

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

ADAA Minor Use/Minor Species Working Group  
Report

**19 August 1998**

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

### **SUMMARY**

The Animal Drug Availability Act of 1996 (ADAA) required the Food and Drug Administration (FDA, the Agency) to develop proposals that would facilitate approvals for minor use<sup>1</sup> animal drugs. Pursuant to that request, the Agency is offering this compilation of proposals to increase the availability of approved animal drugs for minor species and minor uses.

### **I. INTRODUCTION**

The Code of Federal Regulations (21 CFR 514.1 (d)) defines “minor use” as “...the use of: (a) New animal drugs in minor animal species, or (b) new animal drugs in any animal species for the control of a disease that (1) occurs infrequently or (2) occurs in limited geographic areas. “Minor species” are defined as “animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.”

The ADAA (Pub. L. 104-205) recognized 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. Therefore, in section 2(f) of the ADAA, Congress required FDA to announce proposals for legislative or regulatory change to facilitate approval of animal drugs for minor uses. This document makes a number of proposals that the Agency believes may contribute to resolution of 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 these reasons, no single proposal is likely to have a significant effect on the problem as a whole.

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<sup>1</sup> In this document, the term “minor use” means 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 (the Act), a process that was designed for the approval of drugs for humans<sup>2</sup>. When the major portions of the 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 as 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 else from abalone to zebras. For example, in Fiscal Year 1997 there were nearly 80 new animal drug applications (NADAs) 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; the reasons are similar to those leading to the failure to develop human “orphan drugs”.

There are no drugs approved for the overwhelming majority of minor species, even though they may 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. FDA believes that humans have a responsibility to care for other species of animals; we have a responsibility to try to prevent the suffering and death that result from the shortage of approved drugs for the care of such animals.

The following examples illustrate the problem.

- An outbreak of furunculosis 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 few products are available to treat them when they become ill.

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<sup>2</sup> 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. Many of the organisms capable of causing disease in minor species are not confined to such species. Thus, minor species can be 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.

There are also economic ramifications for U.S. minor species producers. Commercially valuable domestic 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 good examples. Domestic aquaculture is a relatively young industry. The U.S. must rely on imports to meet consumer demand for many aquaculture products (e.g., marine shrimp). In contrast, production aquaculture is far advanced for some of our trading partners. These other countries have numerous approved products for therapeutic and production uses available to their aquaculture industries. Different health and safety standards in the use of animal drugs in foreign countries place U.S. aquaculture interests at a competitive disadvantage for the domestic market. Increased availability of approved drugs in the U.S. for these uses could reduce this problem.

## **B. EXTRALABEL USE IS NOT THE ANSWER**

In 1994, the Animal Medicinal Drug Use Clarification Act (AMDUCA) (Pub. L. 103-396) amended the Act to permit veterinarians to use approved human and animal drugs in an extralabel manner under some constraints. For many minor uses, AMDUCA does not make needed treatments available.

First, for AMDUCA to apply, a veterinarian must be treating the animal. However, many minor species are not routinely under the care of veterinarians, instead being treated by other qualified professionals such as zoologists or fish biologists. Second, many minor species can only be treated through 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 that 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 that are not approved for use in other species. This leads to the need to alter formulations, with potentially adverse effects on safety and effectiveness. The need to approve animal drugs in appropriate formulations for the intended minor use is clear. Another shortcoming is the fact that the veterinarian must assume any liability associated with the decision to use approved 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 of this document) underscore the need for a major change in the current system. The FDA has consistently exercised its authority in interpreting the Act with the maximum flexibility relative 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**

Most 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 current system are not without risk and do not necessarily represent the "best way" to increase the availability of minor use animal drugs. From a scientific standpoint, the best way to make these products available remains something very close to the current approval system. However, with respect to drugs for minor uses, almost 30 years of experience has proven that applying this "scientifically- best" standard and process for minor use drugs results in virtually none being approved.

## **II. BACKGROUND**

### **A. ADAA MANDATE**

The ADAA modifies several existing sections of the Act. When the bills that eventually became the ADAA were originally introduced in Congress, specific and limited statutory changes to the Act were proposed in an attempt to streamline the process by which minor species and minor use drugs could be approved. Instead, section 2(f) of 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 Act, of animal drugs intended for minor species and for minor uses and, within 18 months after date of enactment of the ADAA, 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.

A “Discussion Draft” of this document was posted on CVM's Internet Home Page on December 19, 1997. Comments were solicited from responders to the first notice and from other concerned parties. When these were added to the docket, there were over 100 comments received concerning this document.

