DISCUSSION DRAFT

PROPOSALS TO INCREASE THE AVAILABILITY OF APPROVED ANIMAL DRUGS FOR MINOR SPECIES AND MINOR USES

ADAA Minor Use/Minor Species Working Group
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SUMMARY

The Animal Drug Availability Act of 1996 (ADAA) required the Food and Drug Administration (FDA) to develop proposals which would facilitate approvals for minor use[1] animal drugs. Pursuant to that request, the Agency is requesting comment on this discussion draft of proposals to increase the availability of approved animal drugs for minor species and minor uses.

I. INTRODUCTION

The ADAA (Pub. L. 104-205) recognizes that a severe problem exists due to the shortage of approved new animal drugs for use in minor species and for minor uses in major species. As requested by Congress in section 2(f) of the ADAA, this document makes a number of proposals that may contribute to resolving the problem. Some of these proposals are more significant than others and will require Congressional action for implementation. When assessing the various options proposed, it is important to remember that the minor use community includes very diverse constituencies. A proposal that will provide assistance to a subset of this community may offer no advantage whatsoever to another part. For this reason, no single proposal is likely to have a significant effect on the problem as a whole. Neither is it likely that any single proposal affecting a given constituent group will have a profound benefit for that group.

[1] In this document, the term “minor use” will be used to cover both the case of minor use in a major species and any use in a minor species.

A. A SINGLE APPROVAL MODEL FOR HUMANS AND ANIMALS

Originally, there was only one drug approval process permitted by the Federal Food, Drug, and Cosmetic Act (FD&C Act), a process that was designed for the approval of drugs for humans[2]. When the major portions of the FD&C Act were enacted in 1906, 1938 and 1962, no legal distinction was made between drugs for people and drugs for animals. It was not until 1968 that the phrase "animal drug" (as part of the phrase “new animal drug”) was used in the statute.

However, even in 1968, when the need for a separate animal drug approval process was recognized and the statute amended in response, the human drug model was followed in almost every detail. With respect to target species safety, effectiveness, manufacturing, and labeling requirements, the same application review process was established and the same scientific standard of review was required for the approval of animal drugs that had traditionally been applied to human drugs. This drug approval model has worked well for what the FDA has defined as the major animal species: dogs, cats, horses, cattle, pigs, chickens, and turkeys. However, it has not worked for the other animal species, the so-called "minor" species which include everything from abalone to zebras. For example, in Fiscal Year 1997 there were nearly 80 drugs approved for the seven major species, and only 1 for all minor species. The apparent reason for the failure is that the market for minor uses of animal drugs is not large enough for sponsors to earn back the costs of developing drugs for such uses and of obtaining FDA approval, that is, for the same reason that there are human “orphan drugs”.

There are absolutely no drugs approved for the overwhelming majority of those minor species which require the support of humans to maintain their health and well-being or ensure their survival as a species. Furthermore, under the current animal drug approval requirements it is unlikely that this situation will change. However, FDA believes that humans have a responsibility to care for other species of animals. Humans thus have a responsibility to try to prevent the suffering and death that results from the shortage of approved drugs for the care of such animals.

The following examples illustrate the problem. A disease outbreak in a salmon-farming operation can result in greater than 50% mortality (millions of fish) in a matter of days because no approved medications are available for treatment. The only product approved to treat gapeworm infections in gamebirds is no longer manufactured. This leaves these birds susceptible to suffocation from these parasites which block their windpipes. Rare and valuable zoo animals may suffer or die because so few products are available to treat them when they become ill.

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[2] When that process proved to be too burdensome for human products with potentially small markets, such as for rare diseases, the Orphan Drug Act (1983) was passed to address this shortcoming.

In addition to the humanitarian argument on behalf of minor species, there are more pragmatic reasons for increasing the availability of drugs to control disease in these species. Organisms capable of causing disease in minor species are not confined to such species. Thus, minor species are reservoirs and vectors for many diseases affecting humans and major species. It is clearly in the public interest to treat such diseases in minor species before they are transmitted to people or other animals. Furthermore, overuse of the few drugs available for minor species can lead to the development of resistance to those drugs. Finally, the lack of authoritative information regarding appropriate doses and withdrawal times for minor food-producing species can lead to unsafe drug residues in the human food supply.

Another reason for concern occurs because commercially valuable minor species-derived food, fiber, or other types of products may not be able to compete with imported products. Foods derived from production aquaculture are a good example (e.g., salmon net-pen farming). Aquaculture is a relatively young industry in the U.S. In contrast, production aquaculture is more advanced for some of our trading partners, and the U.S. currently relies heavily on imports to meet consumer demand for some aquaculture products (e.g., marine shrimp). Different health and safety standards in the use of animal drugs in foreign countries place U.S. aquaculture interests at a competitive disadvantage.

B. EXTRALABEL USE IS NOT THE ANSWER

In 1994, the Animal Medicinal Drug Use Clarification Act (AMDUCA) (Pub. L. 103-396) amended the FD&C Act to permit veterinarians to use approved human and animal drugs in an extralabel manner under some constraints. For a number of reasons, FDA is concerned that AMDUCA will not solve the problem.

First, for AMDUCA to apply, a veterinarian must be treating the animal. However, many minor species do not have access to the care of veterinarians. Second, many minor species require the use of animal drugs in their feed, but the extralabel use of medicated feed is prohibited under AMDUCA. Third, a number of minor species require the use of drugs which are not approved for any animal, such as bulk chemicals (copper sulfate), disinfectants (chloramine-T), and new entities (Carp Pituitary Extract), and are, therefore, unavailable for extralabel use under AMDUCA. Even when AMDUCA applies, it may not improve the situation. For example, many indications require drugs in formulations which are not approved for use in other species. This leads to the need to alter formulations, with potentially adverse effects on safety and effectiveness. In addition, the veterinarian assumes the liability associated with the decision to use drugs in an extralabel manner.

C. LIMITED FLEXIBILITY IN THE CURRENT SYSTEM

The Agency's past efforts to facilitate approvals for minor species (described in detail in section III) underscore the need for a major change in the current system. The FDA has consistently exercised its authority in interpreting the FD&C Act with the maximum flexibility with respect to the approval of drugs for minor uses. FDA has fostered the extrapolation of data between major and minor species. It has devoted significant resources to working closely with potential sponsors of drugs for minor species, including non-traditional sponsors (e.g., animal producer groups; Federal, state or local government organizations; and academic institutions). It has modified the traditional Investigational New Animal Drug (INAD) process to coordinate the collection of data to support drug approval with the compassionate use of investigational drugs needed to save the lives of minor species. There have been some successes, but the successes are largely associated with those minor species that have significant commercial value, usually as sources of food. Most often, some parts of successful minor species approvals have been supported by public funding.

