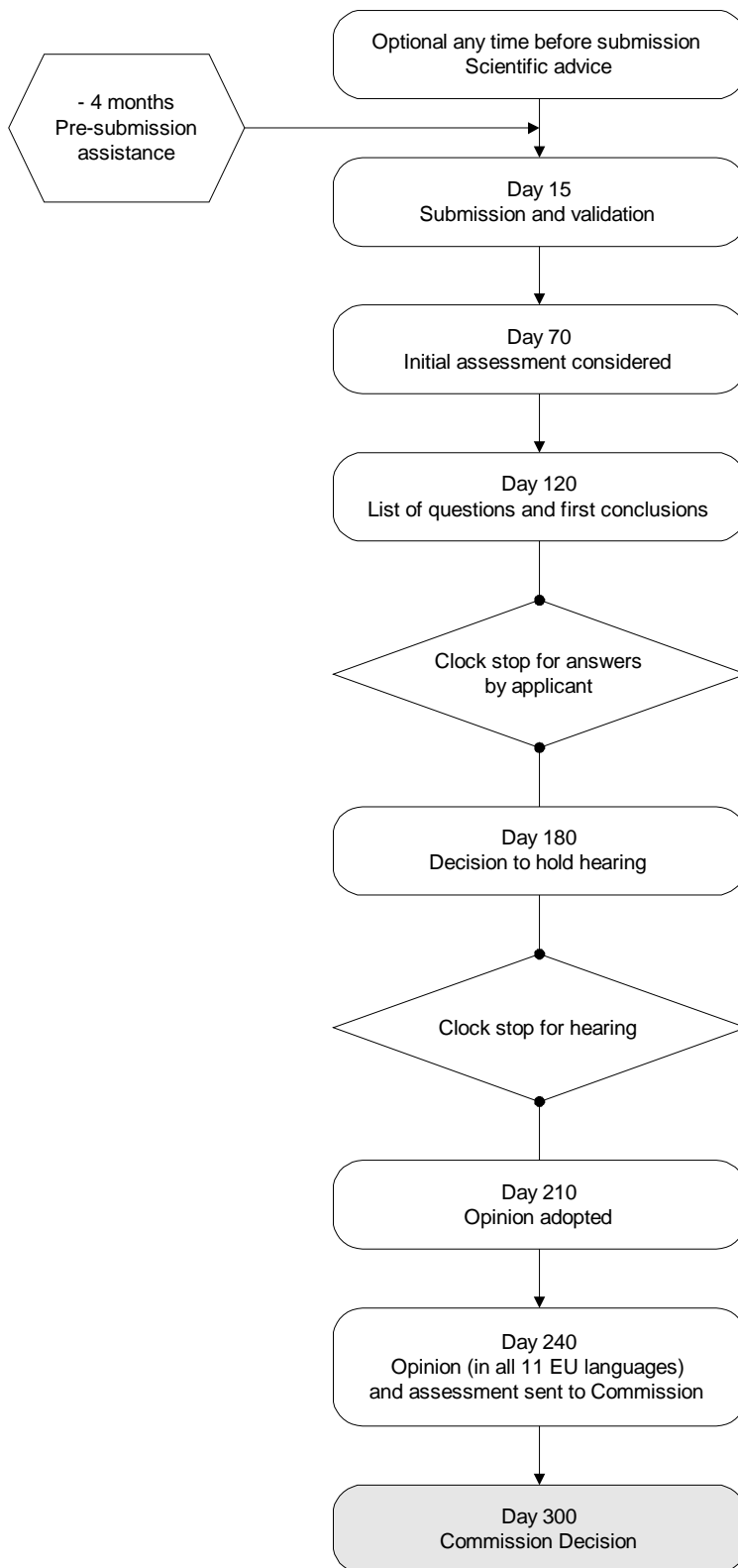
III. CONCLUSIONS

1. The two fundamental objectives underlying the existing pharmaceutical legislation are to ensure a high level of **public health protection** while at the same time to complete the **internal market** in medicinal products. These major goals are indispensable and need to be respected by all future pharmaceutical legislation. Additional objectives however have to be taken into consideration, in particular those necessary to meet the challenges of the forthcoming **enlargement** of the European Union and to further promote the **competitiveness** of the pharmaceutical industry in Europe.
2. It is proposed to keep the **main principles and structures** of the system for authorisation of medicinal products for human and veterinary use, as put in place in 1995. On the whole, they have proven appropriate and suitable for their purpose. The credibility, sustainability and future success of the regulatory framework for medicinal products in Europe will depend on the respect of these principles and structures.
3. When further developing the pharmaceutical legislation, it has to be taken into consideration that the pharmaceutical industry by developing new medicinal products is significantly contributing to ensuring a high level of public health in Europe. The necessary research and development requires considerable financial investments on the part of the industry and quite often it takes up to fifteen years to bring a new innovative product on the market. As a consequence, all amendments need to result in a **transparent, predictable and stable regulatory environment**.