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 described in 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, 5630 Fishers Lane, Room 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday. The comments are also available on the FDA Home Page, [www.fda.gov](http://www.fda.gov).

## **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. 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 Act where scientifically justifiable. This often provides relief from the need to perform many costly effectiveness and human food safety studies. The reduction in the number of required studies, and in 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 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) regarding supplemental applications 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 of FDAMA 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 of FDAMA will not sufficiently facilitate approvals for minor use drugs.

The majority of approved 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 U.S. Department of Agriculture (USDA) National Research Support Project #7 (NRSP-7) encourages the development of Public Master Files (PMFs) to make available public data that can be used in conjunction with data already available in a major use product's original 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), that meets some of the requirements of section 403 of FDAMA. The Agency, through the individual serving as the NRSP-7 liaison and other means, already, as described in section 403(c)(2) of FDAMA, "work[s] with sponsors to facilitate the development and submission of data to support supplemental applications" (Pub. L. 105-115).

### **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 permits 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. HUMAN FOOD SAFETY CONSIDERATIONS FOR MINOR SPECIES**

The Agency recognizes that minor species represent a small component of the human diet. Therefore, FDA may determine that certain specific drugs and drug claims, and certain life-stages provide for a reasonable certainty of no harm to consumers based upon this limited exposure. If the conditions of limited exposure are met, FDA may 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 NADAs. 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**

The USDA's 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 focuses on 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 PMF. Once the data are considered acceptable, CVM publishes a notice of the public availability of the data in the FEDERAL REGISTER. A sponsor may then, at no cost, refer to those data to support an NADA for the minor use.

Since the program's inception in 1982, it has received over 280 animal drug requests from producers, universities, and from veterinarians. 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 data supporting 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 minor species 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 present policies (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.fda.gov/cvm>) on the Internet or from the Communications Staff (HFV-12), CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

#### **IV. PROPOSALS TO INCREASE THE LEGAL AVAILABILITY OF APPROVED ANIMAL DRUGS FOR MINOR USE**

The following subsections present a variety of proposals, made in response to section 2(f) of the ADAA, that should increase the number of animal drugs legally available for minor use. Each proposal is described and the legal and regulatory changes that would be needed to implement it are noted.

The proposals are identified as follows:

- A. Creation by Statute of a “Minor Use Animal Drug” Program
- B. Enhancement of Existing Programs for Data Development
- C. Conditional Drug Approval for Minor Uses With No Human Food Safety Concern
- D. An Alternate Process to Provide for Legal Marketing of New Animal Drugs for Minor Species With No Human Food Safety Concern
- E. Other Legislative Options
- F. Other Changes in Regulation or Policy

##### **A. 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. It is important to approve these products both for animal welfare and for human food safety purposes. A program could be created by amendments to the Act and within 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” would include drugs for minor species as defined in the 21 CFR 514.1(d) (i.e., animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats).

###### **2. Minor Use Animal Drug Development**

Should this proposed program be implemented, it would be necessary for CVM to establish an internal work unit to administer it. 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 (OOPD) 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 OOPD 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, tax credits, protocol assistance, and prolonged periods of marketing exclusivity. These are administered by the OOPD.

The OOPD 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 Orphan Drug Act, there were 500 active orphan designations, with over 100 product approvals, a far greater number than were approved in the decade prior to 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 proposed Minor Use Animal Drug work unit at CVM would differ somewhat from the OOPD by performing 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.
- It would be most desirable to follow the Orphan Products model and have the minor species advocates separate from the reviewers. The ability to keep these processes separate will depend largely on the availability of personnel resources within CVM.

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.

### **3. Financial Incentives**

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.

The incentives proposed should benefit any sponsor seeking an approval for a minor use product. The different incentives may have different degrees of applicability for individual sponsors. For example, small niche companies without large budgets for research and development, may see grants as the strongest incentive. Extended periods of exclusivity and tax credits should benefit any company.

a. Exclusivity for New Claims

We propose that Congress amend the Act to increase the period of protection against generic approval to 7 years (from 3 years) for approval of a supplemental NADA for a minor use and to 10 years (from 5 years) for a minor use NADA that represents the first approval of a new chemical entity. This would allow the sponsor to market a 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). Although enhanced exclusivity is worthwhile, its effect may be only modest. Because the scope of the market limits the incentive for generic sponsors as well as for pioneers, potential generic competition may not be viewed as a major disincentive by pioneer sponsors in the first place.

b. Tax Credits

We propose that sponsors of products for minor use be eligible for tax credits as has been the case for orphan drugs for humans. Orphan drugs are eligible for a 50% (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 that produce data to support an NADA. Representatives of the OOPD report that tax credits are the single most important incentive to encourage pursuit of approvals for human drug products.

c. Grants

We propose that legislation include monies to be allocated in the form of grants to pharmaceutical firms for development of minor use products. Such funds could be used to overcome the largest obstacles to development of such products, including the ability to meet cGMPs requirements.