D. THE NEED FOR SIGNIFICANT CHANGE

Some of the proposals in this document have been used in other contexts, (e.g., orphan drugs for humans), and they should also prove useful with respect to minor species. However, others have either not been used before or have not been used to the extent proposed here. The most far-reaching of the proposals are also the ones with the greatest potential to provide relief. FDA recognizes that proposals that alter the approval process are not without risk and do not necessarily represent, as a matter of science, the “best way” to approve animal drugs. The best way to approve animal drugs, from a scientific standpoint, remains something very close to the current system. However, with respect to drugs for minor uses, almost thirty years of experience has proven that applying this scientifically best standard and process for minor use drugs results in virtually none being approved.

FDA recognizes Congress’ concerns regarding the availability of approved drugs for minor species, and welcomes its invitation to suggest solutions. The Agency encourages debate on all aspects of the following proposals as it seeks to clarify and resolve this important matter of public policy. Finally, the Agency respectfully requests that concerns about major change not be allowed to prevent serious consideration of the more far-reaching solutions proposed in this document.

II. BACKGROUND

A. ADAA MANDATE

The Animal Drug Availability Act modifies several existing sections of the FD&C Act. When the bills that eventually became the ADAA were originally introduced in Congress, statutory changes to the FD&C Act were proposed in an attempt to streamline the process by which minor species and minor use drugs were approved. Instead, the ADAA, as enacted into law, requires that, "The Secretary of Health and Human Services shall consider legislative and regulatory options for facilitating the approval, under section 512 of the Federal Food, Drug, and Cosmetic Act, of animal drugs intended for minor species and for minor uses and, within 18 months after date of enactment of this Act, announce proposals for legislative or regulatory change to the approval process under such sections for animal drugs intended for use in minor species or for minor uses."

B. AGENCY RESPONSE

In order to respond to the ADAA mandate, FDA's Center for Veterinary Medicine (CVM) established a working group of Center experts on drug approval and minor species issues to explore possible solutions to the problem and draft a report outlining them. The working group's charge was as follows.

> "To prepare, on behalf of the Agency, a proposal outlining options to facilitate the approval of new animal drugs for minor species and minor uses, which will be published, or the availability of which will be announced, in the FEDERAL REGISTER. These options include suggested changes to CVM policies relating to New Animal Drug approval, suggested changes to regulations, and suggestions for legislative changes."

To assist the group in drafting this document, comments were solicited from the public through a FEDERAL REGISTER announcement, "Request for Comments on Development of Options to Encourage Animal Drug Approvals for Minor Species and Minor Uses" (62 FR 3378, June 23, 1997). Over 35 groups or individuals submitted comments in response. Among those commenting were minor species producer groups, exotic animal breeders (guinea pigs, ornamental fish), pharmaceutical companies, veterinarians, zoological organizations, the American Veterinary Medical Association (AVMA), pet shop owners, university faculty, and members of other regulatory agencies. The comments were extensive, indicating a high level of concern for this issue. These comments were all reviewed and many have been incorporated into the Proposals (Section IV) of this document. Copies of the comments (which are on file in Docket No. 97N-0217) may be viewed in FDA's Dockets Management Branch, 12420 Parklawn Dr., Room 1-23, Rockville, MD between 9 a.m. and 4 p.m., Monday through Friday.

III. OPTIONS AVAILABLE UNDER EXISTING LAWS ARE INADEQUATE

The Agency has long recognized the lack of available products for minor uses and the reluctance of pharmaceutical sponsors to pursue such approvals. In response, FDA has exercised maximum flexibility to address these needs. However, even the most flexible application of standards and policies has been insufficient to significantly affect the availability of approved products for minor use and minor species. To have a significant impact on product availability for minor uses, additional steps are necessary.

This section documents the efforts FDA has made to facilitate the development of minor use approvals. It should be reiterated that, in spite of FDA's efforts to facilitate approvals for minor uses, there have been very few such approvals attained. The efforts noted in this section not only represent the maximum flexibility possible under the current laws and regulations, but also represent the maximum possible use of existing resources.

A. EXTRAPOLATION FROM MAJOR TO MINOR SPECIES

In 1983, regulations were published (21 CFR 514.1(d)) to allow the use of animal models and extrapolation of data from a major species to a minor species to satisfy the safety and effectiveness, human food safety, and environmental requirements of the FD&C Act where scientifically justifiable. This provides relief from the need to perform many costly effectiveness and human food safety studies. The reduction in the number of required studies, and the cost of those that are required, has made third-party funding of studies more practical, but has not been a potent incentive to pharmaceutical companies directly.

B. SUPPLEMENTAL APPLICATIONS

It has been suggested that Section 403, regarding supplemental applications, in the Food and Drug Modernization Act of 1997 (the Modernization Act) would "push FDA to consider whether an improved supplemental policy will be responsive to the requirement in the ADAA that FDA consider regulatory options to facilitate approvals for uses in minor species and for minor uses."(Covington and Burling memo, dated November 12, 1997). Section 403 requires FDA to take a number of steps to facilitate approval of supplemental applications for approved products. It is FDA's opinion that the change in policy required by Section 403 will not significantly facilitate approvals for minor use drugs.

The majority of minor use drugs have been approved as supplements to products approved for use in major species. FDA already takes a number of steps to encourage sponsors to submit supplements for minor use. FDA's liaison to the National Research Support Project #7 (NRSP-7) encourages the development of Public Master Files to make available public data that can be used in conjunction with data already available in a major use product's original New Animal Drug Application (NADA).

The Agency recently published a notice of availability of a draft guidance document, "FDA Approval of Animal Drugs for Minor Uses and for Minor Species," (62 FR 50952, Sept. 29, 1997), which meets some of the requirements of Section 403. The Agency, through the individual serving as the NRSP-7 liaison and other means, already, as described in Sec. 403 (c)(2) of the Modernization Act, "work[s] with sponsors to facilitate the development and submission of data to support supplemental applications" (Pub. L. 105-115).

The obstacles to submission of supplemental applications include:

- sponsors' concern that original approval packages will be subject to critical review (see Part IV. B. in this document for proposals to remove this disincentive),
- the lack of financial incentive to sponsors to add minor use claims to their labels, and
- the dearth of already published or unpublished studies that could be used to support supplemental applications.

C. MANUFACTURING

CVM reviews the chemistry, manufacturing, and control (CMC) information of animal drugs for minor uses and for minor species on a case-by-case basis and typically allows for more flexibility in the type and extent of CMC information submitted in support of a minor use application.

Animal drugs for minor uses must be manufactured according to appropriate current Good Manufacturing Practices (CGMPs), as specified under 21 CFR 211, 225 and 226. CVM determines the extent to which an animal drug for minor use meets appropriate CGMPs on a case-by-case basis, and typically is flexible in its interpretation of the CGMPs.

D. CONSIDERATION OF NON-FOOD LIFE STAGES

The Agency recognizes that many food-producing animals in their early life stages are not normally used for human food. Therefore, FDA has determined that specific drugs and drug claims may be considered to be of low risk for human food safety if the drug is proposed for use in the early life stages of an aquatic species, and

- there is no significant risk that harmful residues will be present in the market-size animal as a result of treatment at the early life stage, and
- the Agency has no concerns about the use of the drug at later life stages (e.g., a tolerance and analytical method are available or there is no practical use for the drug in later life stages).

