

Veterinary Drug Products and the European Economic Community (EEC)

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The near opening of the single European market promotes a rapid evolution of the Community procedures of veterinary drug marketing approval. A community system of marketing approval, submitted by the Commission, is about to be discussed at the Council level. The basic directives 81/851/EEC which aims at harmonizing member state veterinary pharmaceutical legislations and 81/852/EEC which harmonizes the technical requirements demanded for drug registration are at present being modified. Of course, such a rapid evolution poses some problems which are not yet solved but to which pharmacokinetics could bring an appropriate answer. To reach that goal, it is necessary, and the veterinary drug Committee is presently working in that direction, to precisely define the technical requirements that will allow pharmacokinetics to bring all the benefits which may be expected from it.

Current Problems Regarding Veterinary Drug Marketing Approval in the EEC

Revision of Old Veterinary Drugs

As the provisions of these directives 81/851/EEC and 81/852/EEC apply to all the veterinary drugs marketed in the EEC, their enforcement obviously also concerns so called "old veterinary drugs" that were already marketed prior to the adoption of these directives.

So, Article 52 of Directive 81/851/EEC envisaged a 10 year-period for member states to enforce its disposals to these old drugs. Therefore, all the member states will have to review, before October 1st 1991, marketing approvals already granted, taking into account the technical requirements demanded by Directive 81/852/EEC. Member states who recently set up their veterinary pharmaceutical legislation have the obligation to grant a marketing approval to old veterinary drugs taking these requirements into account before that same date.

Nevertheless, even if there is a 10 year delay for such a revision to be performed, this revision represents a considerable workload for the veterinary pharmaceutical industry as for the regulatory authorities who have to implement the marketing approval procedure. For instance, in France 8 000 dossiers concerning old drugs were received. Their appraisal started in 1979 as soon as the French marketing procedure was decided. So, I hope we shall be able to meet the deadline of October 1991.

It is not sure that all member states, some of them having just started this work, are in such an easy situation. However, this work of revision of old veterinary drugs in the light of the disposals of the 1981 directives is of primary importance since only veterinary drugs having thus being approved will have the opportunity to get an access to the community market through the future decentralized procedure of mutual recognition of national marketing approvals.

However, this evaluation of old veterinary drugs dossiers will allow some flexibility in the implementation of technical requirements defined in Directive 81/852/EEC. Indeed, it is probably not indispensable to systematically ask for clinical trials to prove the efficacy of well-known veterinary drugs, which have for a long time been used in veterinary practice. Most of the time, available published data will, in that case, be able to provide an appropriate technical basis to support the claimed therapeutic indications.

Indeed, Directive 81/851/EEC, in Chapter 2 dealing with marketing approval, indicates that bibliographic references concerning toxicological, pharmacological and clinical trials, as well as indications on the withdrawal times may replace the presentation of experimental data for a veterinary drug which has already been used in animals for a time sufficiently long so that its effects, including the adverse ones, are known and documented.

In contrast, data are often less convincing to establish the appropriate dosages. Indeed, they are often derived from veterinary practice habits and may lack objective validations. Trade competition led to progressively lower dosages at the expense of therapeutic efficacy. This problem is all the more acute, given the great diversity of drugs, formulations, administration routes, and animal species treated. Here, then, is opened a large field of investigation of pharmacokinetic studies and especially plasma bioavailability.

In addition, it is often impossible to determine precise withdrawal times for old veterinary drugs, since the necessary data regarding residue kinetics in tissues, milk, eggs from treated animals are lacking. So, most of the time, conservative withdrawal times have been allocated. They are particularly long so as to be sure the consumer is protected. But such withdrawal times obviously penalize the pharmaceutical veterinary industry and producers of foods of animal origin. Here again, a large field is opened to pharmacokinetic studies in order to determine, on a more accurate scientific basis, withdrawal times necessary to protect public health.

Generic Veterinary Drugs

Directive 81/851/EEC did not retain the principle of generic veterinary drugs. However, in Chapter 2 which deals with marketing approvals, it states that bibliographic references concerning toxicological, pharmacological and clinical trials as well as withdrawal times may replace, if it is appropriate, experimental data for:

- a new veterinary drug the formulation of which is identical to that of a drug already known and used for a long time;
- a new veterinary drug containing only known active substances already associated in comparable proportion in drugs already used for which a good experience is available.