**CONGRESSIONAL ACTION:**

1. Amend the Act to create the category of “Minor Use Animal Drugs” and to provide the associated package of incentives, including grants and the necessary appropriations.
2. Amend the Act to increase protection against generic approval from 3 years to 7 years for NADA supplements for new minor use claims and from 5 to 10 years for new NADAs.
3. 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. Promulgate regulations to implement proposed changes to the Act creating “Minor Use Animal Drug” category.
2. Create a work unit within CVM to assume responsibility for Minor Use Animal Drug tasks.

**B. 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 (GLPs) which can raise the cost even higher. The cost of individual 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 potentially more 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 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 USDA and/or because they are directed specifically at industries such as aquaculture. However, if certain restrictions were removed, ornamental fish and zoo species would also benefit.

## **1. Expand Established Congressional Research Funds**

The NRSP-7 program could be expanded within the 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. FDA contributes financial support for a biennial minor use workshop and the salary of one full-time employee who serves as a liaison to this program. 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 that limits funding of a research project to therapeutic indications were removed. Research on drugs for classes of animals such as ornamental fish and zoo species would be eligible for funding if the food and fiber restriction were removed.

To the best of our knowledge, 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. The Hatch fund provides money for production drug research. Although minor species drugs are eligible for Hatch funds, the funds typically go toward major species drug research. A portion of the Hatch fund could be earmarked for minor species drug development. 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.

Other programs, such as the Small Business Innovation Research Program and Sea Grant could be used to assist in minor use animal drug research, especially in the area of aquaculture. The existing government aquaculture programs at Upper Mississippi Science Center and the Stuttgart National Aquaculture Research Center should continue to be funded. The International Association of Fish and Wildlife Agencies is currently doing very valuable minor use drug work. The fund is matched with monies from the Department of the Interior, but is funded only through Fiscal Year 1998. All of these programs have valuable roles to play in the development of data to support minor use NADAs.

**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. Continue to fund the other programs mentioned.

**USDA ACTION:**

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

**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 to 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 nonfood animals such as ornamental fish and for production purposes. An initial commitment from a pharmaceutical sponsor could 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 an FDA employee and could 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 AVMA, 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:**

Establish the position of FDA liaison to this new program.

### **C. CONDITIONAL DRUG APPROVAL FOR MINOR USES WITH NO HUMAN FOOD SAFETY CONCERN**

The new animal drug provisions of the Act could be amended to allow for the conditional approval of drugs for minor uses in nonfood animals. A conditional drug approval for nonfood minor uses would allow approved minor use drugs to appear on the market more quickly. Conditional approvals would be granted only to sponsors who commit to pursuing full approvals.

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 (9 CFR 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 nonfood animals could be adopted that parallels the conditional veterinary biologicals license, including the limited circumstances under which it would be considered and the “reasonable expectation of effectiveness” definition. Some of the effectiveness data could remain pending after the target animal safety and 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.

Drugs for food-producing animals would not be eligible for a conditional approval. 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 INAD, which requires a preliminary safety assessment and an investigational withdrawal time.

Therefore, use of the conditional approval mechanism would be restricted to products intended for minor uses involving nonfood animals except for those minor species covered under section III.D.(Human Food Safety Considerations for Minor Species) of this document.

Manufacturing chemistry requirements for minor use products would 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 effectiveness testing conducted after the conditional approval is granted).

Under this proposal, the complete package of effectiveness data would not be necessary for a conditional approval to be granted. Demonstration of a reasonable expectation of effectiveness would be required through literature or pilot studies subject to the judgment of the CVM review staff. Reasonable data for establishing a conditional dose must also be provided from the literature or a pilot study. For example, studies conducted in a related species, or extrapolations using pharmacokinetics may be sufficient to support a conditional dose and a reasonable expectation of effectiveness. Other examples of evidence to support a reasonable expectation of effectiveness include, but are not limited to the following:

- Data from a single study,
- Use of surrogate endpoints,
- Data from short-term studies for long-term treatments, and
- Data from closely-related diseases.