If these criteria are met, FDA normally will consider the human food safety data requirements of the Act to be satisfied and the sponsor will not be required to generate additional human food safety data.

E. INTERNATIONAL HARMONIZATION

For some time, the Agency has been involved in discussions with foreign regulatory agencies (primarily from the United Kingdom and Canada) that have resulted in exchanges of information and data concerning specific new animal drug applications. In nearly all instances, the sharing has not been formalized outside of case-specific circumstances, nor has it involved items other than data and information. Such exchanges have been beneficial, but have been limited in scope. Expansion of these efforts could have a significant effect on minor use drug approval.

F. THE NATIONAL RESEARCH SUPPORT PROJECT #7 (NRSP-7)

The USDA's National Research Support Project No. 7 (NRSP-7) Minor Use Animal Drug Program was designed to address the shortage of minor use animal drugs by funding and overseeing the effectiveness, animal safety, human food safety, and environmental studies required for drug approval. The program includes animals of agricultural importance and generally excludes animals such as companion, wildlife, and zoo animals.

The program submits data from successful research projects to CVM for inclusion in a Public Master File (PMF). Once the data are considered acceptable, CVM publishes a notice of the availability of the data in the FEDERAL REGISTER. A sponsor may then refer to those data to support an NADA for the minor use at no cost.

Since the program's inception in 1982, it has received over 280 Animal Drug Requests. Of these, approximately 70 have been accepted as research projects. The program has completed 25 PMFs. To date, sponsors have relied on 19 of these to support successful supplemental NADAs. At any given time, NRSP-7 has approximately 30 funded projects with active on-going studies. This program has been the major source of approvals for drugs for minor species, but because it is essentially limited to food- and fiber-producing animals, it has had a limited impact on the need as a whole. The Agency dedicates one full-time liaison to the program and provides funds to help support biennial workshops.

G. MINOR USE GUIDANCE

CVM has made available a draft of a newly revised guidance for sponsors applying for FDA approval of drugs for minor uses entitled, "FDA Approval of Animal Drugs for Minor Uses and for Minor Species" (62 FR 50952, September 29, 1997).

The original guidance document was made available in 1986 (51 FR 19612, May 30, 1986) and is entitled: "Guideline for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs." When finalized, the new document will provide sponsors with guidance for the development of data to support the approval of NADAs for drugs for minor use by describing the policies in place, prior to ADAA, to facilitate these approvals.

This latter document provides valuable guidance to groups who may be inexperienced with the NADA process and is intended to assist them in securing the necessary data in the most efficient way possible. Copies of this document may be obtained from the CVM Home Page (*http://www.cvm.fda.gov*) on the Internet or from the Communications and Education Team (HFV-12), CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

IV. PROPOSALS TO INCREASE THE NUMBER OF APPROVED ANIMAL DRUGS FOR MINOR USE

The following sections present a variety of proposals, made in response to section 2(f) of the ADAA, which could increase the number of approved drugs for minor use. Each proposal is described and notes the legal and regulatory changes that would be needed to implement it.

The proposals are identified as follows:

A. Modification of Extralabel Provisions

B. Removal of Disincentives

C. Enhancement of Existing Programs for Data Development

D. Incentives to Pursue Minor Use Drug Approvals

E. Data Sharing by Major Species NADA Holders

F. Creation by Statute of a "Minor Use Animal Drug" Program

G. Conditional Drug Approval for Minor Uses Involving Non-Food Animals

H. Alternate Approval Standard/Expert Review Panel for Minor Uses Involving Non-Food Animals

I. International Harmonization

A. MODIFICATION OF EXTRALABEL PROVISIONS

AMDUCA and its resulting regulations specifically prohibit the extralabel use of medicated animal feeds. This provision had the unintended consequence of effectively excluding two minor species industries from access to legal extralabel use. The aquaculture and the gamebird industries use husbandry practices that make medicated feed the only practical method for treatment of many diseases in their animals. Other minor species may require extralabel medicated feeds in some circumstances on a more limited basis.

Some relief could be provided by means of a modification to this provision to allow extralabel use of approved medicated feeds for minor species. This would allow medicated feeds to be considered as a dosage form product, similar to products such as injectable medications or orally administered tablets. A majority of the comments received by the Agency that expressed an opinion on this issue, indicated a desire for modification of this prohibition.

There have been some concerns expressed that the extension of extralabel use of medicated feeds might result in the increased development of antibiotic resistance and environmental contamination.

For the gamebirds, these are not significant issues. The addition of pheasants, partridges, and quail to the population of chickens and turkeys already using these products is a trivial one. The human health concern centers around the exposure of people to pathogenic antibiotic-resistant bacteria. The majority of the products needed by the gamebird industry are not antibiotics, but anthelmintics and coccidiostats for treatment of internal parasites; products seldom used in humans. In fact, the lack of availability of a variety of effective treatments promotes the development of resistance. These parasites are likely to become resistant to a product when it is overused because it is the only one approved.

As for the environmental question, these issues have already been examined in the approval of the products for major species use. The addition of the gamebirds would have no significant impact.

The case of aquaculture is more problematic. There is certainly the potential for environmental impact in some of the husbandry systems used in aquaculture. However, because these facilities are typically associated with public bodies of water, they are strongly regulated by state and federal agencies.

Because the Agency does not believe that extralabel use is a substitute for drug approvals, a ten-year sunset clause could be included in this provision. This would allow time for pursuit of drug approvals in these industries, (a process that is already underway) with the understanding that failure to achieve approvals would result in the needed products once again becoming illegal.

LEGISLATIVE ACTION:

Amend the FD&C Act to modify the prohibition on extralabel use of medicated feeds to allow such use in minor species.

REGULATORY ACTION:

Amend the corresponding regulations to accommodate this change.

CVM FUNCTIONAL CHANGES:

None.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Will the proposed modification of extralabel provisions and suggested sunset period provide adequate and appropriate temporary relief until approved products are made available, or will it serve as a disincentive to the pursuit of approvals?*
- *Should the proposed modifications be extended to include reproductive hormones and implants?*

B. REMOVAL OF DISINCENTIVES

Of greatest importance to the goal of increasing minor use approvals is the removal of existing disincentives to the pursuit of such approvals. This proposal has the potential to affect most of the minor use community. No drug is approved without the involvement of a pharmaceutical sponsor. Sponsors at every level, from huge corporations to small niche companies need to have the assurance that the marketplace will be as fair as possible, and that they will not be taking unnecessary risks when they seek approval for a minor use product. The following three subsections address potential strategies to remove such disincentives.

1. Lack of Enforcement Resources

A very serious disincentive to the approval of animal drugs for minor use is insufficient enforcement against those firms which market unapproved drugs. The reason for insufficient enforcement is related to the resources available to the Agency to be applied to its various enforcement responsibilities. FDA regulates many products, including human drugs, foods and devices, and competition for investigative and enforcement resources is constant. Often, enforcement actions are not taken against an illegal animal drug because other enforcement actions are deemed to have a higher priority. Thus, those firms that might consider seeking FDA approval for their drugs are reluctant to invest in that process because they cannot always be assured of protection from competition with unapproved products.

