



**DISCUSSION PAPER
ON THE AVAILABILITY OF VETERINARY MEDICINAL
PRODUCTS FOR MINOR SPECIES AND MINOR USES**

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INTRODUCTION

Many measures have been taken to harmonise the requirements for the granting of marketing authorisations for veterinary medicinal products and to review the conditions of authorisations of older products.

As a result of these measures, a number of products have been withdrawn from the market. In some cases, residues of such products in commodities derived from food-producing animals were considered to present an unacceptable risk to consumer safety. However, in the majority of cases, products have been withdrawn on financial and economic grounds. On the same grounds, they have not yet been replaced and will probably not be replaced in the future. Indeed the cost of producing a data package for bringing new products onto the market, or simply maintaining old ones is such that it limits the number of products available to practitioners.

Antibiotics, antiparasiticides, non steroidal anti-inflammatory drugs and biological products for major diseases in cattle, swine and poultry are still largely available in all Member States. However, for other species or uses, practitioners are concerned by the reduction of their therapeutic arsenal.

General anaesthetics, antidotes and fluid therapy for all food-producing species are amongst the major veterinary medicinal products which are not or no longer available to the veterinary practitioner.

For some species, such as fish, there are, in some Member States, virtually no products authorised. For other species, such as goat, lactating sheep, rabbit, practitioners must more and more often prescribe products authorised for other species but not for these ones. This extra-label use, whilst tolerated by the European legislation in exceptional circumstances only, is thus becoming the rule.

Finally, products with a low cost and a well established use are disappearing from the market, as a result of the review of their conditions of authorisations.

It is therefore increasingly difficult for practitioners to treat animals under their care. Especially, when these animals belong to minor species, but also, in some cases, even when they belong to major species.

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DEFINITION OF MINOR SPECIES AND MINOR USES

Several attempts have been made to define minor species and minor uses and different definitions have been given (see table below).

There is however one constant feature which is, that for some species and some uses, the market is too small to provide pharmaceutical companies with a fair return on their investment. As a result, companies are no longer willing to develop new products or to defend old ones.

From that point of view, major species can almost be confined to cattle, swine, chicken, dogs and cats and major uses to antimicrobials and parasiticides, minor species and minor uses covering the rest!

The European Agency for the Evaluation of Medicinal Products has defined major food producing species as cattle and sheep (meat); cattle (milk); pigs; chickens (including eggs); salmonidae. Other species have been considered as minor, in particular other ruminants: minor ruminants (*bovidae* including *caprinae*) and their milk, deer (*cervidae*) including reindeer; sheep milk; other avian species and their eggs; other fish species; other mammalian species (horse/rabbit).

In the US a minor use is defined in the Code of Federal Regulations as the *use of: (a) New animal drugs in minor animal species, or (b) new animal drugs in animal species for the control of disease that (1) occurs infrequently or (2) occurs in limited geographic areas.* Minor species are defined in the same Code as *animals other than cattle, horses, swine, chickens, dogs and cats.* *Sheep are a minor species with respect to effectiveness and animal safety data collection; sheep are a major species with respect to human safety data collection requirements resulting from the possible presence of drug residues in food.*

SITUATION TODAY

In the last two decades, the requirements for the authorisation of veterinary medicinal products have increased from virtually nothing to a comprehensive range of studies to demonstrate the quality, the safety and the efficacy of these products. The costs associated with the development and registration of these products have increased in parallel to these new requirements.

The constraints imposed on practitioners have also increased, mainly to protect public health from potential harmful residues of veterinary medicinal products.

The combination of these has resulted in a situation where the number of products authorised has declined and the conditions of use of such products are more limited. In some cases, this has even resulted in compromising animal health and animal welfare. In that respect, the situation is particularly alarming for minor species and minor uses.

Furthermore, this situation is leading in some cases, such as fish medicine, to the overuse of the few products available. With molecules like antibiotics and antiparasitics this might contribute to the development of resistance. Also, this situation is preventing practitioners from having access to the latest products developed and from practising a state-of-the-art medicine.

Development and registration costs

Concerns over the hazard of residues for the consumer and, more recently, about the fate of these same residues in the environment, have led to a number of legislative changes. Pharmaceutical companies must now demonstrate that residues from their products are safe for both the consumer and the environment. This is a heavy burden which for new molecules is balanced by the protection of the data submitted for the registration of these molecules for a period of 10 years. Return on their own investments is thus somehow guaranteed to those companies willing to develop new products.

Pharmaceutical companies must also give assurance that residues of old molecules are safe, both for the consumer, and for the environment. Some costly studies must thus also be carried out to defend these molecules. Some of them have however been on the market for sometimes more than 20 years. As a consequence, they no longer benefit from either patent or data protection. They have even been copied and many generics of the original product are now available. There is consequently little interest for an individual company to produce data to defend an old molecule as it is indeed likely that data will also be of benefit to its competitors.

