Regulation of immunological veterinary medicinal products in the European Union

P. BRUNKO *

Summary: Since 1990, immunological veterinary medicinal products have been covered by the pharmaceutical legislation of the European Union (EU) and, as a consequence, these products are now subject to the relevant general provisions regarding manufacturing and marketing authorisation.

For new veterinary immunologicals, the legislation entered into force on 1 April 1993. For products already on the market, a transitional period of five years was granted, during which Member States must proceed with the review of these products. Member States are coordinating this review and have set a calendar for the various species-specific products.

Despite the extensive harmonisation of requirements and criteria, and the existence of procedures for marketing authorisation involving the Committee for Veterinary Medicinal Products (CVMP), the actual decision whether to authorise a product was still taken by individual Member States, thus leading to divergences at the very last stage of the process. Therefore, in 1993, the European Council adopted a Regulation and Directives; this legislation modified the current system, introduced two new procedures for veterinary medicinal products and established the European Medicines Evaluation Agency. Under the new system, innovatory medicinal products obtained through biotechnology will be authorised centrally and marketed throughout the EU. Conventional medicinal products will be subject to mutual recognition of authorisations, with binding arbitration by the Agency in case of disagreements between Member States.


INTRODUCTION

The European Economic Community (EEC: now European Union [EU]) was founded by the Treaty of Rome in 1957. The objective of this Treaty was to lay the foundations for an ever closer union between the peoples of Europe, through the establishment of a common market in which people, products, services and capital could move freely without regard to national frontiers. Subsequently, the Single European Act of 1986 fixed 31 December 1992 as the deadline for the attainment of the Single Market, and enlarged the objectives of the Community to include economic and social cohesion, research and technological development, and protection of the environment. In 1992, the Maastricht Treaty (Treaty of the EU) brought the prospect of economic and monetary union and of a common foreign policy.

* European Commission, DGIII/E/3, rue de la Loi 200, B-1049 Brussels, Belgium.
The EU is currently composed of fifteen countries, with a total population of over 350 million, representing the largest single market in the world.

The institutional structure of the EU is unlike any other. It is governed by five institutions: the European Commission, the Council of Ministers, the European Parliament, the Social and Economic Committee and the Court of Auditors. The role of each institution is clearly defined in the Treaty of Rome (as modified by successive Acts).

Draft legislation is generally proposed by the European Commission and adopted by the Council of Ministers. This legislation (i.e. Regulations and Directives) is binding on all Member States. On some specific matters, however, the Commission has been empowered by the Council to adopt legislation itself, by a regulatory process involving a Committee of governmental experts from the Member States. This legislation has the same value and status as Council legislation.

EU pharmaceutical legislation, which has evolved over a thirty-year period, covers medicinal products for both human and veterinary use.

Harmonisation of requirements in the area of veterinary medicines began in 1981 with the adoption of Directive 81/851/EEC (1), which laid down common requirements for manufacturing and marketing authorisation, based on the evaluation of the quality, safety and efficacy of the product. Many additional measures were taken to further harmonise the procedures and the criteria for the evaluation of veterinary medicinal products, such as framework requirements and interpretative guidelines for testing them, principles and guidelines for ‘good manufacturing practice’ (GMP), and a procedure for the evaluation of high-technology products. Granting of authorisations, however, remained national. Consequently, although applications were evaluated on the basis of these harmonised criteria and procedures, and in some cases in common by the authorities of the Member States, there were differences in the decisions reached by the Member States on individual products. The Commission therefore made proposals in 1990 for a new system of marketing authorisation for medicinal products, which was adopted by the Council of Ministers in 1993 and entered into force on 1 January 1995.

MARKETING AUTHORISATION PROCEDURES FOR VETERINARY MEDICINAL PRODUCTS IN THE EUROPEAN UNION PRIOR TO 1 JANUARY 1995

Multi-State procedure

In addition to introducing mandatory marketing authorisation for veterinary medicinal products throughout the EU, Directive 81/851/EEC (1) also introduced the first Community authorisation procedure for veterinary medicines, commonly called the ‘Multi-State’ procedure. This was based on the principle of mutual recognition of national authorisations, and allowed an applicant for a marketing authorisation in a given Member State to request recognition of an authorisation granted by another Member State. According to the terms of the Directive, Member States receiving such a request were to take into account the authorisation delivered by the first Member State when making their decision. The Directive provided that, in exceptional cases, the concerned Member State could raise objections. The Committee for Veterinary Medicinal Products (CVMP) was created ‘in order to facilitate the adoption of common decisions by the Member States on the authorisation of veterinary medicinal products.
on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of veterinary medicinal products' (1). This Committee comprised representatives of the Member States and the Commission; in the spirit of the Directive, it was to be called upon only in exceptional cases to resolve divergences of views on specific applications for authorisation. The veterinary products industry made little use of the original procedure, and this was therefore amended by Directive 90/676/EEC (5) to make it more attractive. Subsequent experience showed that mutual recognition did not occur, and that the CVMP procedure was triggered for each request for mutual recognition. The CVMP was called upon to deliver an opinion, which was then transmitted to the Member States for implementation at national level.