In the future, sponsors might be provided with significant tax incentives and extended periods of market exclusivity. However, such incentives may not be sufficient unless they are accompanied by a reasonable assurance that market exclusivity will be protected through enforcement activities against competing unapproved drugs.

This disincentive certainly exists now. For example, there are very few therapeutic drugs approved for fish, yet numerous unapproved drugs and other chemicals are marketed for use in aquaculture. Enforcement activities must first address those unapproved drugs which present significant human food safety concerns. This leaves few resources to curtail the marketing of products which are illegally competing with those few products which are approved.

Resources must be increased and earmarked for additional enforcement activities. Increased resources in CVM could fund a Minor Use Advocate in the Office of Surveillance and Compliance. The Minor Use Advocate would provide education and assistance to the field and other Agency components involved in enforcement. It is important to incorporate minor species enforcement activities into an overall enforcement strategy. The success of any blueprint to increase minor use approvals is contingent upon an Agency commitment to protecting the resource commitment of the companies that seek NADA approval.

2. Changes in the Standard for Regulatory Action

It has been proposed that a change in the FD&C Act to make enforcement actions against unapproved animal drugs less resource-intensive. Under current law, it is not sufficient for FDA to establish that a drug is being marketed without FDA approval. The government is required to establish that an unapproved animal drug is a "new animal drug," i.e., is not generally recognized by qualified experts as having been shown to be safe and effective for its labeled use(s) (21 U.S.C. 301(v), 351(a)(5), & 360b (a)(1)). This requirement involves significant resources to document, and thus is a real impediment to regulatory action. Accordingly, the FD&C Act could be amended to remove this requirement with respect to animal drugs and require only demonstration of the lack of approval of a product for the uses for which it is intended.

3. Assurance that an Existing Approval Would Not Be at Risk

Another significant disincentive is sponsors' concern that filing a supplemental NADA to obtain FDA approval to add a minor use indication to the label of a drug approved for a major use will "open up" the prior approval to another review. This concern is most frequently expressed with respect to older approvals. The regulations could be amended to assure prospective supplemental NADA sponsors for minor use drugs that their parent application will not be jeopardized by the submission of a minor use supplement.

CONGRESSIONAL ACTION:

1. A line-item budgetary change to increase resources for CVM minor use enforcement.

2. Amend the FD&C Act to permit the removal of a minor use animal drug from the market on the sole basis that it lacks FDA approval for the purposes for which it is labeled or promoted.

FDA ACTION:

Amend 21 CFR 514.106 to define supplemental NADAs for the addition of minor species to major species labels as a category that would not trigger critical reviews of the original major species data packages.

CVM ACTION:

Designate a Minor Use Advocate within the Office of Surveillance and Compliance and ensure that minor use actions are included in CVM's overall enforcement strategy.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Will the suggested strategies be sufficient to remove the existing direct regulatory disincentives?*

- *Are there additional disincentives to gaining approvals that should be removed? How might this be accomplished?*

C. ENHANCEMENT OF EXISTING PROGRAMS FOR DATA DEVELOPMENT

The costs of completing data requirements for an NADA are often extensive. Not only are numerous studies needed, but the data must be generated from well-designed and conducted studies, some of which must be conducted according to Good Laboratory Practices which can raise the cost even higher. The cost of the studies can range from a few thousand dollars to hundreds of thousands of dollars.

Minor use drug manufacturers are often small companies with few financial resources to commit to research projects, or larger companies with more potentially profitable products competing for resources in research and development. Minor use drugs do not have the large market value that major species drugs have that allows manufacturers to recover their financial investment. Finally, unlike the major species producers, minor use producer associations lack the resources to gather support for research efforts to support drug approvals.

While there currently are some efforts being directed toward funding and coordinating research projects for minor use drug approvals, the unmet resource needs of such applications could be addressed in several significant ways.

Expansion of these existing programs will primarily benefit animals of agricultural importance; the so-called food- and fiber-producing animals. This is because these programs are funded by the US Department of Agriculture and/or because they are directed specifically at industries such as aquaculture.

1. Expand Established Congressional Research Funds

The NRSP-7 program could be expanded within the U.S. Department of Agriculture (USDA) to allow more minor use research projects to be eligible for funding. The USDA currently provides approximately $550,000 annually to fund NRSP-7, with FDA contributing financial support for a biennial minor use workshop and the salary of one full-time employee. NRSP-7 identifies the critical drug needs of the various producers of minor livestock species, supports research directed toward generating data and assists in preparation of reports necessary for FDA approval of drugs in minor species.

A number of restrictions limit the type of products that are eligible for NRSP-7 funding. Currently, priority for funding is given to minor drug uses for food- or fiber-producing animals raised for commercial purposes, for treatment and prevention of diseases, for indications where drugs are unavailable, and for supplemental applications rather than new entities. In addition, NRSP-7 seeks a commitment of nonfinancial support from a drug company sponsor before funding a project.

Production drugs such as spawning hormones which are needed by some aquaculture groups would be eligible for funding if the restriction which limits funding of a research project to therapeutic indications were removed. Research on drugs for classes of animals such as ornamental fish and zoological species would be eligible for funding if the food and fiber restriction were removed.

Three congressional funds support animal drug research. The Saltonstall-Kennedy Grants Program, which funds aquaculture research, could be increased to allow money to be earmarked for drug research for use in aquaculture. The Hatch fund provides money for production drug research. Although minor species drugs are eligible for the Hatch funds, the funds typically go toward major species drug uses. A portion of the Hatch fund could be earmarked for minor species drug use. The National Coastal Research Institute provides funds for research projects that impact coastal regions. Again, this fund could have a portion set aside specifically for minor use research projects.

CONGRESSIONAL ACTION:

Increase appropriations for the budgets of NRSP-7, Saltonstall-Kennedy Grant Program, Hatch Fund, and National Coastal Research Institute and earmark the funds for minor use research.

FDA ACTION:

None.

USDA ACTION:

Expand the scope of the NRSP-7 program to allow the funding of research for non-therapeutic drugs and drug for non-food producing animals.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Are there additional existing congressional research funds which could be expanded for minor use research?*

2. Establish New Programs Based on the NRSP-7 Model

The NRSP-7 program could be used as a model for another research support program that would address the needs of the minor use groups currently excluded from NRSP-7. This new research support program could be funded by private and/or public groups with contributions from FDA. This research support program could provide funding for minor use drugs for non-food animals such as ornamental fish and for production purposes. An initial commitment from a pharmaceutical sponsor would be a requirement for funding consideration. CVM would need a full-time employee to act as liaison between this research project and CVM.

