



AMERICAN VETERINARY MEDICAL ASSOCIATION

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

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Dear Sir or Madam:

We are pleased to offer comments on the development of options to encourage animal drug approvals for minor species and minor uses (Docket No. 97N-0217). The American Veterinary Medical Association is the national organization of veterinarians, and the voice of nearly 60,000 members. The AVMA will also submit comments to address the need for approved drugs in aquaculture under separate cover.

It is well established that there is currently little or no economic incentive for sponsors to develop the data necessary for the approval of drugs for minor species or minor uses. Consequently, few drugs are approved for such uses. In this situation one of a couple things may happen. Veterinarians may use drugs in an extralabel manner under AMDUCA, but lack of food safety data may remove this option from the veterinarian who is caring for a food animal species. In addition, AMDUCA limits extralabel use to dosage form drugs (not medicated feed) and cases of animal suffering (not production use of drugs). Secondly, it may be that no drug exists to treat a condition. If diseases in minor species are left untreated, there may be severe injury or death to the animal as well as potential public health hazards to man.

The difficulties encountered with such drug approvals are as diverse as the species to be treated. The following three examples illustrate some of the hardships.

- 1) The wildlife and exotic industries, which include species which live in an unconfined free-range environment and those which live in zoos and private collections, respectively, are faced with unique challenges to drug approvals. The range of involved species is enormous. Approving labels on a species by species basis will never cover all species. Approvals for family group designations should be considered by the FDA. Additionally, the availability of animals to serve as safety and efficacy test animals may be limited (i.e. panthers), necessitating the use of appropriate extrapolation between species.
- 2) An obstruction to drug approvals for sheep is the regulation that states sheep are considered a major species for determinations of food safety, despite low per capita consumption. In its

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September 1996 Draft Minor Use Guidance Document the FDA-CVM wrote "According to current regulations, sheep are minor species except in the area of human food safety where they are considered major species. This regulation has been reconsidered and will be rewritten in the near future. In the interim, CVM is considering both sheep and veal calves to be minor species for all areas of the drug approval process." We urge the FDA to incorporate this promise into regulation and announce the change to sponsors. There are an unremarkable number of drugs approved for use in sheep. Recognition of the reclassification of sheep as minor species for food safety purposes will encourage approvals. Such drug approvals will enable adequate treatment and prevention of disease and enhance the competitiveness and profitability of the U.S. sheep industry, without compromising public health.

3) Currently there are no FDA approved drugs available for embryo transfer indications. One reason is that small entrepreneurial companies who wish to enter the animal drug market have problems gaining drug approvals. Embryo transfer includes a process whereby premium cattle are induced to superovulate. Normally a cow would produce one calf in 9 ½ months. Superovulation induces a cow to produce large numbers of eggs which are fertilized, flushed, and implanted into grade cows. The process allows for a number of genetically high quality calves to be produced that year, rather than just one calf by the natural mother. Embryo transfer is dependent on a drug containing follicle stimulating hormone (FSH) to induce superovulation. This indication is an example of a minor use in a major species. The drug is not currently available and because this drug is so necessary, the FDA has lifted an import alert to allow veterinarians to access foreign approved FSH. This action was preceded by the withdrawal from the market of a drug judged by veterinarians to be clinically ineffective. Years ago veterinarians lost what they considered a good drug due to the enforcement of good manufacturing practices and the nature of the approval process. Implementation of performance standards which emphasize the quality and purity of the final product rather than the command and control approach to good manufacturing practices would encourage small entrepreneurial companies to seek minor species drug approvals.

The examples illustrate the complexity of minor species and minor use drug approvals. Numerous other minor species exist (rabbits, llamas, alpacas, game birds, goats, ferrets, ducks, mink, ostrich and many fish, wildlife and exotic species to mention only a few), each with their own circumstances.

A series of questions pertaining to minor species/minor use approvals were asked by FDA in the Federal Register. The AVMA responses to the questions are as follows:

Creating Additional Statutory Authority

1. Should there be different standards for target animal safety and effectiveness of new animal drugs intended for use in minor species or for minor uses?