The remainder of the 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. This process does not alter the requirements for a full approval. It simply allows the product to be marketed once initial indications of target animal safety, effectiveness, environmental safety, and occupational safety have been demonstrated, but before all the data requirements have been met.

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 specific circumstances and nonfood minor use products.

Conditional approvals provide a means for small companies, with more limited cash flow, to sponsor drugs with limited markets 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.

The conditional approval would be renewable for up to 5 years and would be subject to annual review. If, at the end of each year, progress toward completion of the effectiveness requirements was considered satisfactory, the conditionally-approved minor use product would be renewed for another year, until the 5-year total was reached.

If the effectiveness requirements were not completed within the 5-year limit, the conditional approval would expire. 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 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 Act, as amended 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 may 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 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 Act to allow conditional approvals of minor use drugs.

**AGENCY/CVM ACTION:**

Promulgate regulations to implement the statutory change.

## **D. AN ALTERNATE PROCESS TO PROVIDE FOR LEGAL MARKETING OF NEW ANIMAL DRUGS FOR MINOR SPECIES WITH NO HUMAN FOOD SAFETY CONCERN**

The FDA is both a scientific regulatory agency and a consumer protection agency. As previously noted, the current review process has resulted in the approval of very few drugs for minor species. The purpose of this alternate process is to enhance the availability of drugs for minor species while appropriately considering animal health and public health needs.

### **1. The Legally-Marketed Unapproved Animal Drug Index**

For certain minor species, the Agency proposes that the statute be amended to adopt an alternate process to provide for legal marketing of new animal drugs. These products together would be referred to as the Legally-Marketable Unapproved Animal Drug Index (the Index).

The current statutory standard for proof of drug safety is, “adequate tests by all methods reasonably applicable,” and for proof of effectiveness, “substantial evidence ... consisting of adequate and well-controlled studies”. For eligible minor species products, inclusion in the Index would be based instead on a statutorily-mandated risk:benefit analysis. This would be based upon sufficient evidence of drug safety and effectiveness to convince qualified experts that the benefit to the species of a particular drug use outweighs the risk to that species of that use. The quality of the evidence needed to support inclusion in the Index would vary on a case-by-case basis. It would depend, in part, upon the amount of harm being caused by the absence of a legally- marketed minor species drug.

The Index would be restricted by statute to products intended for minor nonfood species as defined by regulation, except for those cases covered under section III. D. (Human Food Safety Considerations for Minor Species) of this document.

The Index would primarily benefit zoo and wildlife species, aquarium fish, reptiles, caged birds, small pet mammals, and wildlife as well as some commercially-produced species such as crickets or earthworms and possibly nonfood life stages of some minor food-producing species such as oysters and abalone. For virtually all of these species, there will never be economic justification for development of standard drug approval packages, even if the other proposals in this document are adopted. If these products are to be made legally available at all, an alternate process must be considered. For many of these species, which are too valuable or rare to be used in controlled studies, the recommendations of experts with extensive experience in their care would be invaluable.

The indexing process would involve an assessment of target animal safety and effectiveness for the subject new animal drug by means of a non-FDA, expert review entity. Thus, the risk:benefit analysis would be applied by panels of experts operating external to FDA, at little or no cost to the agency. The outside expert panels could operate under the auspices of a recognized professional organization or could be a non-affiliated *ad hoc* panel. The expert panels would typically comprise a minimum of three experts. The required minimum qualifications (including conflict of interest requirements) would be defined, and an individual's inclusion on the panel would be subject to review by FDA. Experts could become special government employees for the purpose of serving on a panel.

The expert panels would review not only data from adequate and well-controlled studies, but also data from other than adequate and well-controlled studies and from other than studies conducted under GLPs. For example, a panel could review written reports such as patient records, (including dose and route of administration).

Expert panels could also consider data gathered using a product other than the proposed final market formulation with minimal bridging information. The panels 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 could also be included.

An expert panel could extrapolate not only from major to minor species but also within drug classes in a given species. Such extrapolations may not require any pharmacokinetic or pharmacodynamic data.

## **2. FDA Recognition Process**

The proposed recognition process for inclusion in the Index could function as follows:

Subsequent to the proposed statutory changes, FDA would establish, by regulation, general requirements for: entry into the process, establishment of expert panels, product labeling, conditions of manufacture, distribution and promotion, and regulatory action against products or persons violating these requirements. However, the decision to recommend inclusion of a minor species product in the Index would be made by an expert panel operating external to FDA.