This new research support program could be administered by a Minor Use Coordinator who would organize research activities for minor use drug applications. The Minor Use Coordinator would not be a FDA employee and would perform as the equivalent to a pharmaceutical company's regulatory affairs manager. There is a precedent in the aquaculture field with the National Aquaculture NADA Coordinator who works to organize activities to expedite approval for aquaculture drugs. The Aquaculture Coordinator receives funds from USDA, CVM, the U.S. Department of the Interior, the American Veterinary Medical Association, and various public and private aquaculture associations. The Aquaculture Coordinator serves as a liaison between sponsors and CVM.

CONGRESSIONAL ACTION:

Appropriate funds for the research program.

FDA/CVM ACTION:

None

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Would the proposed model program provide a useful supplement to the existing NRSP-7 program?*

3. Establish a Minor Use Database

In order to provide a central source of information regarding needed research and product development for minor uses, multiple related databases could be established. At least one full-time equivalent (FTE) would be designated to establish and maintain them. These databases would be accessible to parties interested in and capable of furthering the approval of minor use products. This should include a database listing of known minor use diseases or conditions for which there are no active submissions, along with an associated list of chemical entities that may be promising for the disease or condition on the basis of having been approved for similar diseases or conditions in major species and/or humans.

The databases would also include a list of lead-researcher practitioners from among veterinary research organizations, industry sponsors, university animal science departments, and veterinary medical schools with expertise in areas related to one or more of the minor use conditions or diseases. In addition, a query of the diseases and conditions database should link to sources of potential funding. Notice of the existence of and modifications to the databases would be made through FEDERAL REGISTER notices and the CVM Internet home page (*http://www.cvm.fda.gov*).

CONGRESSIONAL ACTION:

None

FDA/CVM ACTION:

Establish and maintain the minor use database.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Would the proposed database be useful to parties interested in furthering the approval of minor use products? If so, how might it be developed most cost-effectively?*

D. INCENTIVES TO PURSUE MINOR USE DRUG APPROVALS

A major consideration in all drug development is the expected return on investment once a drug is approved. Animal drug development for minor use in the current regulatory and commercial environment is difficult to justify based on economic return. Research leading to drug approval in animals is time consuming and expensive, and the potential profits from the sale of most minor use products cannot directly pay for developmental costs.

These proposed incentives should have a positive effect for any sponsor seeking an approval for a minor use product. The different incentives may have different degrees of applicability for sponsors. For small niche companies without large budgets for research and development, grants may be the answer. Larger companies may be more attracted to the ability to negotiate shorter timeframes for review of more economically important products. Exclusivity and tax breaks probably would be welcomed by any company.

1. Financial Incentives

a. Exclusivity for New Claims

It has been proposed that Congress amend the FD&C Act to increase the period of protection against generic approval from three years to seven years for approval of a supplemental NADA and from five to ten years for an original minor use NADA. This would allow the sponsor to market its product for the minor use claim without generic competition for an extended period. This provision could serve as an incentive to pursue claims for smaller markets, especially in cases where the product is a new entity or being developed solely for the minor species use (disinfectants, bulk chemicals). However, it must be recognized that the scope of the market would tend to limit the incentive for generic sponsors as well as for the pioneers, so that potential generic competition may not be viewed as a major disincentive by "pioneer" sponsors in the first place.

b. Tax Credits

It has also been proposed that sponsors of products for minor use be eligible for tax credits as has been done for orphan drugs for humans. Orphan drugs are eligible for a fifty percent (of the clinical testing expenses) tax credit in the year of the expenditure. Since animal drugs cannot recover costs as easily as human drugs (no third-party reimbursement), a 100% tax credit could be implemented. In addition, tax credits could be granted to producers of minor species animals who participate in the clinical field trials which produce data to support an NADA. Representatives of the Office of Orphan Drugs report that this is the single most important incentive to encourage pursuit of approvals for human drug products.

2. Negotiation of a Shorter Timeframe for the Review of a Major Product

Pharmaceutical companies have expressed an interest in having FDA adopt shorter review times for major uses as an incentive for filing for minor uses. This is based on the significant increase in revenue that the company can expect through getting a major product to the market faster.

3. Consider Residue Depletion Studies as "Significant New Data" for Exclusivity

Under current law, exclusivity (i.e., protection against generic competition) is granted for a supplemental claim when that claim is supported by significant new data generated by the sponsor. The phrase "significant new data" is defined to include effectiveness studies, target animal safety studies, and studies to support calculation of tolerances for residues of new animal drugs in food. Residue depletion studies do not confer this privilege even though they are costly and time-consuming.

It is far easier for producer groups or other programs, such as NRSP-7, to provide data in support of effectiveness and target animal safety than it is for them to perform residue depletion studies. Residue depletion studies must be very carefully performed and involve considerable laboratory analysis. These studies can be conducted more easily by the pharmaceutical company because it usually has laboratory standards and methods already approved by FDA for the major species approval. If the sponsor could gain exclusivity through performing these studies, it is very likely that the rest of the components could be provided through public data. More approvals would be likely because producer groups and programs like NRSP-7 could perform a greater number of less expensive studies if they were relieved of the necessity to perform the residue studies.

CONGRESSIONAL ACTION:

1. Amend the FD&C Act to increase protection against generic approval from three years to seven years for NADA supplements for new minor use claims and from five to ten years for new NADAs.

2. Amend the Internal Revenue Code to allow tax credits to the sponsors of minor use research and to producers who participate in field trials.

FDA/CVM ACTION:

1. Revise policies relating to NADA review priorities to allow for shorter review times for major use NADAs of sponsors of minor use NADAs.

2. Revise policy relating to food safety data to permit residue depletion data to qualify as "significant new data" when appropriate.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Is the benefit of extended exclusivity, with respect to fostering initial approval, more important than the risk of increased drug costs that could be associated with decreased competition from generic approvals?*

- *Would it be a more significant incentive to provide for an extended period of exclusivity for all the claims of the product?*

E. DATA SHARING BY MAJOR SPECIES NADA HOLDERS

Currently, the regulations allow sponsors of drugs for minor uses to use data from pioneer major species applications. Under 21 CFR 514.1, CVM allows the use of animal models and extrapolation of data from a major species to a minor species to satisfy the safety and effectiveness, human food safety, and environmental requirements of the act where scientifically appropriate. In many cases, when sponsors of minor species applications request permission from a major species sponsor to allow CVM to refer to the data from the major use application, the major species sponsors refuse to share the data. This is because of the perception of a potential liability and because there is no incentive to disclose the information. Thus, despite the existing regulations, very few sponsors of minor species applications obtain access to data that would facilitate completion of an application for drug approval.

The Act could be amended to create a system that would permit the Agency to consider data in underlying NADAs for major uses when reviewing NADAs for minor uses, once the drugs are subject to generic competition under GADPTRA (Generic Animal Drug Patent Term Restoration Act of 1988) or have been abandoned or withdrawn (paralleling 512(p) of the FD&C Act). The end result would be a label held by the minor use sponsor with only the indication for the minor use appearing on it. The label would not contain the pioneer's claims and the pioneer sponsor could not place the minor use claim on its label without permission of the minor use sponsor.