Yes, there should be different standards for target animal safety and effectiveness of new drugs intended for minor species and minor uses. Interpretation of the efficacy requirements, in particular, should be approached in a minimalist sense to curb costs and provide incentive. For some minor species, animals may not be very available for testing (i.e. zoo animals) and may

require appropriate extrapolation of data. Approval of drugs for animal family groups rather than species may be of great benefit to the numerous wild and exotic species.

2. Should there be different standards for human food safety for new animal drugs intended for minor species and for minor uses?

The AVMA asks the FDA to consider the scientific reasoning by which it arrived at the conclusion that sheep are minor species for food safety purposes, and apply that logic to other minor species. Additionally, FDA should recognize non-food stages of animal life cycles.

3. If so, what should those standards be?

This requires future dialogue between interested parties.

4. Should the standards be the same for all minor species or uses?

Probably not.

5. Why?

Given the diversity of the species and uses, it is not likely that a universal standard could be applied.

6. Should products be labeled to reflect the use of different standards?

If practical, products should be labeled in the package insert to inform the end user that the approval was made under minor species/uses standards.

7. If not, why not?

8. If the Act were amended to permit FDA to approve new animal drugs for a minor species or minor use under different standards, how would appropriate doses be determined and how would residue depletion and withdrawal times for food animals be determined?

To borrow from the concepts of the Professional Flexible Labeling initiative, the upper dose limit should be based on target animal toxicity and food safety data. The lower dose should represent the effective dose of one indication. Residue depletion should be set at the toxic dose level. Such action might preclude approval of those few drugs with a long half-life, but long withdrawal intervals generally create few problems in the field. "Long" is a relative event determined by production cycles and application. Unless therapy is needed all the way to slaughter, use of such withdrawal intervals should be possible.

- 9. Would sponsors and users accept conditional approvals and postmarket surveillance as a tradeoff for requiring less in the way of premarket target animal safety and effectiveness studies for new animal drugs for minor species or minor uses?**

Yes, users would accept conditional approvals. Conditional approvals and postmarket surveillance in conjunction with standards for approval of minor species/use drugs could greatly increase drug availability. For such a system of conditional approvals to work, however, it must not become too costly or complex.

- 10. Should a drug approved under such a mechanism bear labeling that reflects its conditional status?**

Yes, labels should reflect conditional status to be sure the end user understands the conditions of approval and cooperates in postmarketing surveillance.

- 11. Should the Act be amended to allow FDA to accept foreign reviews or approvals of new animal drugs for minor species or for minor uses?**

Yes, FDA should be allowed to use foreign drug approval data, providing the data is generated under requirements similar to those in the U.S and validated by a credible agency of that country.

- 12. How should Congress or FDA determine whether the reviews or approvals of a particular country or countries are acceptable as a basis for approval of uses for minor species or for minor uses?**

Trends in improved harmonization between countries should enable the U.S. to assess which countries have comparable approval standards. Furthermore, if the U.S. currently accepts importation of food products derived from foreign animals which were treated with foreign approved drugs, it seems reasonable that the foreign approval data would be adequate to gain FDA approval of the drug.

- 13. Should the current statutory standard for new animal drug approval for drugs intended for minor species or minor uses or any alternative standard be implemented through a primary review process external to the agency?**

It would be advantageous for the Agency to be able to utilize sanctioned third party reviewers of new animal drug applications. We recognize that oversight and qualification of these reviewers has resource implications for FDA-CVM.

14. If so, how might this process be administered?

FDA could recognize reviewer panels. Such panels might be composed of individuals from species oriented veterinary associations and the United States Pharmacopeia-Veterinary Advisory Panel, who could serve as well informed reviewers. One person in the Agency could oversee the administration of the third party review process.

15. Who should pay for the external reviews?

To reduce the perception of bias, the third party reviews could be paid through an intermediary such as a University out of funds generated by drug sponsors, professional veterinary associations, humane organizations, species/breed organizations, and producer groups.