As a result, some molecules have disappeared from the market and more will continue to disappear between now and January 2000, when the establishment of maximum residue limits (MRLs) for these old molecules must be completed (see Annex I).

The same might also happen tomorrow as a result of the new requirements introduced for assessing the impact of residues of veterinary medicinal products on the environment.

Restrictions imposed upon the prescriber

Practitioners are not allowed to use any other products but those which have been authorised by the competent authority of their own Member State for the species concerned. However, when no product is available, practitioners are very tempted to use products which are authorised for another species or for humans, or to use products authorised in another Member State but not in their own.

For companion animals, Article 4.4 of Directive 81/851 - the so-called cascade system (see Annex 3) -, gives flexibility to ensure that practitioners will have in most cases access to what they require by allowing recourse, when necessary, to products authorised for human use or to extemporaneous preparations. For food-producing animals, the system is however far more stringent and the current wording of the cascade limits the prescriber's choice to those molecules authorised for use in food-producing animals only.

Many molecules which are not authorised for food producing animals are however necessary to treat those species. Nevertheless, having recourse to halothane to anaesthetise a horse or to fusidic acid for topical treatment of conjunctivitis in cattle is illegal.

PROPOSALS FOR THE FUTURE

Firstly, practitioners must be given access to all products which are essential for animal health and animal welfare, when the use of such products would do no harm to public health. Protection of public health from harmful residues must then be based on risk analysis. Secondly, incentives must be developed to maintain and, where necessary, restore the number of products authorised for minor species and minor uses. Indeed, as explained above, the removal of products from the market and the paucity of replacement products is less due to concern for public health than to the costs associated with the studies required to demonstrate that there is indeed no risk for the consumer or for the environment.

RISK ASSESSMENT AND RISK MANAGEMENT

Cascade

The current wording of the cascade must be modified to allow practitioners, when no molecule is authorised for use in food-producing animals, to have access to those molecules used in companion animals and in human medicine. If necessary, extemporaneous preparations should also be allowed.

Having in mind that most of the molecules that could then be used by practitioners would respond to specific needs and would therefore be used in a limited number of animals, consumer exposure to residues of such molecules would anyhow be limited. In addition, the withdrawal periods currently applicable when recourse is made to the cascade (e.g. 28 days for meat) could be retained and would thus limit even further consumer exposure to any residues.

In terms of risk assessment and of risks for the consumer, it is difficult to believe that the modification of the cascade as indicated above would add anything to the risk currently associated with the use of major therapeutic molecules on a much wider scale.

Finally, restricting the use of molecules when there is no means to control such restrictions is not appropriate. It would instead be preferable to promote the reasonable use of molecules and to monitor that practitioners fulfil their responsibilities.

Specific uses

These principles of risk assessment and risk management could also be applied to some molecules which have been withdrawn from the market because their residues presented a hazard to the consumer at whatever level. However, in some cases, little consideration was given to the real risk and to the likelihood of consumers being exposed to such residues.

Indeed, a number of treatments are only indicated far from slaughter and consumer are unlikely to be exposed to any residues. This is in particular the case of medication which is administered during the early life stages of fish.

In such cases, and when no alternative exists, it is not acceptable to ban the use of molecules which are essential for animal health and animal welfare. A sound application of risk assessment and risk management principles would consist in allowing the use of such molecules but in restricting the conditions of their use.

European list of essential products

Today, some practitioners, especially in small Member States, have no other alternative but to seek, in some cases, recourse to products illegally imported from other Member States, when the required products are not available in their own.

It is difficult to believe that such practice could present a risk either for public or for animal health as these products are legally authorised in other Member States along principles and requirements which have been harmonised within the Community since 1981.

Furthermore, food-products derived from animals treated in another Member State may be imported without any restrictions and indeed the treated animals themselves may be imported and subsequently enter the food chain in a Member State in which a specific product is not licensed.

Finally, Directive 81/851 explicitly states that, *where the health situation so requires, a Member State may authorise the placing on the market or administration to animals of veterinary medicinal products which have been authorised by another Member State in accordance with this Directive.*

Member States must therefore be encouraged to make full use of this provision. This would indeed solve a number of problems, especially in those Member States where the market-size is too small to attract products with a low turnover.

A European list of the products that practitioners consider as essential to fulfil their duties could therefore be drawn up by the profession. This list should only contain products which have been authorised in a minimum of Member States prior to 1 January 1995, at a time when the new Community registration procedures were not available (see Annex 2). Each Member State could then allow the import and use by

practitioners of those products on the list for which no other therapeutic alternative is available in their own country.