**Concertation procedure**

In 1987, Directive 87/22/EEC (3) entered into force. This Directive introduced the second Community procedure. This procedure was mandatory for products obtained by recombinant deoxyribonucleic acid (DNA) technology, controlled expression of genes and hybridoma/monoclonal antibody methods, and was optional for a series of other products which – subject to the agreement of the competent authorities – constituted a significant innovation or presented a significant therapeutic interest. The special feature of this procedure was that no Member State could take a decision with regard to marketing authorisation, refusal or withdrawal from the market of a high-technology product before the product had been considered at Community level. The competent authorities were thus obliged to consult each other within the CVMP before making their decision. A Member State, acting as rapporteur, followed the application throughout the procedure. Within a strict time-schedule, the CVMP issued an opinion on the application, which was then formally transmitted to the Member States for implementation.

**THE SPECIAL CASE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS**

Immunological veterinary medicinal products were initially excluded from the scope of this legislation and continued to be regulated nationally until 1993. With the objective of the Single Market, it became necessary to include these products within the harmonised legislation. On a proposal from the Commission, the Council adopted Directive 90/677/EEC (6), thus extending the pharmaceutical legislation to immunologicals. This legislation entered into force on 1 April 1993 for new products; for existing products, a transitional period of five years (from 1 April 1993) was granted, during which these products are reviewed for compliance with the requirements of the Directives, according to an agreed harmonised chronology with regard to the different species-specific vaccines.

Since the entry into force of Directive 87/22/EEC (3), however, veterinary vaccines derived from biotechnology were already covered by the Community requirements and had access to the Community 'concertation' procedure as products of biotechnology. On these matters, the CVMP was assisted by a specialised group of experts from the Member States.

In the veterinary medicines sector, the Commission has been charged with updating testing requirements, whenever the need may arise. These requirements were updated
in 1991, to take into account the technical progress achieved since the adoption of the
original testing legislation – Directive 81/852/EEC (2) – and to cover immunologicals,
which were thus introduced into this legislation for the first time. This resulted in
Directive 92/18/EEC (9), which described the testing requirements to be followed by
manufacturers intending to file an application for marketing authorisation. Special
requirements for immunologicals were agreed in the Directive, relating to the
demonstration of quality, safety and efficacy of the product. Given the framework
aspect of this Directive, it was felt necessary to supplement this by a series of guidelines
representing the detailed and harmonised interpretation of these requirements (12).
These guidelines are intended to assist manufacturers in complying with the framework
provisions of the Directive. Compliance with these guidelines provides an assurance to
the industry that the research and development work undertaken will be considered
valid by the Member States. To avoid placing too many constraints on scientific and
technical developments, other approaches to those described in a guideline may be
followed if it can be shown that this is justified. The current guidelines address both live
and inactivated vaccines in general, with specific provisions for a series of species-
specific vaccines. In addition to guidelines which specifically address the testing of
immunologicals, some general guidelines apply; for example, those relating to ‘good
clinical practice’ for the conduct of clinical trials.

MANUFACTURING AUTHORISATION

In accordance with Directive 81/851/EEC (1), authorisation is also required for the
manufacture of veterinary medicinal products, including immunologicals. This
Directive provides for regular inspections, and requires that manufacture be supervised
by a ‘qualified person’ who certifies that each batch conforms with the approved
specifications for the product. For the implementation of these requirements, the
Commission has adopted Directive 91/412/EEC (7), relating to the principle and
guidelines of GMP, and has published a detailed guide on GMP – developed by a group
of pharmaceutical inspectors from the Member States (8).

Unlike conventional medicinal products, which are produced using chemical and
physical techniques capable of a high degree of consistency, the production of biological
medicinal products involves processes and materials which are subject to variability and
which, by virtue of their biological nature, provide good substrates for the growth of
microbiological contaminants. In-process controls therefore take on a major
importance. This line of thought led to the adoption of supplementary provisions
addressing the manufacture of immunological veterinary medicinal products.

