

# Legal and Regulatory Aspects of Veterinary Drug Use in the EEC

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All the EEC countries have by now adopted a veterinary pharmaceutical legislation which mainly aims at warranting the hygienic quality of foods of animal origin and protecting the consumer's health.

But, while the oldest legislations date back some fifteen years, others have just been adopted. So, a regulatory harmonization, which was already felt to be a pressing need when the directives were adopted in 1981, has now become an urgent necessity, less than three years before the opening of the single European market.

The aim of this presentation is to examine successively, the stage reached by:

- the community harmonization regarding marketing approval for veterinary drugs;
- the proposals for modifying Directive 81/851/EEC recommended by the commission and currently studied by the Council;
- the considerations in progress towards Community harmonization in preparation for 1993.

## Present State of Community Harmonization Regarding Veterinary Drug Approval

### Directive 81-851 EEC

The objectives of directive 81/851/EEC, which was adopted on the 28th of September 1981 (official Gazette EEC 6.11.81) regarding the approximation of member state legislations concerning veterinary drugs are as follows:

- harmonization of technical requirements to set up a coherent system at the level of the community to warrant the hygienic quality of food and to protect public health;
- reducing differences between national approval procedures and facilitating delivery of marketing approvals in several member states for the same medicine, so as to

promote common market functioning and to gradually bring about a free trade of veterinary drugs.

This directive concerns:

- pharmaceutical preparations,
- manufactured veterinary drugs,
- premixes for medicated feeds.

On the contrary, it does not concern:

- medicated feeds,
- feed additives encompassed in directive 70-524-EEC, adopted on November 23rd (official Gazette EEC 14.12.70),
- biological products,
- homeopathic drugs,
- drugs containing radioactive isotopes,
- extemporaneous drugs,
- practitioner - compounded drugs

### Directive 81-852 EEC

To obtain this marketing approval, the sponsor has to apply to the national competent authority by providing a dossier containing technical information justifying the pharmaceutical quality, therapeutic efficacy and safety for both the target animal and the consumer.

Directive 81-851 EEC, concerning the approximation of veterinary pharmaceutical legislations, was completed by Directive 81-852 EEC which details the trial procedures intended to ascertain quality, efficacy and safety of veterinary drugs. This directive also provides the framework to which analytical, pharmacotoxicological and clinical expertise must conform.

The approval may be refused for the following reasons:

- the drug is unsafe in the way it is to be used;
- the therapeutic effect is not sufficiently

- justified;
- the actual qualitative or quantitative composition of the drug does not correspond to the stated one;
- the withdrawal time indicated is not sufficient to ensure the absence of harmful residues for the consumer of foods of animal origin;
- the drug is presented for a use which is forbidden by other community regulations.

### Committee of Veterinary Medical Products

Despite the community harmonization for assessing quality, safety, and efficacy of veterinary drugs, promoted by the disposals of both directives, discrepancies between regulatory decisions taken by member states for the same veterinary drugs are nevertheless frequently encountered.

To reduce these differences in appraisal, Directive 81-851 EEC decided to create a Committee of Veterinary Medicinal Products (CVMP). It was established in November 1983 and at present meets 5 times a year. It is made up of representatives from the 12 member states and from the Commission. It is chaired by a representative from a member state. I have had the honor to be the chairman of this Committee since September 1988.

### Multi-State Procedure

This procedure is one of the main purposes of the CVMP. It aims at allowing a marketing approval granted by a member state to be extended to at least 5 other member states. If a member state has an objection to recognize this approval, the CVMP examines this objection and the member states which granted the approval act as rapporteur for this dossier. It has to be underlined that the CVMP is only an advisory body working for the commission. Therefore it gives only opinions which are not binding for the member state which, at the end, will take the final decision. Nevertheless, member states are invited to take in due consideration the opinion of the CVMP. The rapporteur may give the necessary explanations or ask the applicant to provide the additional information required.

The advantages of this multi state procedure for the veterinary pharmaceutical industry are obvious. It is:

- simpler: Once the first marketing approval is granted, the applicant need not apply separately to each other member state. The

applicant has just to submit the same dossier to the Committee and member states concerned.

- quicker: The whole procedure does not exceed 210 days.

In order to promote the harmonization of national decisions within the multistate procedure, the Committee has to help member states in their appraisal of veterinary drug quality, efficacy and safety. Working groups were set up to reach that goal.

The first one, presently chaired by Dr. Arnold, FRG, was created in January 1985. It has to examine all the problems relevant to veterinary drug residues, that is:

- assessment of veterinary drug residue safety,
- determination of maximum limits for these residues,
- proposals of routine methods to detect veterinary drug residues,
- elaboration of guidelines in the pharmacotoxicological requirements.