The options for such a system range from the generic model, which would allow FDA to rely in-house on scientifically relevant data in a major use application when making human food safety determinations for minor use of that drug, to the Public Master File model, which would make data from major use applications available to minor use sponsors for use in INAD and NADA applications. Any system would have to address the "takings" issues under the Due Process clause of Article 5 of the U.S. Constitution. In addition, if liability was a valid concern, it too would need to be addressed.

CONGRESSIONAL ACTION:

1. Amend the FD&C Act to create a system whereby the Agency can consider data underlying NADAs for major uses when reviewing NADAs for minor uses, once the drugs are subject to generic competition or have been abandoned or withdrawn.

FDA/CVM ACTION:

None.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Is it fair to require the sharing of data?*
- *How could potential liability be ameliorated under such a data sharing system?*

F. CREATION BY STATUTE OF A "MINOR USE ANIMAL DRUG" PROGRAM

Like human orphan drugs, minor use animal drugs have limited markets and thus may not be profitable. Because these drugs are important both for humanitarian purposes and for human food safety purposes, a program could be created in the Act and the Agency that is specifically designed to foster their development and approval.

1. Create a Statutory Category of Minor Use Animal Drugs

The human orphan drug provisions of the Act could be adapted to provide for minor use animal drugs. The category of "Minor Use Animal Drugs" includes drugs for both minor species (i.e., animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats) and minor uses (i.e., the use of new animal drugs in a major species to control a disease that occurs in a small number of animals or in a limited geographic area). In addition, the Agency could be given the discretion to designate a new animal drug to be a minor use animal drug based on public health needs.

CONGRESSIONAL ACTION:

Amend the FD&C Act to create a category of Minor Use Animal Drugs.

AGENCY /CVM ACTION:

Develop regulations to implement changes in the Act creating Minor Use Drugs.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Would a statutory designation of "minor use animal drug" similar to the statutory designation of "human orphan drug" be useful?*

2. Minor Use Animal Drug Development

Should any or all of the proposed programs and policies in this document be implemented, it may be expedient for CVM to establish an internal work unit to administer them. If established, this work unit could be identified using the phrase "Minor Use Animal Drugs."

A reasonable model for this organization would be the FDA's Office of Orphan Products Development for human pharmaceuticals, established by the Orphan Drug Act of 1983. Currently, it resides in the Office of the Commissioner of FDA. The purpose of the Office of Orphan Products Development is to review applications for orphan status to determine whether proposed products (drugs, biologics, devices) qualify for the designation and its resulting incentives. A product granted orphan status is eligible for monetary grants for clinical studies, for tax credits, for protocol assistance, and for prolonged periods of marketing exclusivity. All of these services are administered by the Office of Orphan Products Development.

The Office of Orphan Products Development does not review the studies performed to support a New Drug Application (NDA). The data are filed by the sponsor directly with the appropriate FDA Center (drugs, biologics, devices) and are handled as any other new product.

This program has been extremely successful for human products. Ten years after the passage of the Act, there were 500 active orphan designations, with over 100 product approvals. Only 10 drugs for rare diseases were approved in the 10 years prior to passage of the Act.

It should be noted that, at the time of the passage of the Orphan Drug Act, it was speculated that the tax credit incentive would prove too costly to maintain. The program has been in place for over a decade now, and has proven to be cost effective and extremely successful.

The work unit at CVM would perform multiple functions.

- It would have the responsibility for evaluating submitted claims to determine whether or not to grant Minor Use Animal Drug status. Such status would make the product eligible for incentives such as grants, tax credits, and extended periods of exclusivity.

- Liaison and outreach responsibilities to affected industries and other agencies (e.g. USDA's NRSP-7) would also be part of the responsibilities of this unit.

- Assuming implementation of some of the changes described in this document, the number of minor use applications could increase significantly. This unit could assume the burden of minor use application review from the Office of New Animal Drug Evaluation (ONADE) within CVM. This would permit ONADE reviewers to provide better service to the major species applications, increasing the efficiency of the approval process for all applications.

The staff in such a new work unit could comprise "species-group experts" (e.g., avian, ruminant, aquaculture, wildlife). An expert in avian projects would understand the husbandry, physiology, and pharmaceutical needs of gamebirds and ratites. Such an individual would attend professional and producer-group meetings centering on these species. Familiarity with pertinent literature and its sources will also be valuable. This approach is efficient and cost-effective. Such expertise and familiarity with associated issues of policy would make such an individual invaluable in educating the associated industries and in guiding sponsors through the most appropriate path to approval of their product.

A work unit that encompasses "Minor Use Animal Drugs" would provide optimal service to the minor use community. With additional resources for review, its existence would also allow for the more efficient review of major use products.

CONGRESSIONAL ACTION:

Amend the Act to create the category of "Minor Use Animal Drugs" and to provide the associated package of incentives.

AGENCY/CVM ACTION:

Create a work unit within CVM to assume responsibility for Minor Use Animal Drug tasks. Promulgate regulations to implement proposed changes to the Act creating "Minor Use Animal Drug" category.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Are the incentives associated with this strategy a necessary component of the overall proposed "Minor Use Animal Drug Program"?*

G. CONDITIONAL DRUG APPROVAL FOR MINOR USES INVOLVING NON-FOOD ANIMALS

The new animal drug provisions of the Act could be amended to allow for the conditional approval of drugs for minor uses in non-food animals. A conditional drug approval for non-food minor uses would allow approved minor use drugs to appear on the market more quickly. Currently, there is no interim approval status for animal drugs as described in section 512 of the Act. However, there are precedents for the use of an interim approval mechanism; it is a key component of licensure in the veterinary biological field.

A conditional licensure from USDA currently is available for veterinary biological products such as vaccines to meet emergency conditions, limited markets, local situations, or other special circumstances (see 9 CFR Section 102.6). Although the purity and safety requirements of the Virus-Serum-Toxin Act of 1913, amended in 1985 (Pub. L. 99-198) do not change, the effectiveness data requirements are limited to those that establish a "reasonable expectation of effectiveness."

A conditional approval for minor use drugs for non-food animals could be adopted that parallels the conditional veterinary biologicals license. Some of the target animal safety and effectiveness data could remain pending after the manufacturing chemistry data were accepted and marketing was conditionally approved. Based on an initial data package, the drug could be marketed with a clearly designated conditional approval label. Upon satisfactory completion of the pending data requirements, the minor use product would receive full approval.

Although such a mechanism would require an additional cycle of review within the Agency, this is not seen as a major hurdle. In effect, data review is simply being spread out to allow some components of an approval to be accepted while the product is being marketed. The additional burden comes with the need to monitor progress toward the final approval. This should be manageable given the limitations of this mechanism to non-food minor use products. In any case, the benefits should be well worth the costs.

This type of approval could be a boon to small companies, with more limited cash flow, sponsoring drugs for use in wildlife, zoo animals, or exotic pets including ornamental fish. The ability to get the product to market faster would help to offset the research and capital expenditures required to support the approval of the product.