BATCH CONTROL/RELEASE

As stated above, manufacturers are required to have the services of a qualified
person at their disposal, to certify that each batch of product has been manufactured
and checked in accordance with the conditions for marketing authorisation. This is a
basic requirement of the pharmaceutical legislation. In the case of batches imported
from third countries, each batch must undergo – under the supervision of a qualified
person – a full qualitative analysis, and a quantitative analysis of at least the active
In the first Member State of the EU into which it is imported. Only when this control by the qualified person has been completed may a batch circulate within the EU without further control.

In the special case of immunological veterinary medicinal products, an additional step may be introduced. Directive 90/677/EEC (6) allows Member States — if they consider it necessary — to request that samples of each production batch of the bulk and/or finished product be submitted for examination by a control laboratory before that batch is placed on the market. This official batch release is not intended to waive the requirement of batch control by the 'qualified person'.

Except in specially-justified circumstances, batch release authorised by one national control laboratory must be recognised without repetition of testing by the other Member States. To ensure the smooth operation of this provision, an administrative information exchange procedure has been agreed between the competent authorities. Although not all Member States require official batch release for veterinary immunologicals, all felt the need to be involved in this information exchange scheme.

NEW SYSTEM FOR AUTHORISATION OF VETERINARY MEDICINAL PRODUCTS IN THE EUROPEAN UNION

Despite the extent of harmonisation of quality, safety and efficacy requirements, as well as authorisation procedures, the decisions on whether to grant marketing authorisation remained with the Member States, leading to divergent decisions on individual products at this final stage.

To remedy this situation, which led to fragmentation of the market, a new European authorisation system was agreed in July 1993 to promote the free circulation of medicinal products throughout the EU, while reinforcing the protection of public health. This new system presents two completely novel features: binding decisions for products evaluated at EU level, and the creation of the European Medicines Evaluation Agency.

From 1995 onwards, two new European authorisation procedures will be available for veterinary medicinal products, as follows:

- a centralised authorisation procedure reserved for innovatory medicinal products (such as those derived from biotechnology), leading to a single authorisation valid throughout the EU
- a decentralised procedure which will apply to other medicinal products, based on the principle of mutual recognition of previous national authorisations.

In addition, for products of local interest, a national procedure is maintained, limited (in principle) to a single Member State.

Centralised procedure

Use of the centralised procedure will be mandatory for medicinal products derived from biotechnology and will be available for other innovatory products on request from the applicant, as defined in the Annex to the Regulation (EEC) No. 2309/93 (11). Veterinary vaccines produced from biotechnology, such as gene-deleted vaccines, will be covered by the mandatory use of this procedure. Applications will be submitted directly to the European Medicines Evaluation Agency.
The scientific evaluation of the applications will be conducted by the CVMP, within the Agency, and coordinated by a rapporteur assisted by experts from the Member States. At the end of the evaluation period, which is governed by a strict time schedule (maximum 210 days), the CVMP will deliver its opinion on whether the product satisfies the requirements for marketing authorisation. This opinion will then be transmitted to the applicant, the Commission and the Member States. The applicant will then have a right of appeal before the final decision on the application is taken by the Commission. This decision is taken on the basis of the advice of a regulatory Committee within which all the Member States are represented, where the votes of the Member States are weighted according to population. In the event of an unfavourable vote from this Committee, the decision is referred to the Council of Ministers.

**Decentralised procedure**

The decentralised procedure is established by Directive 93/40/EEC (10). The objective of this procedure is the extension of a marketing authorisation granted by one Member State to other Member States by recognition of the original authorisation. In the case of serious objections to this recognition, and after exhaustion of all possibilities of bilateral resolution by the Member States concerned, the dispute will be referred to the CVMP for a scientific assessment, leading to binding arbitration.

**Vaccines containing live genetically-modified organisms**

Veterinary vaccines are also concerned by a particular provision of Regulation (EEC) No. 2309/93 (11), integrating the requirements laid down in Directive 90/220/EEC (4) on the deliberate release into the environment of genetically-modified organisms (GMOs). The deliberate release of vaccines containing or consisting of GMOs for the purpose of placing these on the market will fall within the scope of the pharmaceutical legislation. Thus, in giving an opinion on an application for marketing authorisation for such a veterinary medicinal product, the CVMP must ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of GMOs.