The importance of this working group activity has been enhanced since the creation in 1985, by the Codex Alimentarius Commission, of a specific committee devoted to the safety of veterinary drug residues in food. This committee has been meeting once a year since 1986, in Washington, DC. Its essential missions consist in the:

- determination of veterinary drug residues in food designated for priority scrutiny by FAO/WHO Joint Expert Committee on Food Additives (JECFA);
- recommendation of maximum limits for these residues;
- determination of criteria for the selection of analytical methods to be used for detection of veterinary drug residues in food;
- elaboration of codes of practice so as to ensure a proper use of veterinary drugs.

The activities of the working group on the safety of veterinary drug residues belonging to the Committee of veterinary drugs are now planned in accordance with those of the Codex Committee and of the JECFA. Thus the opportunity is given to member states of harmonizing their points of view before attending the meetings of the Codex Committee.

The second working group, chaired by Dr.

Kidd from the United Kingdom, was created in 1989. It has to develop protocols for clinical trials so as to permit a common approach to the appraisal of the therapeutic efficacy of veterinary drugs.

The third one, set up at the beginning of 1990, has to make proposals regarding analytical, pharmacological and toxicological trials of immunological veterinary products. It is chaired by Dr. Leunen, Belgium.

The fourth one, created last May, has to make proposals to promote the exchange of information regarding adverse effects of approved veterinary drugs. It is chaired by Dr. Jelicher, the Netherlands.

#### **Directive 87-22 EEC**

Directive 87-22 EEC, adopted on December 22, 1986 (official publication 17/1/1987) concerns the approximation of the member state procedures used to approve veterinary drugs derived from high technology. It is enforced since July 1, 1987.

Directive 81-851 EEC foresees a community procedure for the marketing in other member states of a veterinary drug already authorized in a member state. Directive 87-22 goes further in the trend of harmonization of decisions. It requires, for the drugs concerned, the CVMP's opinion before a national approval can be granted. Here too, a member state, chosen by the applicant, has to present the committee with an assessment report about the dossiers. After examination by CVMP, the rapporteur collects all the objections and keep contact with the applicant to facilitate the submission of additional data, if needed.

As for the multistate procedure, CVMP gives just an opinion which is not binding for the member states which, nevertheless, are invited to take this advice in due consideration.

#### **Directive 88-146 EEC**

Directive 88-146 EEC, which was adopted on March 7, 1988, (official publication EEC 16.3.88) led to the ban of hormones in animal fattening, since the regulations concerning these substances varied according to member states. Those divergences caused discrepancies in trade of food of animal origin subjected to a common marketing organization and consequently gravely hindered intra community exchanges. Moreover, European consumers were hostile to the use of hormones to fatten animals.

This directive authorizes, nevertheless, the use of natural steroid hormones,  $\beta$ -estradiol,

testosterone, and progesterone only for therapeutic uses. CVMP has been asked by the commission to set up a community list of veterinary drugs which can be used in this respect by the member states. This list has been set up and is currently evaluated by this standing veterinary committee.

#### **Directive 88-299 EEC**

Directive 88-299 EEC, adopted on May 17, 1988, (official publication 21.5.88) completes the disposals of Directive 88-146 EEC since it deals with hormonal substances permitted for well defined zootechnical purposes such as:

- synchronization of the estrous cycle,
- interruption of an untoward gestation,
- improvement of fertility,
- preparation of donors and receivers of embryos.

Here too, CVMP has been asked to set up a community list of veterinary drugs which can be used in this respect by member states. This list will be adopted by CVMP next September and forwarded to the standing veterinary committee for consideration.

#### **Proposals for Modifying Directive 81-851 EEC**

In December 1988, the Commission presented the Council with a series of three regulatory proposals intended to promote intra community trade. These texts were scrutinized at Council level since this date and, consequently, could soon be adopted. Broadly speaking, the three proposals have three main objectives.

#### **The Setting Up of a Centralized Community System to Determine Maximum Residue Limits**

At present, no mechanism exists to enforce the proposals of the CVMP concerning maximum residue limits in the whole community. Consequently, the Council should have to adopt these maximum residue limits by a series of specific directives, after the European parliament expressed its view.

In order to harmonize more easily the MRLs at the Community level to protect public health and to favor the single market, the Commission suggested that a simplified adequate procedure should be set up so that maximum limits proposed for veterinary drugs by the CVMP should be binding and therefore

formally admitted by the whole Community.