4. The optimal legislative framework in the area of medicinal products depends to a large extent on the current state of play of the relevant branches of science, which are developing rapidly. It is proposed therefore to introduce in the pharmaceutical legislation a certain degree of **regulatory flexibility** in order to allow a sufficiently prompt adaptation of the technical requirements to the developing scientific knowledge.
5. With regard to the **future enlargement** of the European Union, an important part of the future review proposals will be justified by the need to accommodate the system to the increasing number of Member States, which will be involved in the authorisation of medicinal products for the European market.

ANNEX

CENTRALISED PROCEDURE



MUTUAL RECOGNITION PROCEDURE

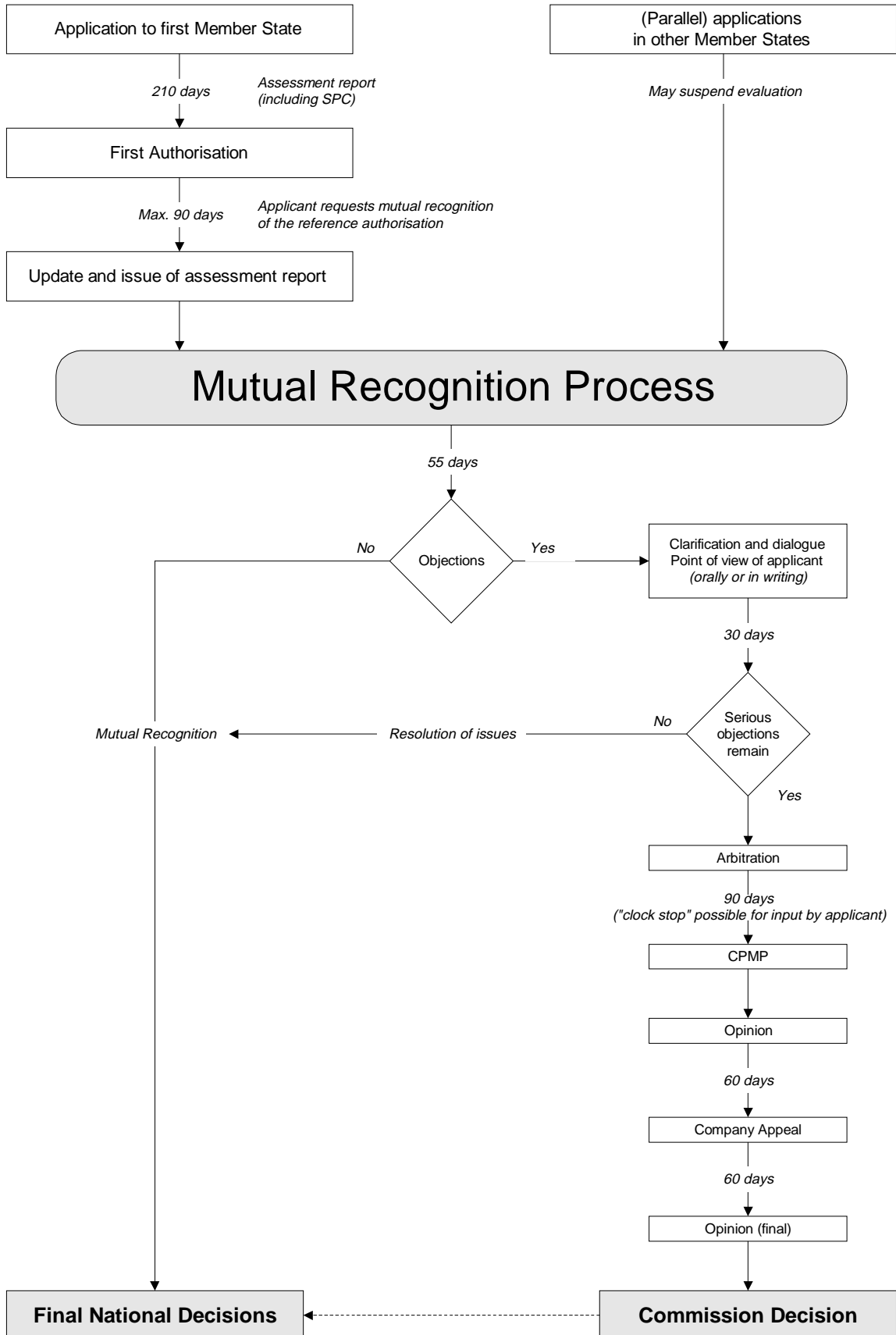


Table 1: EMEA BUDGET EVOLUTION

YEAR	BUDGET IN EUROS (in Ecus until 1998)
1994	6 813 085
1995	14 412 000
1996	22 550 000
1997	28 530 000
1998	31 900 000
1999	42 650 000
2000	55 287 000
2001	62 152 000

**Table 2: EU CONTRIBUTION TO EMEA BUDGET
in Euros (in Ecus until 1998)**

YEAR	Contribution	Special Orphan contribution	EEA-EFTA
1994	6 800 000	-	-
1995	10 150 000	-	-
1996	10 497 149	-	-
1997	13 546 500	-	-
1998	13 926 040	-	-
1999	10 481 649	-	-
2000	12 477 536	1 000 000	245 220
2001	14 000 000	1 300 000	250 000

