COMMUNICATION FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT

Availability of veterinary medicinal products
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Introduction

Community legislation relating to veterinary medicines has a twofold aim: to guarantee a high level of safety and medicinal efficacy for the animal being treated, and to protect the health of the consumer of foods of animal origin. This has led to a high degree of harmonisation, one of the indirect consequences of which has been a reduction in the range of veterinary medicinal products available. With the high cost of scientific research, including that resulting from the establishment of Community maximum residue levels (MRLs) in foodstuffs of animal origin, pharmaceutical firms are abandoning certain market segments which no longer permit a satisfactory return on investment. Perceptions of this problem became particularly acute with the approach of 1 January 2000, the date at which Member States were required to withdraw marketing authorisations for all old veterinary medicinal products containing substances for which no MRL had by that date been established. The Commission had been alerted to this situation, specifically during the course of the meetings of the "Agriculture" Councils of June and December 1999 and by means of questions to the European Parliament\(^1\). The Commission gave assurances that it would seek appropriate solutions to the problem.

1. **Context: Conditions for Marketing Authorisations for Veterinary Medicinal Products**

Before a medicinal product is given a marketing authorisation, it must be shown on the basis of scientific tests to have fully met three criteria: quality, safety and efficacy.

In the specific case of veterinary medicinal products destined for animals producing food products, the safety assessment must also take account of an additional factor associated with the possible persistence of residues of medicinal products in the foodstuff and possible consequences for the consumer.

To these ends the competent authorities establish a minimum waiting time to be observed by the animal's owner when appropriate to the proper use of a veterinary medicinal product. This waiting time corresponds to the period during which the foodstuffs produced by the animal in question may not be marketed for human consumption. It is determined by reference in particular to the rapidity with which the active substances of the product are eliminated, to the point below which the residues present in the foodstuffs produced by the animal can be regarded as no longer representing a risk to the consumer. These thresholds are defined as Maximum Residue Levels (MRLs).

\(^1\) See, inter alia, oral questions H-62/00 or H-400/00.
MRLs for active substances used in veterinary medicinal products have been harmonised, by Council Regulation No 2377/90\(^2\).

The process by which an MRL is established for an active substance is begun by the manufacturer, who submits an application to the European Agency for the Evaluation of Medicinal Products, which was established by Council Regulation No 2309/93\(^3\). The Agency, through its Committee on Veterinary Medicinal Products, drafts an opinion for the Commission, with a view to the substance's possible inclusion in one of the annexes to Regulation No 2377/90 setting Community MRLs\(^4\).

For "old" veterinary medicinal products authorised by Member States before 1992, the Regulation No 2377/90 provides a transition period to permit pharmaceutical firms to submit their applications for Community MRLs for the "old" active substances concerned. And since 1 January 2000, by virtue of Article 14 of the Regulation in its current drafting, the administration to food-producing animals of "old" veterinary medicinal products is prohibited in the Community, unless the pharmacologically active substances concerned have been included in annexes I, II or III of the Regulation.

The establishment of an MRL is an essential, but not the only condition prior to the granting of a marketing authorisation for any veterinary medicinal product destined for animals producing foodstuffs. The marketing authorisation procedure for the product will later be the task of the competent authorities either nationally (mutual recognition, for the Member States concerned) or at Community level ("centralised" procedure). Council Regulation No 2309/93 sets out the Community procedure for granting applications for marketing authorisation. At this stage, however, most existing veterinary medicinal products have national marketing authorisations. And not all categories of new medicinal products can follow the centralised authorisation procedure.

2. **THE PROBLEM: THE NARROWER RANGE OF VETERINARY MEDICINAL PRODUCTS AVAILABLE**

2.1. **The origin of the problem and its manifestations**

Economically, several features distinguish the veterinary medicinal products sector from that of human medicine. The animals to be treated, particularly farmed animals, have a finite economic value, whilst the totality of treatment costs must be borne by the owner. In addition, the markets are much weaker and more fragmented than that of human health-care, because of


\(^4\) Council Regulation (EEC) No 2377/90 comprises four annexes. Following evaluation of pharmacologically active substances used in veterinary medicinal products, Annex I lists those for which an MRL has been set, and Annex III those for which a provisional MRL is set subject to subsequent scientific study.

Annex II identifies substances for which there is no need on health protection grounds to set an MRL. Annex IV is for substances for which no MRL can be set because they pose a risk to health in whatever quantity.
the number of animal species concerned, the restricted size of certain populations, the wide range of pathologies the diversity of regional situations and the continued existence of national authorisation systems. Lastly, the food products produced by the animals must present no risks to the consumer, which means specific constraints on the evaluation of risks associated with residues.

The constant concern for safety and quality and the ever-higher requirements to be satisfied before a marketing authorisation can be granted have added substantially to the costs of research and development for these products. This being the case, the veterinary pharmaceutical industry no longer finds it sufficiently attractive to invest in medicinal products targeting species or therapeutic conditions representing only small market segments.