This regulation is expected to be enforced in January 1992. At this date, any new active substance, intended for food producing animals will have to be evaluated by the CVMP before being approved by a member state. All the active substances already used for food producing animals will have to be assessed by the CVMP and allocated fixed or temporary MRLs by 1997.

#### Extension to Veterinary Immunological Products of the Directive Ruling Veterinary Drugs

This proposal will constitute a frame directive that would extend to immunological veterinary products the fundamental requirements given in directive 81-851 EEC regarding marketing approvals.

However, the extension to veterinary biological products of the current regulation will have to take into account specificities of these products and particularly:

- the necessary homogeneity of batch quality;
- the epidemiology, in the country considered, of the disease to protect against.

Thus a member state might, for epidemiology's or prophylactic strategy's sake, prohibit the approval of immunological veterinary products notwithstanding their conformity to the quality, safety, and efficacy criteria.

#### Modification of Directive 81-851 EEC

On one hand, this general proposal to update this directive aims at extending to veterinary drugs many modifications already adopted for human drugs. It proposes, specially:

- to improve the multistate procedure. Despite the advantages of this procedure, it must be admitted that, up to now, few manufacturers have availed themselves of it. As a consequence, the Commission proposed several modifications that could make the procedure more attractive by reducing the minimal number of member states from five to two and by introducing the right for the applicant to be heard by the CVMP;
- to grant veterinary drug manufacturers a 10 year protection period against simplified applications presented as copies for generic drugs;
- to improve the quality assurance of

manufacturing procedures by requiring from all veterinary drugs manufacturers compliance with the future Community code of good manufacturing practice;

- to develop information about veterinary drugs. The authorities of the member states or of the Community will have to adopt a summary of the main characteristics of each approved drug.

On the other hand, this proposal contemplates several measures specific to veterinary drugs. It is, in particular, proposed:

- to determine cases when a non-approved veterinary drug could be prescribed: severe epidemiological situation, lack of an approved drug for a specific pathology, clinical trials, veterinarians providing services on a transfrontier basis;
- to introduce a series of controls to make sure veterinary drugs and medical substances intended for veterinary drug composition can only be distributed through authorized ways.

#### Towards a Single Market for Veterinary Drugs

In the prospect of the European single market which is to open in 1993, it is obvious that the present veterinary pharmaceutical legislation and the modifications proposed by the Commission which could be soon adopted by the Council represent but stages towards the free trade of veterinary drugs within the EEC.

As a matter of fact, the Commission has just given the final touches to a project soon to be laid before the Council for discussion and adoption. The objective of this project is the determination of the future community system for veterinary drug registration. Basically, it tends to:

- gradually replace the various national procedures by a centralized, single, high-level evaluation, the conclusions of which would be binding for all the member states;
- increase technical cooperation between member states so as to entice them to mutually recognize national approvals;
- promote access to community trade of innovative drugs.

The goal of the submitted texts, which

concern both human and veterinary drugs, is:

- to set up three different registration procedures: 1) *centralized procedure*, compulsory for drugs derived from biotechnology and available, on an optional basis, for drugs derived from other high technologies or containing new chemical entities; 2) *decentralized procedure* for other veterinary drugs, relying upon mutual acceptance of national marketing approvals; and 3) *national procedure* for veterinary drugs to be marketed only in one member state;
- to develop a European network in pharmacovigilance to exchange data about adverse effects of veterinary drugs in animals and to coordinate consecutive regulatory steps;
- to create a European agency for drugs in order to coordinate all the activities concerning veterinary drug registrations.

This agency would be made up of:

- the two existing scientific committees, the Committee of Pharmaceutical Products and the Committee of Veterinary Medicinal Products, being together in charge of the scientific evaluation of dossiers for marketing approval;

- a scientific body which will have to give its opinion on critical topics be they of a scientific or ethical nature;
- an administrative structure which will have to coordinate the work of the agency.

To conclude, drawing ever nearer to the mythical date of 31.12.1992, which will see the creation of the European single market, has had a spectacular effect on the evolution of the rules concerning veterinary drug marketing approvals in the EEC.

I personally hope that the appraisal criteria taken into consideration for the assessment of veterinary drugs will still be defined as they presently are by the following four characteristics:

- precision: to avoid any conflict between an authority and an applicant;
- objectivity: to guarantee the scientific nature of the assessment procedure of veterinary drugs;
- duration: to allow industry to be informed sufficiently in advance about the evolution of regulatory requirements which have consequences on its research and development activity;
- evolution: to take into account new developments of knowledge in the relevant scientific areas.