16. Could determinations of animal safety and effectiveness by expert panels or compendia be used to support drug approvals for minor species and minor uses?

Animal safety and effectiveness, determined by a expert panel or compendia, could be used to support such drug approvals.

17. If so, what information would serve as the basis for such determinations?

Scientifically derived safety and efficacy data (generated by FARAD, for example), as well as experience gained from extralabel use, would serve as the basis of a panel's conclusions.

18. Should the determinations of these panels or other information be used to issue monographs or similar standards?

This information should be incorporated into monographs, but the creation of monographs should not become an additional requirement in the minor species/minor use approval process.

19. Who would draft monographs or similar standards and why?

The United States Pharmacopeia is a recognized, credible source of monographs.

Administrative and Regulatory Changes

20. Should there be different standards for manufacturing of drugs for minor species or minor uses?

The manufacturing standards should allow the sponsor flexibility in the way it produces a quality drug. Performance standards which emphasize the quality and purity of the final product and allow sponsors to validate their own good manufacturing practice would be advantageous. Performance standards would be better than command and control techniques which impose requirements in every segment of the manufacturing process.

21. If so, what should those standards be?

These standards should be produced after dialogue amongst interested parties. Manufacturing standards dialogue is occurring through the mechanism of the FDA's Veterinary Medicine Advisory Committee. The unique minor species/uses perspective should be incorporated.

22. Should products be labeled to reflect the use of different manufacturing standards?

If the product can be deemed safe and effective through compliance with a performance standard, no further labeling differentiation should be required.

23. Would a strategy similar to that used by the agency to facilitate drug approvals for some aquatic species be successful if extended to other minor species?

A similar strategy might prove of some use. The aquatic species coordinator has been in place for only two years and it is too early to judge whether the program will have successes. The fact remains that there have been no approvals of aquatic species drugs in the past several years. Many drugs which are already in use under the extralabel regulations are in the midst of the approval process.

24. That strategy includes coordination of investigational new animal drug (INAD) information collected or generated by end users. It also includes a centrally-organized and CVM-operated field education program directed at end users as potential INAD sponsors. In which species/uses would such an approach work or not work?

The North American Game Bird Association might be a potential candidate.

25. Why?

This approach would require a strong industry association or coalition.

Creating Incentives

26. Would economic incentives, such as tax breaks, grants, and periods of market or label exclusivity, encourage the pursuit of approvals or supplemental approvals for labeling modifications for minor species or minor uses?

Yes, economic incentives would be very helpful in encouraging sponsors to pursue approvals or supplemental approvals.

27. If so, what kinds of incentives would be most effective?

Tax breaks and grants might be most helpful to the sponsor pursuing a minor species drug approval. Manufacturers of "major species drugs" would be encouraged to seek supplemental approvals, to add minor species and minor use indications to the labels of existing products, if doing so resulted in an extension of the period of marketing exclusivity granted for the use of the drug in the major species.

28. Would different kinds of incentives be appropriate for different classes of new animal drugs, such as drugs for hobbyist-owned tropical fish as contrasted with production drugs for fish intended for human consumption?

Greater economic incentives may be required as the projected market for the drug decreases. On the other hand, some hobbyist groups may contribute substantial amounts of money based on their fondness for their hobby.

29. What incentives would encourage sponsors to pursue approval of a drug for a minor species or for a minor use using data in public master files (PMF'S)?

No response.

30. Are there concerns about data in PMF's that make new animal drug sponsors reluctant to rely on such data?

No response.

31. What are those concerns?

No response.

32. How could they be addressed?

No response.

33. If producer groups or other organizations were willing to conduct or otherwise fund studies to demonstrate safety and efficacy for new animal drug approvals for minor species or minor uses, would sponsors be willing to use the data from the studies to support approvals and new or revised labeling?

No response.

34. If not, why not?

No response.