A gradual reduction in the available range of authorised therapies can consequently be observed in these sectors. Pharmaceutical firms are developing scarcely any new drugs, and in addition are regularly abandoning certain old products, particularly when the competent authorities call for additional studies to meet the latest requirements of product quality, efficacy or safety when the marketing authorisation comes up for its five-yearly renewal.

The problem became even more acute on 1 January 2000. The legislative and scientific page was turned for old veterinary medicinal products by the establishment of Community MRLs, Not all had adequate market prospects, and only those still offering their firms some significant economic prospects have been defended. Thus, as the cut-off date approached, there arose the threat of overnight prohibition for a large number of previously used veterinary products, for lack of a Community MRL.

The European Agency for the Evaluation of Medicinal Products has thus identified more than 100 pharmacologically active substances used in veterinary medicine for many years and for which no MRLs had been established by 1 January 2000. In most cases this was because inadequate information had been submitted by manufacturers, and their lack of interest in carrying out the necessary additional research. All medicinal products containing any of these substances are now prohibited for all foodstuff-producing animal species throughout the Community.

2.2. Whose problem is it?

* Those responsible for the animals' health and welfare: farmers and veterinarians

These are the first to be concerned by the lack of available medical products. Frequently, for lack of a treatment, they will have no alternative but to administer active substances available only outside the legal framework, without any approved indication of dosage or of the need to observe a waiting time. These substances are thus used without known therapeutic efficacy and without any safety evaluation for the final consumer of the foodstuffs concerned.

This conduct is forced upon the persons concerned by two factors: unwillingness to allow sick animals to suffer, and/or unwillingness to accept the large potential economic costs of the animal's sickness. The sudden reduction in the available therapeutic armoury has thus resulted in a significant risk of more widespread illegal and unmonitored use of active substances.

* Consumers

Foodstuffs should not contain residues of medicinal products capable of representing a health risk to the consumer. Strictly speaking, when no authorised medicinal products have been used, there should be no residues either.
However, account must be taken of the true situation (illegal use) and of the limits inherent in any control system when evaluating a strategy for the management of risk to the consumer, resulting from the persistence of residues of unauthorised products.

* The veterinary medicinal product industry

Given the time taken to develop new products and the need to anticipate and define medium- and long-term economic aims, the veterinary medicinal product industry is economically unable to defend its "old" products for animal species and conditions whose commercial prospects are negligible. The industry would certainly find it profitable to continue marketing certain medicinal products which have been available for many years, but over recent years the decision to invest additional resources to take account of new regulatory requirements (principally the establishment of Community MRLs) has mainly been directed to more profitable products.

Furthermore, although the centralised procedure is compulsory for the granting of a marketing authorisation for any innovative product in particular, it does not necessarily follow that the product will then be available throughout the Community. Only the markets that have enough economic or strategic attraction will justify the costs of manufacturing and effectively marketing the product.

* The competent authorities

As already mentioned, 1 January 2000 was the date at which Member States were required to definitively withdraw marketing authorisations for all old veterinary medicinal products intended for food-producing animals containing substances for which no MRL had by that date been included in annexes I, II or III of Regulation No 2377/90.

Not only had these products often been on the market for many years (since before 1992), but for certain species they represented a significant part of the available therapeutic armoury.

The Commission is thus aware of the need to take account of this situation, whilst fully heeding its obligation not to endanger public health.

The Commission is also conscious of the importance of and need for checks on residues of unauthorised substances in foodstuffs. This responsibility lies with Member States.

3. WHAT CAN BE DONE?

In such a situation, the task is thus to find:

- possible answers to the health-care and welfare needs of food-producing animals;
- a basis guaranteeing a high level of consumer protection;
- a satisfactory economic context for the veterinary medicinal products industry.

The heart of the problem, and its urgency, reside in the absence of Community MRLs for a large number of "old" active substances used to treat certain species. These are thus the questions which must be answered first.

Thought must also be given to measures aimed at a sustainable broadening of the range of new veterinary medicinal products on offer in the "minor" segments of the market.
3.1. **Short term: adapt the scientific requirements for establishing MRLs**

Precaution is the policy underlying risk evaluation and management through the establishment of MRLs aimed at determining a waiting period for veterinary products. This policy of precaution has developed in parallel with the rising level of scientific requirements aimed at guaranteeing the quality and safety of pharmaceutical products.

Originally, the determining of MRLs did not depend on an approach specific to each animal species concerned. Considerations of comparative metabolism and pharmacokinetics now result in residue risk evaluations base on the animal species concerned.

As a result, for numerous active substances, MRLs under Regulation No 2377/90 have been determined only for one or other animal species. For certain species (bees and fish, but also goats, sheep, laying hens, horses and others) only a very small number of MRLs exist.