Table 3: PERCENTAGE OF EU CONTRIBUTIONS TO EMEA BUDGET

YEAR	Contribution	Including special Orphan contribution	Including contribution from EEA-EFTA
1994	99,80 %		
1995	70,42 %		
1996	46,55 %		
1997	47,48 %		
1998	43,65 %		
1999	27,57 %		
2000	22,56 %	24,37 %	24,82 %
2001	22,52 %	24,62 %	25,01 %

Table 4: STAFF EVOLUTION (Number of Posts)

YEAR	STAFF	DNE⁵⁹	EXTERNAL STAFF
at 1.10.1994	6	-	-
at 31.12.1995	50	0	17
at 31.12.1996	100	3	10
at 31.12.1997	143	2	9
at 31.12.1998	154	3	9
at 31.12.1999	181	3	9
at 31.12.2000	194	3	13
2001	-	-	-

⁵⁹ Detached national experts.

**Table 5: CENTRALISED PROCEDURES (human medicinal products):
(Figures on applications submitted in the EMEA from 1995 to 2000)⁶⁰**

	1995-2000		
	Part A	Part B	Total
Applications submitted	97	182	279
Withdrawals	12	37	49
Positive CPMP opinions	64	112	176
Negative CPMP opinions⁶¹	1	3	4

	1995-2000		
	Part A	Part B	Total
Variations type I	265	551	816
Positive opinions, variations type II	159	224	383
Negative opinions, variations type II	0	2	2
Extensions (Annex II applications)	34	20	54

⁶⁰ Parts A and B referred to lists A and B of the Annex to Regulation (EEC) n° 2309/93.

⁶¹ In case of appeal the opinion will not be counted twice.

**Table 6: CENTRALISED PROCEDURES (veterinary medicinal products):
(Figures on application submitted in the EMEA from 1995 to 2000)⁶²**

	1995-2000		
	Part A	Part B	Total
Applications submitted	18	21	39
Withdrawals	3	2	5
Positive CVMP opinions	11	26	37
Negative CVMP opinions	0	0	0

	1995-2000		
	Part A	Part B	Total
Variations type I	14	43	57
Positive opinions, variations type II	2	4	6
Negative opinions, variations type II	0	0	0
Extensions (Annex II applications)	0	9	9

Table 7: CENTRALISED PROCEDURE (Figures on Marketing Authorisations granted by the European Commission (status in 05/2001))

	AUTHORISED	SUSPENDED	REVOKED
Human medicinal product	171	2	12
Veterinary medicinal product	26	1	0

⁶² Parts A and B referred to lists A and B of the Annex to Regulation (EEC) n° 2309/93.

Table 8: COMMUNITY REFERRAL PROCEDURES

	Number of Community Referral procedures from 1995 to 05/2001	Number of concerned medicinal products
Human medicinal product	21	33
Veterinary medicinal product	3	3

Table 9: MUTUAL RECOGNITION PROCEDURES (Human Medicinal Products)

(Number of mutual recognition procedures and variations from 1995 to 2000)

	1995-1997	1998	1999	2000	TOTAL
Number of finalised procedures	249	180	253	306	988
Variations type I (minor variations)	166	339	671	1 007	2 183
Variations type II (major variations)	253	222	301	320	1 096

Table 10: MUTUAL RECOGNITION PROCEDURES (veterinary medicinal products since)

(Number of mutual recognition procedures from 1996 to 2000)

	1996	1997	1998	1999	2000	Total 5 years
Number of finalised procedures	13	16	19	31	32	111

Table 11: Applications for human medicinal products with new active substances⁶³ submitted under the centralised procedure and the mutual recognition procedure since 1995

Year	Applications centralised procedure	Applications mutual recognition	% Centralised	% Mutual Recognition
1995	8	2	80 %	20 %
1996	15	15	50 %	50 %
1997	25	26	49 %	51 %
1998	26	11	70 %	30 %
1999	19	12	61 %	29 %
2000	20	7	77 %	23 %
Total 6 years	113	73	61 %	39 %

⁶³ New active substance is any substance, which has not been part of an authorised human medicinal product in any of the Member States by 1st January 1995.

Table 12: Applications for veterinary medicinal products with new active substances⁶⁴ submitted under the centralised procedure and the mutual recognition procedure since 1995

Year	Applications centralised procedure	Applications mutual recognition	% Centralised	% Mutual recognition
1995	1	0	100 %	0 %
1996	5	1	83 %	17 %
1997	1	4	20 %	80 %
1998	6	3	67 %	33 %
1999	5	4	56 %	44 %
2000	2	2	50 %	50 %
Total 6 years	20	14	59 %	41 %

⁶⁴ New active substance is any substance, which has not been part of an authorised veterinary medicinal product in any of the Member States by 1st January 1995.