35. Should a program similar to the U.S. Department of Agriculture/s National Research Support Program #7 (NRSP-7), which currently funds studies for minor use therapeutic uses for food- and fiber-producing animals, be developed for wildlife and zoo animals and/or for production uses?

While any headway made by the NRSP-7 program is appreciated, historically its success has been limited. The AVMA supports the inclusion of wildlife, zoo and production uses in the program in concept, but fears progress toward approvals would not be measurable.

36. Should the NRSP-7 program be expanded to cover such uses?

The program should be expanded only if it can meaningfully contribute to increased drug approvals.

37. Could and should philanthropic, public interest, or other not-for-profit organizations be encouraged to fund research for the development of new animal drugs intended for use in minor species or for minor uses?

Research funded by such groups would be welcomed. A program of such contributions would be most effective if economic incentives concurrently encouraged sponsors to approve the drug. Most progress would be made if a sponsor considered the development of the drug a priority.

38. If so, how, and by whom?

Professional veterinary associations, humane organizations, species/breed organizations, and producer groups might all be interested in helping. Donations in the form of money or expertise could be arranged.

39. Are there mechanisms other than the new animal drug approval process and extralabel uses of animal and human drugs under the AMDUCA that could enhance drug availability for minor species and for minor uses?

Under the Professional Flexible labeling concept, a sponsor could include data regarding minor species and/or minor use on the drug label, providing the sponsor makes meaningful and timely progress toward completing a supplemental NADA.

We support the efforts of the Minor Species Animal Health Coalition to make medicated feeds available to minor species. The concept uses the Veterinary Feed Directive in concert with FDA issued compliance guides to permit certain uses in minor species.

Extending Existing Legal Authority

40. Would legislation be desirable to extend the AMDUCA to permit extralabel use of: (1) Medicated feeds or (2) reproductive hormones and implants?

Since treatment via the feed is often the most effective route of treatment for certain minor species (game birds, fish, lambs in feed yards, etc.), it would be highly beneficial to permit the extralabel use of medicated feeds in minor species.

The verbiage of AMDUCA prevents the extralabel use of reproductive hormones and implants, since the animal's health is not suffering. It is highly important that extralabel use of these drugs be permitted, since several industries rely upon such use.

41. What are the pros and cons of approval versus extralabel use under the AMDUCA?

Approval provides an assessment of efficacy and safety, determined in laboratory settings and possibly the field. Approval requires that a sponsor adhere to certain manufacturing standards. The approval process is costly and time consuming.

Extralabel use increases the veterinarian's options when an approved drug does not exist or is judged clinically ineffective. Extralabel use requires a veterinarian to make professional judgements regarding the use of a drug based on training, experience, research and label information. The practitioner is held liable for situations resulting from extralabel use.

Extralabel drug use by a veterinarian is a necessary tool in practice, but drug approval is still the ideal.

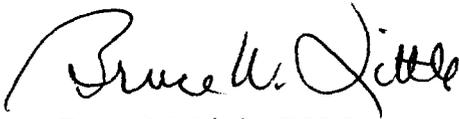
In summary, the AVMA believes the following approaches would most effectively increase drug approvals for minor species and minor uses:

- ◆ Different criteria for target animal safety and efficacy (with strong consideration of cost vs. value when evaluating test requirements)
- ◆ Conditional approvals
- ◆ Acceptance of documented foreign approval data
- ◆ Third-party review of approvals
- ◆ Approvals for broader family groups of animals, rather than species
- ◆ Manufacturing standards which allow flexibility in the production of a quality drug

- ◆ Tax incentives, grants, and marketing exclusivity
- ◆ Professional Flexible Labeling
- ◆ Minor Species Animal Health Coalition efforts
- ◆ Provision for extralabel use of medicated feeds and reproductive hormones

The AVMA is grateful for the opportunity to comment on this important issue. We look forward to the prompt implementation of sound ideas.

Respectfully,

A handwritten signature in black ink that reads "Bruce W. Little". The signature is written in a cursive style with a large, sweeping initial "B".

Bruce W. Little, DVM
Executive Director

BWL/ECG



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