A proposal for a directive, presently discussed at the Council, aimed at modifying Directive 81/851/EEC, goes a little further in the recognition of generic drugs. Indeed, it envisages that the applicant will not have to provide the results of toxicological, pharmacological and clinical trials, if he is in a position to prove that:

- either the veterinary drug is essentially similar to a drug authorized in the concerned

country. In addition, the manufacturer of the original product must agree to the toxicological, pharmacological or clinical data given in the dossier of the original veterinary drug being used for the examination of this generic drug;

- or the veterinary drug is essentially similar to a product that has been approved, according to the enforced community disposals, for at least 10 years and is being marketed in the member state concerned by the application.

What is important in the disposals of this project of modification of Directive 81/851/EEC is the fact that the applicant has to demonstrate that the veterinary drug concerned is essentially similar to another drug. This requirement opens a large field of investigation to bioequivalence studies.

Extra Label Use

The enforcement of Directives 81/851/EEC and 81/852/EEC provisions leads the competent authorities to agree only upon therapeutic indications which are more and more precise and justified by controlled clinical trials. Because of the pressure due to the dossier costs, this evolution naturally entices applicants to reduce their claims in therapeutic indications. As a consequence, some therapeutic indications are no longer taken into consideration because the disease is either not frequent or concerns species regarded as minor ones.

A reflexion has already been developed at the Community level. It emphasizes the interest of the European single market in this field. Indeed, the above mentioned problems have had to be faced by each member state. Thanks to the change in scale of the veterinary drug market due to the establishment of the single market, a therapeutic indication, considered as minor within a national market, may become more attractive, from an economic viewpoint, in the wider context of the single market. As a consequence, a solution to this problem of extra label use lies in the effective enforcement of centralized or decentralized procedures in the foreseen framework of the future community system of veterinary drug marketing approval.

However, until the establishment of the single market, the project of modification of Directive 81/851/EEC, at present examined by the Council, contemplates that member states may exceptionally allow veterinarians to take the necessary

measures when dealing with a small number of animals, on a given farm, particularly if those measures are intended to spare them unacceptable sufferings, when no authorized therapy exists for this disease.

In such conditions, they may administer:

- a veterinary drug authorized in the member state concerned for another animal species or for animals of the same species but for a different disease. If such a drug doesn't exist, then
- a drug authorized, in the member state concerned, for human use. If it doesn't exist, then
- a veterinary drug compounded by an authorized person according to the national legislation and in agreement with a veterinarian's prescription.

If the veterinary drug concerned is to be administered to food producing animals, it must contain only substances already approved for food producing animals in the member state concerned. Moreover, the veterinarian responsible must impose a suitable withdrawal time so as to ensure that food derived from the treated animals are free from residues that could be detrimental to consumers.

If no withdrawal time is indicated on the label of the drug for the animal species concerned, the withdrawal time prescribed must be at least:

- 7 days for eggs,
- 7 days for milk,
- 28 days for meat, fat and offals of either birds or mammals,
- 500 degrees/days for fish.

The veterinarian has to record all relevant data, such as the date on which he examined animals, the identity of their owner, the number of animals treated, diagnosis, drugs prescribed, quantities administered, length of the treatment as well as the withdrawal time prescribed. These data have to be ready to be presented to the competent authorities, upon request, for at least three years.

The Community Requirements About Pharmacokinetics

Present Requirements About Pharmacokinetics

Directive 81/852/EEC, which harmonizes

the protocols of analytical, pharmacotoxicological and clinical trials, in its Chapter C about the study of pharmacological properties, deals with requirements regarding pharmacokinetic data. But, in fact the disposals confine themselves to general considerations. It defines the implementation area of pharmacokinetics studies and the methods that could be used.

New Definitions of Requirements Concerning Pharmacokinetics

The too general character of these directives makes a more precise text necessary. The Committee of Veterinary Medical Products requested two working groups to submit proposals on this topic in order to update this directive by early 1991. The working group on residue safety devoted itself to the requirements concerning residue kinetics in foods derived from treated animals. The working group on the safety of veterinary drugs has to take into consideration the importance and necessity of pharmacokinetic studies to determine dosage, regimen, administration routes.

This work, which is still going on, led to development of a three-fold objective to pharmacokinetic studies. The first one is the determination of basic parameters relevant to absorption, distribution, metabolism and elimination of the drug. The second objective consists in the comparison of the bioavailability of several formulations through bioequivalence studies. The third one more specifically concerns the evolution of drug residue concentrations in the edible tissues of treated animals so as to establish appropriate withdrawal times.

Before outlining the main proposals of this draft, I would like to point out that this work is being prepared for the CVMP's working group by Dr. Toutain, Professor in the National Veterinary School at Toulouse. Dr. Toutain obtained, in this work, contributions from different experts of international repute such as Dr. Koritz of the University of Illinois who is attending this meeting and I would like to thank him very much for his valuable help.