DEVELOPMENT OF NEW PRODUCTS

In addition to these measures, a number of wider measures should also be investigated to facilitate the development of new products.

Efficacy and safety data required for the authorisation of new products intended for minor species and minor uses

The European Agency for the Evaluation of Medicinal Products (EMA) and the Committee for Veterinary Medicinal Products (CVMP) have already recognised that Regulation 2377/90 as it was implemented until recently did not favour the establishment of MRLs for minor species. The CVMP has therefore developed and adopted a Note for Guidance¹ which allows for the extrapolation from results obtained for major species to minor species (e.g. from pigs to horses) or the submission of an abbreviated data package when the substance is used only in minor species and when no data is available for a major species. This concept could however be extended to the whole of the safety and efficacy data to be submitted for the granting of a marketing authorisation and could relieve pharmaceutical companies of the need to perform some costly studies.

Community minor species and minor uses programme

Wider incentives could also be developed, modelled on the Community Orphan Drugs policy which is intended to provide human patients affected by a rare disease with medicinal products which respect the required standards of quality, safety and efficacy. Such incentives could range from the granting of an extended period of exclusivity on the scientific data used to support the application and thus make the return on investment more attractive, to the facilitation of the development of new products for minor species or minor uses by means of a dedicated Community research programme.

Fee waiver and fee reduction for the registration of veterinary medicinal products intended for minor species or minor uses

The level of fees to be paid to the competent authorities for the evaluation of applications for the granting of marketing authorisation has risen significantly in recent years. Indeed, many authorities are now relying on independent agencies, which are responsible for carrying out the scientific evaluation and providing recommendations. Such agencies must often rely on self-funding and therefore largely depend on fees paid to them by the pharmaceutical industry.

¹ Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMA/CVMP/153a/97) adopted in November 1997.

As an example, the basic fee to be paid to the EMEA for a product intended for food-producing animals might rise from ECU 70 000 to ECU 100 000².

Such costs are however prohibitive for products intended for minor species or minor uses. The development of policies on the waiving of fees and on fee reduction for the registration of such products, should therefore be encouraged.

The EMEA, like some national agencies, has already established such policies. However, alternative funding must be made available to cover the costs associated with the evaluation. In the case of the EMEA, these resources should come from the EU budget as it is a matter of community interest to ensure that products for minor species and minor uses are still available throughout the EU.

DEFENCE OF OLD MOLECULES

It is also essential that the costs associated with the defence of old molecules with a low turnover, be balanced by incentives. Otherwise no company will be prepared to defend them and to produce data for the protection of consumers and of the environment.

Funding of research

The Community research programme detailed above for the development of new molecules could also serve the purpose of providing new data for the defence of old molecules intended for minor species or minor uses.

Data protection

Finally, as any public funding can only be limited, other incentives must be developed. Means to protect data submitted, in particular for the establishment of MRLs or for the assessment of the environmental risk, should therefore also be explored.

²Commission Proposal for a Council Regulation (EC) amending Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products (COM(1998)21 final).

CONCLUSIONS

The constraints imposed on the availability of medicinal products for minor species and minor uses are principally due to the obligation to protect public health from harmful residues of veterinary medicinal products.

However, the current legislation and measures go, in some cases, beyond what is necessary to protect public health and are not designed to accommodate for the recent changes which have introduced risk assessment, risk management and risk communication at the heart of consumer protection.

These principles must however also be applied to the protection of consumers from residues of veterinary medicinal products. Not only the toxicity of product residues must be taken into account when assessing the risk to the consumer, but the conditions of use of the product must also be fully integrated.

The choice between products lawfully available to practitioners could then be extended and practitioners be relieved of their current dilemma when essential products for animal health and animal welfare are no longer available and when they must nonetheless treat animals under their care.

The market rule of thumb remains nonetheless the main threat for products intended for minor species and minor uses. In that respect, risk assessment and risk management principles might not be enough to maintain or restore the therapeutical arsenal of practitioners. Public action might be necessary to introduce measures for assisting those companies willing to develop new products for minor species and minor uses and maintaining old ones on the market.

ANNEX I

MAXIMUM RESIDUE LIMITS MUST BE ESTABLISHED FOR ALL SUBSTANCES CONTAINED IN VETERINARY MEDICINAL PRODUCTS INTENDED FOR USE IN FOOD-PRODUCING ANIMALS

In order to protect public health, the Community has adopted measures to establish the level of residues which can be accepted in foodstuffs without constituting a hazard to the health of the consumer. In particular, Council Regulation (EEC) No 2377/90 lays down a procedure for the establishment of maximum residue limits (MRLs) of veterinary medicinal products in foodstuffs of animal origin.