Food-producing animals should be excluded from this proposal. Data used for evaluation of human food safety cannot be incomplete for an approval because all of the toxicity and residue chemistry components contribute to CVM's calculation of a tolerance and a withdrawal time. The only way for a product to be available if the human food safety data are not complete is under an investigational new animal drug (INAD) exemption which requires a preliminary safety assessment and an investigational withdrawal time.
In addition, many of the human food safety studies depend upon the establishment of a dose which is effective and safe for the target animal. Therefore, target animal safety and effectiveness studies must be completed prior to conducting some of the human food safety studies.

Manufacturing chemistry requirements for minor use products should be completed prior to obtaining a conditional approval. This would ensure that the formulation of the proposed product would be reviewed and accepted by CVM to provide for batch to batch consistency of the marketed product (which would be the same product used in the target animal safety and effectiveness testing conducted after the conditional approval).

Under this proposal, the complete package of target animal safety and effectiveness data would not be necessary for a conditional approval to be granted. Demonstration of reasonable expectations of target animal safety and effectiveness would be required through literature or pilot studies subject to the judgment of the review staff. Reasonable data for establishing a conditional dose must also be provided from the literature or a pilot study. The remainder of the target animal safety and effectiveness data collection would be completed after the conditional approval was granted. The conditionally-approved product would be subject to full post-approval reporting requirements.

The conditional approval would be valid for up to 5 years and would be subject to annual review. If progress toward completion of the animal safety and effectiveness requirements was considered satisfactory, the conditionally-approved minor use product would be renewed for another year. If the animal safety and effectiveness requirements were not completed within the 5-year limit, the conditional approval would be revoked. Finally, safeguards would need to be put in place to swiftly remove a conditionally-approved product from the market if safety concerns were to arise prior to the 5-year sunset provision.

There would be some limitations associated with a conditional approval for minor use drugs. These would include the following:

- Extralabel drug use of a conditionally-approved minor use drug product would not be permitted. Accordingly, the extralabel use provisions of the FD&C Act added by the AMDUCA would have to be modified to specify that extralabel use of a conditionally-approved drug is not allowed.

- The quantity of conditionally-approved product that would be expected to be produced would be established prior to the conditional approval. The amount of the conditionally-approved product that was actually produced would be reported to CVM. Evidence of production of quantities of animal drug in excess of anticipated production amounts that cannot be satisfactorily explained would be a basis for revoking the conditional approval.

- The label of a conditionally-approved minor use drug product would be required to state that the product had a conditional status. Promotion of the conditionally-approved product would be permitted as long as the "conditionally-approved" statement was prominently included.

- Minor use drug products with conditional approvals could not be added to a major species label. Products with conditional approvals would be required to have separate labeling and packaging.

- There could be more than one sponsor of a conditional approval for the same product. However, if one of these conditionally-approved products were granted a full approval, the conditional approval status of the others would be revoked.

- A sponsor who failed to complete the animal safety and effectiveness requirements prior to the end of the 5-year period could not obtain a second conditional approval for the same product.

CONGRESSIONAL ACTION:

Amend the FD&C Act to allow conditional approvals of minor use drugs.

AGENCY/CVM ACTION:

None.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Would the proposed constraints upon conditional approval provide sufficient consumer protection and still provide adequate incentive to pursue a conditional drug approval to final approval?*

- *Is the proposed process appropriately restricted to minor uses involving non-food animals?*

H. ALTERNATE APPROVAL STANDARD/EXPERT REVIEW PANELS FOR MINOR USES INVOLVING NON-FOOD ANIMALS

The FDA is both a scientific regulatory agency and a consumer protection agency. To accomplish these missions, a high scientific standard has been maintained for the approval of human and animal drugs. This standard is appropriate and has been very effective for human drugs and for animal drugs for major species.

For certain minor species, it has been suggested that the statute be amended to adopt an alternate approval standard. Such a standard would replace the current statutory standard for proof of drug safety, "adequate tests by all methods reasonably applicable," and for proof of effectiveness "substantial evidence ... consisting of adequate and well-controlled studies" with, for example, "sufficient evidence of drug safety and effectiveness to convince qualified experts that the risk to the species of approving a drug for a particular use is clearly outweighed by the risk of not approving the drug." Stated another way, the standard might be "sufficient evidence to convince qualified experts that the consequences of approving a drug are preferable to the consequences of not approving it." The quality of the evidence needed to support approval would vary on a case-by-case basis. In some cases, it would equal that required by the current statute, while in other cases it would be lower. It would depend largely upon the amount of harm being caused by the absence of an approved drug.

A component of such a standard could include full disclosure labeling to distinguish products approved under this standard from those approved under the current standard. Use of this alternate standard would be restricted to products intended for minor uses involving non-food animals.

To most efficiently implement this alternate approval standard, the use of "Expert Review Panels" (ERP) could be considered. It has been suggested that even with an improved incentives package and increased enforcement, there are classes of minor uses that need additional support. Therefore, an alternate approval process involving both an alternate standard and review by Expert Panels could be considered. In addition to the understanding that an alternately approved product would be an approved new animal drug, it should be made clear in labeling and advertising for such drugs that approval has been gained via less stringent requirements than those of a standard NADA.

This alternate standard and mechanism for data review would primarily benefit zoological and wildlife species as well as exotic pets and ornamental fish. For these species, which are often too valuable or rare to be used in controlled studies, the recommendations of experts with extensive experience in their care would be invaluable. These species are the ones that will never be able to provide economic justification for development of standard drug approval packages. If these products are to be approved at all, this mechanism should be considered.

The alternate approval process would entail an assessment of target animal safety and effectiveness for the subject new animal drug by means of a non-FDA, expert review entity. The FDA would provide concurrence (or non-concurrence) by reviewing the expert assessment report and any accompanying documentation or raw data, as appropriate. Following FDA's concurrence of the ERP assessment, the Agency would proceed with the review of the remaining (normally required) technical sections (manufacturing chemistry, user safety, environmental safety, freedom of information summary, labeling) of this new animal drug application.

The Expert Review Panel would have certain attributes and operate under specified conditions.

1. The Expert Review Panel (ERP)

The outside expert review entity could operate under the auspices of a recognized professional organization or may be a non-affiliated *ad hoc* panel. The ERP would not be funded by FDA.

The ERP would comprise a minimum of three experts, none of whom would be FDA staff. The required minimum qualifications (including conflict of interest requirements) of the experts will be defined, and an individual's inclusion on the panel would be subject to review by FDA. CVM would review the proposed membership of a committee prior to the undertaking of ERP assessment.

Upon completion of their assessment, the ERP would provide to FDA:

- a report summarizing their review of the efficacy/target animal safety data,
- the documentation/data submitted to the ERP intended to support the claim of target animal safety and effectiveness, and
- the ERP's recommendation of a supported claim and appropriate conditions of use.

FDA would establish a list of species and uses for which new animal drugs might be assessed via the ERP process. The overriding criterion for eligibility in the ERP process would be that the drug is to be labeled for use in non-food minor species.