Moreover, pharmacokinetics studies are very useful for scientific reasons since they allow using veterinary drugs in the best conditions of efficacy and safety. Also, for ethical reasons, they allow reducing the number of animals to be used in the development of a veterinary drug.

Determination of Basic Pharmacokinetic Parameters

Pharmacokinetic studies may, as a whole, be divided into two distinct fields:

- descriptive studies leading to the determination of basic parameters such as body clearance, volume of distribution, withdrawal time;
- utilization of these parameters to examine the relationship between dosage, plasma concentration and pharmacological, therapeutic or toxicological effects.

Five main parameters have to be studied: bioavailability, absorption, distribution, metabolism and elimination.

- **Bioavailability**
The study of the bioavailability process of a drug is necessary when dissolution is the limiting stage. It is particularly important in the case of a slow-release drug.
- **Absorption**
It is important to determine the bioavailability of an active principle so far as a systemic effect is expected or when the quantity of drug to pass into the circulating blood is significant. The bioavailability is measured by comparing either an absolute reference which is intravascular, or a relative one, which is extravascular.
- **Distribution**
If necessary, given the therapeutic claims, the distribution of the drug in body liquids and tissues has to be studied. In the same manner, it may be useful to know both the level and the characteristics of the binding of drug to plasma protein.
- **Metabolism**
If a therapeutic or adverse effect is suspected to be due to the formation of a pharmacologically active metabolite, then the rate of formation, distribution and elimination of the metabolite has to be determined.
- **Elimination**
If necessary, given the therapeutic claims, the elimination routes, through urine, bile, milk, must be known.

The determination of basic pharmacokinetic parameters, of course, implies the codification of the procedures to be used. So, the draft guideline which

is being elaborated by the Committee of Veterinary Medicinal Products will provide the necessary data concerning:

- the number of animals,
- the method of administration of the drug,
- the specifications of the drugs,
- the dosage to be used,
- the sampling techniques,
- the pharmacological effects to be taken into account,
- the analytical methods,
- the experiment protocol,
- the kinetic interpretations.

Bioequivalence Studies

Bioequivalence studies allow comparing for one active principle, different formulations, drugs, or administration routes.

Two drugs are bioequivalent when under identical and appropriate experimental conditions, their bioavailabilities differ only within acceptable limits. Drug bioavailability is defined by the rate and extent to which the drug reaches the systemic circulation or its site of action.

The importance of the bioequivalence concept to solve the problems considered in this session is such that a specific guideline explaining the requirements regarding this issue is also being prepared at the level of the CVMP.

First, this guideline states:

- the definitions of bioavailability and bioequivalence,
- the contents of the bioequivalence concept,
- the usefulness of bioequivalence for veterinary drug development;
- the cases when bioequivalence studies are not necessary,
- the various types of bioequivalence either in vivo or in vitro.

Then, this guideline states the conditions for setting up such a study in vivo, which particularly concerns:

- the reference product,
- the reference administration route,
- the animals,
- the dosage,
- the sampling,
- the analytical method.

It also provides the same information when

two drugs have to be compared after repeated administrations in order to determine the steady-state level of their active ingredients. Finally, it gives information on the statistical analysis of the parameters to be used in bioequivalence studies.

Conclusions

Pharmacokinetics, a recently employed technique in the veterinary drug field, is being utilized to better know and use veterinary drug products.

The National Laboratory on Veterinary Drugs, in Fougères, tries to favor, as it can, this trend. A research unit has been created which is specifically devoted to this activity. Up to now, work undertaken is mainly focused on antibiotics.

On the other hand, an international symposium on this topic was organized in Fougères, last October. More than 200 people attended it, half of whom were from EEC member states. We also had the pleasure of welcoming an important delegation from USA. The main theoretical and practical aspects of pharmacokinetics, relating to

veterinary drug efficacy and safety were presented and discussed. EEC and USA regulatory authorities and experts from universities and pharmaceutical companies were given the opportunity to exchange their points of view on the necessary regulatory requirements. This meeting was interesting for all the participants, and particularly for CVMP which is, at present, defining the technical requirements in this field.

In closing, I would like to express my pleasure by seeing the increase of international cooperation, mainly between the US and the EEC, in this important area. I have already given some examples with the CVMP's guideline currently underway and the international meeting held in Fougères in late 1989. I can add the JECFA's meeting, held once a year, where kinetics of residues are dealt with, and the bilateral FDA-EEC meetings held now twice a year. All these meetings provide valuable opportunities to develop exchanges of experience and to promote quick progress towards the harmonized criteria needed to assess the quality of veterinary drugs.