This Regulation stipulates that MRLs must be established for any substance intended for use in food-producing animals prior to its use in the Community. For substances which were already used in food-producing animals before the entry into force of this Regulation (1 January 1992), there is an ongoing transitional process, at the end of which (1 January 2000) MRLs would also have been established. If not, products intended for food-producing animals and containing these substances would have to be withdrawn from the market.

For the establishment of MRLs, pharmaceutical companies must submit applications supported by specific data relating to the pharmacological and toxicological profile of the substance, as well as the results of residue depletion studies in the species for which the substance is intended.

Such applications must be submitted to the European Agency for the Evaluation of Medicinal Products (EMA), where they are evaluated by the Committee for Veterinary Medicinal Products (CVMP). Eventually, the recommendation of the CVMP is transmitted to the European Commission, which turns it into Community law.

Substances are then classified in one of the four annexes of Regulation 2377/90:

▲ Annex I lists substances for which maximum residue limits have been established.

▲ Annex II contains those substances for which it is not necessary for the protection of public health to establish a maximum residue limit.

▲ Annex III lists substances for which provisional maximum residue limits have been established, whilst the sponsor company is carrying out further studies. Inclusion in this Annex is however conditional on the absence of any grounds for supposing that residues at the level proposed may present a hazard to the health of the consumer.

▲ The residues of some substances constitute a hazard to the consumer at whatever limit. Such substances are therefore prohibited in the Community for use in veterinary medicinal products intended for food-producing species and are listed in Annex IV.

ANNEX II

AUTHORISATION FOR THE PLACING ON THE MARKET OF VETERINARY MEDICINAL PRODUCTS

Besides the establishment of MRLs, Community legislation requires that no veterinary medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued³. To obtain such authorisations, pharmaceutical companies must submit an application to:

▲ the EMEA, via the so-called centralised Community procedure, whereby the company could obtain a Community marketing authorisation valid throughout the Community. This procedure is, however, currently limited to products derived from biotechnology, to innovative products or to products containing a new active substance;

▲ Member States' competent authorities, via the so-called decentralised Community procedure, whereby the company could obtain national marketing authorisations. This procedure relies on the mutual recognition by Member States of the first marketing authorisation granted by one of them;

▲ a single Member State, if the product is to be marketed in this Member State only. Otherwise if the product is to be marketed in more than one Member State, the company must use one of the two Community procedures outlined above.

This application must contain the results of tests and trials demonstrating that the product has met with the required standards of quality, safety and efficacy⁴, including maximum residue limits for food-producing animals.

³Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of Member States relating to veterinary medicinal products.

⁴Council Directive 81/852/EEC of 28 September 1981 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 veterinary medicinal products.

ANNEX III

ARTICLE 4 of COUNCIL DIRECTIVE 81/851/EEC

1 . No veterinary medicinal product may be placed on the market in a Member State unless authorisation has previously been granted by the competent authority of that Member State.

However, where the health situation so requires, a Member State may authorise the placing on the market or administration to animals of veterinary medicinal products which have been authorised by another Member State in accordance with this Directive.

[...]

4. However, where there exists no authorised medicinal product for a condition, Member States may exceptionally, in particular in order to avoid causing unacceptable suffering to the animals concerned , permit the administration by a veterinarian or under his/her direct personal responsibility to an animal or to a small number of animals on a particular holding:

- (a) of a veterinary medicinal product authorised in the Member State concerned for use in another animal species, or for another condition in the same species; or
- (b) if there is no product such as referred to in point (a), of a medicinal product authorised for use in the Member State concerned in human beings in accordance with Directive 65/65/EEC of 26 January 1965; or
- (c) if there is no product such as referred to in point (b) and within the limits of the law of the Member State concerned, of a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national legislation in accordance with the terms of a veterinary prescription,

provided that the medicinal product, where administered to animals whose flesh or products are intended for human consumption, contains only substances to be found in a veterinary medicinal product authorised for such animals in the Member State concerned and that in the case of food-producing animals the veterinarian responsible specifies an appropriate withdrawal period to ensure that food produced from the treated animals does not contain residues harmful to consumers.

Unless the product used indicates a withdrawal period for the species concerned, the specified withdrawal period shall not be less than:

7 days : eggs,

7 days : milk,

28 days : meat from poultry and mammals including fat and offal,

500 degree days : meat from fish.

The veterinarian shall keep adequate records of the date of examination of the animals, details of the owner, the number of animals treated, the diagnosis, the medicinal products prescribed, the dosages administered, the duration of treatment and the withdrawal periods recommended, and make these records available for inspection by the competent authorities for a period of at least three years. This requirement may be extended by the Member States to animals whose flesh or products are not intended for human consumption.