Similarly aware of the problem of the availability of veterinary medicinal products, the Committee on Veterinary Medicinal Products, which brings together the best experts and scientific representatives in the field, is working on the possibility of defining MRLs for certain species by extrapolation from those established for others. The methodology developed by the Committee, together with its experience in evaluating medicinal products, should enable it to evaluate risks without either jeopardising the high level of consumer protection or calling for more supplementary data than are strictly necessary (in order not to weaken the interest of the pharmaceutical industry in investing in such research). The Committee on Veterinary Medicinal Products is preparing guidelines reflecting these ideas.

The Commission accepts the principle that, for any given active substance, MRLs should be established by extrapolation from the MRLs set for other species on a strictly scientific basis. It hopes that guidelines in this direction may be finalised by consensus before the end of 2000. The Commission also hopes that applications for MRLs will then be submitted as quickly as possible by interested organisations. But since such guidelines have not yet been laid down, it is at this stage difficult to estimate how much incentive the measures will in fact generate. The speed with which MRL applications are submitted will also depend directly on the time required to complete the requisite research.

MRL extrapolation is intended to be applied as soon as possible to existing substances with the aim of expanding the number benefiting from MRLs in respect of species whose economic importance is limited. But the principle could also apply to new substances and thus become a factor encouraging the development of new medicinal products for those species.

The establishment of an MRL is essential, but not the only condition prior to the granting of a marketing authorisation for a veterinary medicinal product. Other research also represents a significant investment, notably that aimed at demonstrating the substance's efficacy in the species and indications concerned. As a result, the Committee on Veterinary Medicinal Products' work on guidelines for demonstrating the efficacy of medicinal products in limited market segments and species should also help solve the problem of availability.

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5 Pharmacokinetics is the study of the absorption, distribution, metabolism (transformation) and elimination of a substance.
3.2. **For the medium term: adapt the law**

These seems to be a need for a broad review of all aspects of the problem of availability, and for a coherent set of measures aimed at improving the availability of certain therapeutic substances for species and indications which are of little economic interest.

To this end, the Commission has two objectives:

- To enhance pharmaceutical firms' interest in certain market segments by making the investments required prior to marketing more attractive, by adapting as far as possible the system of marketing authorisation to the particularities of the animal health sector whilst maintaining the high level of consumer health protection. The costs and constraints of developing a veterinary medicinal product should not be a barrier to innovation or to making available to stock raisers and the profession the products necessary to maintain their animals' health.

- To permit and, if possible, facilitate the veterinary use of medicinal products not available in the Member State concerned but authorised elsewhere in the Community.

Under the terms of Article 71 of Regulation (EEC) No 2309/93, the Commission must publish a general report on the experience acquired as a result of the operation of the marketing authorisation procedures. This report, which will also relate to Directive 81/851/EEC, should be available by the end of 2000 with a view to appropriate revision of the law on veterinary medicinal products.

The Commission thus proposes, as part of the general process for revision of the marketing authorisation system, to take account of the special features of the veterinary sector and the question of the availability of veterinary medicinal products. The Commission intends to finalise its proposals along these lines in 2001. The process will, however, take several years to complete.

The Commission trusts that the prospects opened by the measures for the short term (MRL extrapolation) and the medium term (revision of existing legal instruments) will reverse the current trend and also facilitate the sustainable development of new therapies for the species and indications which are currently ignored by the veterinary pharmaceutical industry.

The Commission is nevertheless continuing its reflections on the possibility of developing in parallel a policy analogous to the "orphan drugs for human use" scheme for veterinary medicinal products, by means of a specific legal instrument. The paths to be explored should seek in particular to define indirect incentives to promote the development of new veterinary medicinal products specific to these abandoned market segments (reduced registration fees, technical assistance from the Agency, longer exclusive market rights, and others). Direct incentives could also be considered (financial contributions to R&D, reimbursement of certain investments on granting of marketing authorisation, voluntary co-financing by associations of breeders of the species concerned, etc.) But the Commission considers that if such a proposal should see the light of day, the scope and the ways and means of its application will need to be precisely identified.

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It is important to recall that such an approach will take a decade or so to achieve tangible effects. The fact is that, in such a context, pharmaceutical firms will commit themselves to the development of new substances only if they have all the requisite guarantees: the legislation in force and the assurance that the drug will indeed meet the specific eligibility criteria of the provisions. Only at that stage will they begin the long and complicated research needed before a marketing authorisation can be submitted.

In order to define more closely the field of medicinal products or active substances which might benefit from such special conditions, it may be necessary to carry out an exhaustive review of the situation in the Member States. The competent authorities in each Member State should contribute actively to identifying as closely as possible the veterinary medicinal products which are felt to be truly indispensable for animal health and welfare, but which are not of interest to the veterinary pharmaceutical firms and cannot be replaced by other, available, veterinary medicinal products. In addition, the scope of such an approach will be limited by the actual results of any measures taken for the short and medium term.