2. Alternate Standard for Approval Under This Model

Products reviewed under the alternate approval standard would be assessed by criteria different from those applied to conventional new animal drugs. The alternate standard would be relative, and would be expected to vary on a case-by-case basis. This standard would, in essence, be risk-based. It would be defined as comprising sufficient evidence of drug safety and effectiveness to convince qualified experts that the risk to the animal of approving the drug for a particular use is clearly outweighed by the risk of not approving the drug.

The ERP would be permitted to accept data other than adequate and well-controlled studies, or studies conducted under Good Laboratory Practices (GLPs). Historical controls and animals acting as their own controls would be permitted. Data from studies with positive control drugs, commonly accepted as effective by veterinary practitioners, may also be reviewed. The Panel could review and accept reports with some documentation (e.g., patient records, including dose and route of administration) in lieu of a formal study.

The Expert Panel would be permitted to accept data gathered using a product other than the proposed final market formulation with minimal bridging information. The Panel would provide an explanation of how the product formulation that they are reviewing (including excipients) could be bridged to the proposed market formulation.
Such an explanation would not necessarily have to be drawn from the results of a formal study. Information regarding what is generally known regarding bioavailability and other comparable characteristics of the two formulations would be acceptable. Examples could include data from non-sterile implants, if the data already exist, for a sterile implant that a sponsor is pursuing or comparison of one salt of a drug to another.

The Expert Panel may extrapolate not only from major to minor species but also within drug classes in a given species. Examples may include comparison of an unapproved drug with pharmacologically similar drugs that have an abundance of data in a target species for which they are approved. In another case, a compound could be approved in the same species based on information from a limited number of animals because of the known clinical history in that species of an approved similar drug (as when comparing narcotics, which, depending on the family, may differ only in relative potency). Such extrapolations need not require any pharmacokinetic or pharmacodynamic data.

3. Limitations of Approvals Under This Model

The FDA would maintain inspection authority. As part of the alternate approval process, FDA would establish review, inspection and appeals procedures.

The FDA would maintain all other post-marketing authority and requirements including, but not limited to, adverse drug experience reporting, and the record-keeping and reporting provisions of the FD&C Act. These products would not be eligible to be copied under the provisions of the Generic Animal Drug and Patent Term Restoration Act of 1988.

Provisions of the Animal Medicinal Drug Use Clarification Act (AMDUCA) pertaining to legal extralabel drug use (ELDU) would not apply to new animal drugs approved under the alternate standard, necessitating an amendment to those provisions.

Upon favorable assessment by the ERP and approval by FDA, such a product would be

marketed with a label approved by FDA. The label would include, but not be limited to, the following: a concise statement defining the product as having been held to alternate standards of target animal safety and effectiveness, a statement of FDA's acceptance of the ERP assessment, the conditions and contraindications for use which have been recommended by the ERP (as accepted or modified by FDA), and the general marketing status of the product (Prescription, Over-the-Counter, or Veterinary Feed Directive).

These products could be supplemented with new claims/indications. However, supplements would be restricted to the same general category as the original approval, i.e., supplemented only with claims for non-food minor species or uses.

CONGRESSIONAL ACTION:

1. Amend the FD&C Act to create an alternate approval standard for minor use drugs intended for non-food animals.
2. Amend the FD&C Act to allow for the creation and use of expert panels to review minor use drugs intended for non-food animals.

FDA/CVM ACTION:

None.

PARTICULAR ISSUES ON WHICH FDA SEEKS COMMENT

- *Will animal caretakers find drugs approved under the proposed alternate standard (with associated restrictions) acceptable?*
- *Do the affected industries have the needed expertise and/or will they be willing to fund the expert review panels?*
- *Is the proposed process appropriately restricted to minor uses involving non-food animals?*

I. INTERNATIONAL HARMONIZATION

1. Harmonization of the Review Process

It has been suggested that providing prospective pharmaceutical sponsors with more harmonization in the international approval of their products could greatly increase the availability of approved drugs for minor uses in the United States. Certain uses that are considered minor in the United States may not be minor in other parts of the world, either because foods derived from the species are in greater public demand, or because the disease or condition is more prevalent.

It has been further suggested that if FDA could accept reviews for minor uses approved in

other countries with equivalent regulatory systems, then obtaining approval in the U.S. would be potentially less costly and thus more attractive to sponsors. However, any system that accepts foreign reviews must be designed to take into account the often significant differences among different countries in the ways a drug may be used due to different management practices or life stage utilization.

The Agency could develop a system to assess the equivalency of approval systems in other countries and could then accept reviews from equivalent systems. Many nations require that new animal drugs obtain approvals from their regulatory agencies prior to the drug being used in that country. However, more than one agency in a country may be involved in the approval of new animal drugs as they have been defined in the FD&C Act. In addition, as noted above, a drug's conditions of use may vary in significant respects in different countries. Thus, the design of any system to recognize equivalence must take these critical factors into account.

The primary beneficiaries of such harmonization would be those US animal species which are raised more extensively in other countries. Examples include sheep in New Zealand and Australia, or shrimp in South America. Far more extensive data would exist for these animals where they are more economically significant than in the US. Such data sharing would be of great assistance to the approval of products for minor species of agricultural importance in this country.

In order to accept reviews from other countries:

- CVM would need to determine that the foreign country's requirements and systems for approving animal drugs were equivalent to the United States' requirements and systems;
- the drug would need to be intended for use in the same species, and
- the labeling of the drugs would contain the same claims as the approval in the originating country, or the sponsor would need to provide data in support of the differences.

CONGRESSIONAL ACTION:

None.

AGENCY/CVM ACTION:

To establish a system to determine that a foreign country's requirements and systems for approving animal drugs are equivalent to the United States' requirements and systems.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Could non-governmental input facilitate equivalency determinations?*

2. Identification of Existing Foreign New Animal Drug Approvals and/or Data

Currently, CVM accepts foreign data when the conditions of use are the same, or when the sponsor can demonstrate that the differences are not relevant. As part of its outreach to potential sponsors of drugs for minor uses, CVM could institute a program to identify drugs that are approved in other countries that could be considered for approval in the USA. At the very least, some existing data from the foreign approval(s) could be submitted to support an approval in the United States.

CONGRESSIONAL ACTION:

None.

AGENCY /CVM ACTION:

Establish program to identify minor use drugs approved in other countries and work with sponsors to submit data in support of approvals in the United States.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Are there sufficient numbers of foreign approvals to justify establishing this program?*

3. Harmonizing Approval Requirements

If NADA requirements were harmonized for minor species across several countries, obtaining approval would be less costly and more attractive. There are presently several international groups (e.g. European Union, and Veterinary International Committee on Harmonization) that exist solely or partly to harmonize drug approval activities among nations. Attempts should be made to ensure that minor uses are included.

CONGRESSIONAL ACTION:

None.

AGENCY/CVM ACTION:

Add minor use component to its current harmonization activities.

PARTICULAR ISSUE ON WHICH FDA SEEKS COMMENT

- *Should the proposed differences in approval, standards, processes, and data requirements between major and minor species be included in international harmonization activities?*