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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr.
Room 1-23
Rockville, MD 20857

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RE: Docket No. 97N-0217

To whom it may concern:

I am submitting the following comments concerning the request for comments about the Animal Drug Availability Act, with specific reference to the questions asked in the Federal Register Notice, June 23, 1997.

These comments are based on my 15+ years of working as the regional coordinator of the USDA Minor Use Animal Drug Program in close coordination with FDA/CVM personnel and the minor animal industries. If there are any questions in relation to my comments I will be pleased to answer them. Thank you.

Sincerely yours;

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Extension Toxicology Specialist
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Standards for target animal safety (TAS) and human food safety (HFS).

The standards for TAS and for HFS should be no different for minor species, however the data requirements to fulfill these high standards may differ substantially, and should be reduced for the minor species **based on experience with the drug in one or more major species**. For example, if a drug is approved for use in one or more major species, there will be complete data packages on TAS and HFS in these species. If the pharmacokinetic profile of the drug in the minor species is not radically different (and this is an area in which the CVM reviewers can be helpful by utilizing their considerable expertise) then less data will be required to fulfill the TAS and HFS portions. Maximum flexibility should be built into this process to prevent the development of rigid data requirements for all cases. As an example, the Western Region Animal Drug Program is involved in performing studies to fulfill requirements for the approval of Naxcel™ for use in dairy goats, and generated most of the data to attain it's approval for use in sheep. Naxcel™ is approved in cattle, dogs, horses, and sheep, and thorough TAS studies were done in each of these species. There was no reason to do a full scale TAS study in dairy goats, which would have included the necropsy of animals for histopathology studies of organs and injection sites. Based on the flexibility currently inherent in the review process, the data requirements were reduced, but the standards were not. It is important to differentiate between the two.

With regard to HFS, again, the data requirements can be reduced when there are sound reasons to do so. And again, the standards have not been compromised when there are sound scientific reasons to reduce the data necessary to fulfill the standard.

My personal opinion is that the tissue tolerances or safe levels of drug in tissues would be the same for minor species as for major species, however it may be that the target organ may differ for setting the appropriate withdrawal time (WDT), and this can be determined by performing limited tissue residue studies.

Acceptance of Foreign Data

Foreign data must be accepted for the purpose of attaining approval in the US, however, a foreign approval should not guarantee a US approval since the data requirements may differ. If the data requirements are similar then there should be no problem with acceptance of the data in the US, unless there are some specific reasons (e.g. carcinogenicity) which would not allow it. Maximum flexibility must also be brought into consideration with this aspect to insure that rational decisions can be made on a case by case basis.

Expert Panels to determine TAS and efficacy

Most of the drugs for which minor use approvals are sought are already being used in the minor species, and some have been used for years. Panels could be a mechanism for reviewing published and proprietary data on safety and efficacy,

however it might be cumbersome and not worth the effort, with the exception of the U.S.P./DI, which already is doing this for extralabel uses. To be effective the determinations would have to be sanctioned by the CVM anyway, which means CVM review, although this could be avoided by including the CVM reviewers as members of the panels. Target animal safety studies with reduced data requirements can be performed quickly and inexpensively as long as the animals do not need to be slaughtered, and in most cases, they would not.

Manufacturing Standards

There should be no difference in the standards for manufacturing drugs for use in minor species. Some limited exceptions to the requirements for fulfilling the standards might be made on a case by case basis in exceptional circumstances (e.g. aquaculture drugs which are not used in any other species and which might only require dissolution).

Strategies for facilitating approvals

The question asked if a strategy similar to that used for aquaculture might be successful for other species. I would have to ask if that strategy has actually been successful? Are there any drugs for which extensive useful data have been collected under the "coordinated INAD" aquaculture program? Certainly coordination of effort is a must, and this might work especially well for those animals whose treatment needs are not covered by AMDUCA (aquaculture and game birds).

Programs for wildlife and zoo animals

Wildlife and zoo animals should be covered very well under AMDUCA since they are not considered food animals. Why develop a program to fulfill needs which do not threaten public health with residues? Most of the animals in these categories are too expensive for detailed data collection anyway. The NRSP-7 program could cover those cases for which there might be residue concerns. These are truly minor-minor uses.

Other Mechanisms

I would like to propose consideration of a phased or "conditional" approval approach to the approval of drugs in minor species. The idea would be to fill the most important data requirements first, then fill in the others based on actual use of the drug under field conditions. Firstly, the data requirements for drug approvals are appropriate; efficacy, target animal safety, human food safety and environmental safety.

Environmental: Minor uses of drugs approved in major species should not be an environmental concern unless their use pattern is very different from that in major species. CVM has been very realistic in this approach in providing categorical exclusions for most minor uses in terrestrial animals. An environmental assessment

must be done for any new chemical entities for which CVM has not already reviewed an environmental assessment.

Efficacy: In most cases proof of the efficacy of minor use drugs should not be a sticking point and collection of supportive data could take place for several years following conditional approval. During this time, the drug would be in use, and veterinarians would be gathering clinical data about efficacy, not necessarily in controlled studies, but through clinical impressions which would be reported in the literature along with controlled clinical trials. After several years it would be quite apparent if the drug is working or not and this requirement would be slowly satisfied over time.

Safety: The same is true for the TAS. However, in this case, limited studies should be performed prior to conditional approval to be sure that serious adverse effects are not seen at 5X doses (or less depending on the major species safety data). Through the collection of adverse reaction reports, the CVM would gather information which would support or question the safety of the drug and establish the conditions under which adverse effects have occurred.

Human Food Safety: This is by far the most important element of the process, and the one for which there must be some data before the drug could be conditionally approved. Pharmacokinetic studies and limited tissue residue depletion studies should be performed to help establish a "conditional WDT" which would be sufficient to protect the public health when the drug is used. The NRSP-7 program is the ideal program to perform these studies which would be done under GLPs to insure that the data could be used later to obtain full approval.

In essence, this approach would fall somewhere between extralabel use (AMDUCA) and a full approval, and would fully protect the public health, minimize animal suffering, and ultimately lead to full approval of many drugs which would otherwise continue to be used under AMDUCA anyway. Virtually everyone benefits in this process. In many ways this is similar to the aquaculture situation, however this approach is more loosely organized and thus less burdensome to the producer and veterinarian, and assumes that researchers will publish their findings (which is a fairly sure bet).

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