**THE FUTURE FOR VETERINARY VACCINES**

With the adoption of this new authorisation system, it can be assumed that all regulatory needs have been fulfilled within the EU. This system will indeed provide innovatory products with access to a continental-wide market and will facilitate access for other products to the markets of Member States. This should have a clearly favourable impact on the veterinary vaccines industry.

On a world-wide scale, however, progress still needs to be achieved, not only for the European industry, but also for the industry in other parts of the world, to provide a renewed impetus through better access to world-wide markets. Negotiations on mutual recognition agreements with regard to GMP and 'good laboratory practice' (GLP) should be seen as making a considerable contribution to achieving this goal. In addition, there are clear signs at present that harmonisation of technical requirements - similar to the process of the International Conference for Harmonisation in the field of medicinal products for human use - is placed high on the agenda of both the regulatory authorities and the veterinary medicines industry.
RÉGLEMENTATION DES MÉDICAMENTS VÉTÉRINAIRES IMMUNOLOGIQUES DANS L'UNION EUROPÉENNE. - P. Brunko.

Résumé : Depuis 1990, les médicaments vétérinaires immunologiques sont couverts par la législation pharmaceutique de l'Union européenne (UE). Ces médicaments sont donc maintenant soumis aux conditions générales régissant les autorisations de fabrication et de mise sur le marché.

Pour les médicaments immunologiques nouveaux, une législation est entrée en vigueur le 1er avril 1993. Pour les médicaments existants, un délai de cinq ans est accordé aux États membres pour procéder à leur réexamen. Les États membres coordonnent leurs travaux en la matière et ont établi un calendrier selon l'espèce animale cible.

En dépit de l'harmonisation des exigences scientifiques et techniques impliquant le Comité des médicaments vétérinaires (CMV), la décision d'autoriser un médicament appartenait encore toujours en dernier ressort à chaque État membre, d'où des divergences dans la toute dernière phase du processus. C'est pourquoi le Conseil européen a adopté en 1993 un règlement et des directives modifiant le système en vigueur. Deux nouvelles procédures applicables aux médicaments vétérinaires ont de ce fait été introduites et l'Agence européenne pour l'évaluation des médicaments a été instituée. Désormais, les nouveaux médicaments issus de la biotechnologie doivent faire l'objet d'une autorisation centralisée pour la mise sur le marché dans toute l'UE. Quant aux médicaments obtenus par des techniques conventionnelles, ils sont soumis à la reconnaissance mutuelle des autorisations accordées par les États membres, les litiges entre ceux-ci étant tranchés par l’Agence, dont les avis seront rendus contraignants par des décisions communautaires.

MOTS-CLÉS : Agence européenne pour l'évaluation des médicaments – Autorisation de fabrication – Autorisation de mise sur le marché – Union européenne – Vaccin vétérinaire.

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REGLAMENTACIÓN DE LOS PRODUCTOS INMUNOLÓGICOS VETERINARIOS EN LA UNIÓN EUROPEA. - P. Brunko.

Resumen: Desde 1990, los medicamentos inmunológicos veterinarios vienen regidos por la legislación farmacéutica de la Unión Europea (UE). A consecuencia de ello, dichos medicamentos están ahora sujetos a las pertinentes disposiciones generales relativas a la concesión de licencias de fabricación y de comercialización.

En lo que concierne a los nuevos medicamentos inmunológicos, la legislación entró en vigor el 1 de abril de 1993. Para los productos ya existentes fue previsto un período de transición de cinco años, durante el cual los Estados miembros deberán proceder a su revisión. Los Estados miembros coordinan su labor en la materia, y han establecido un calendario según la especie animal del caso.
Pese a la armonización de las exigencias científicas y técnicas que implican la intervención del Comité de Medicamentos Veterinarios (CMV), la decisión de autorizar un medicamento era todavía exclusiva de cada Estado miembro, lo cual provocaba divergencias en la última fase del proceso. Por ello, en 1993, el Consejo de Europa adoptó una norma reguladora y una serie de directivas que modificaron el sistema vigente. Dos nuevos procedimientos aplicables a los medicamentos veterinarios han sido introducidos y se creó la Agencia Europea para la Evaluación de Medicamentos. Según establece el nuevo sistema, las licencias a los nuevos medicamentos obtenidos mediante el empleo de biotecnología se concederán de forma centralizada para su puesta en venta en todo el territorio de la UE. Los productos convencionales estarán sujetos al reconocimiento mutuo de las autorizaciones por los Estados miembros, y los desacuerdos entre los mismos serán arbitrados por la Agencia, cuyos avisos tendrán valor apremiante por decisión comunitaria.


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REFERENCES