FDA would determine eligibility of a minor species product based on a formal request from a minor species animal drug sponsor. Eligible products would include those intended for nonfood minor species as outlined in the previous section.

The request would be required, as defined by regulation, to contain proposed indications



and a description of the product formulation. The request must be supported by information allowing FDA to determine that there is no food safety, environmental, user safety, or bioavailability concern associated with the proposed indications/formulation. Eligibility to participate in the indexing process could also be dependent upon limiting annual production of the drug.

If FDA agreed that the minor species product was eligible to be included in the Index, the sponsor would be required to gather information from all available sources to support target animal safety and effectiveness. The safety and effectiveness package would then be submitted to an expert panel deemed acceptable by FDA. At limited or no cost to the FDA, the expert panel would evaluate the information in accordance with a statutorily-mandated risk:benefit analysis procedure.

If the panel found the target animal safety and effectiveness data to be acceptable, it would prepare supporting review(s) and appropriate draft labeling, which would include a statement that the minor species product is “legally-marketable” but not “approved” by FDA. The expert panel will further specify Rx/OTC status as well as all other requirements for such labeling established by FDA, and would return the submission to the product sponsor.

The sponsor would submit to FDA a request to be added to the Index. The request would be supported by: a copy of FDA’s prior determination of eligibility, a draft Index entry, the expert panel review, draft labeling and a commitment to manufacture, label and distribute the minor species product only in accordance with the Index entry, cGMPs and any other general requirements for such products (such as extra-label use prohibition, promotional restrictions, adverse drug event record-keeping) established by FDA.

Only the sponsor of an indexed minor species product could legally market the product.

Minor species products not in the Index (or not approved), not marketed in compliance with the appropriate Index entry (or approved NADA), not manufactured in accordance with cGMPs or not labeled, distributed and promoted in accordance with other requirements established by regulation would be subject to regulatory action by FDA. Minor species products could be removed from the Index by FDA for cause. The FDA would maintain full inspectional authority over such products.

The minor species products included in the Index would not be eligible to be copied under the provisions of the Generic Animal Drug and Patent Term Restoration Act of 1988 (GADPTRA). Provisions of AMDUCA pertaining to legal extra-label drug use would not apply to new animal drugs accepted for legal marketing under this process.

Following initial inclusion in the Index, product labeling could be revised via the same process to include additional indications.

**CONGRESSIONAL ACTION:**

Amend the Act to create an Index to provide for legal marketing of new animal drugs for minor species with no human food safety concerns.

**FDA/CVM ACTION:**

Promulgate regulations to implement the statutory changes

**E. OTHER LEGISLATIVE OPTIONS**

**1. Changes in the Standard for Regulatory Action**

Of greatest importance to the goal of increasing minor use approvals or inclusions in the Index is the removal of existing disincentives to the pursuit of legal marketing. This proposal has the potential to affect most of the minor use community. No drug is approved or indexed without the involvement of a pharmaceutical sponsor. Sponsors at every level, from large corporations to small niche companies, need to have the assurance that the marketplace will be as fair as possible when they seek approval or inclusion in the Index for a minor use product.

A major disincentive to the application for NADAs for minor use is a prospective sponsor's knowledge that there is insufficient enforcement against firms that market competing illegal animal drugs. The reason for insufficient enforcement is related to the resources available to the Agency to be applied to its various enforcement responsibilities. Resources for this purpose should be increased.

We propose that the Act be amended to make enforcement actions against animal drugs that are not approved or included in the Index 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 illegally-marketed 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), and 360b (a)(1)). This requirement involves significant resources to document which hinders regulatory action. Accordingly, the Act should be amended to remove this requirement with respect to animal drugs and require only demonstration of the lack of approval or inclusion in the Index of a product for the uses for which it is intended. This would allow timely removal of an unapproved product marketed for the same claim as an approved product or one listed in the Index.

**CONGRESSIONAL ACTION:**

1. A line-item budgetary change to increase resources for CVM minor use enforcement.
2. Amend the Act to permit the removal of an animal drug from the market on the sole basis that it lacks FDA approval or inclusion in the Index for the purposes for which it is labeled or promoted.

## **2. 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 should 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 or have been abandoned or withdrawn (paralleling 512(p) of the 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.

There may be several options for such a system. One example might be 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. A second example might be a PMF model, which would make data from major use applications available to minor use sponsors for use in INAD and NADA applications.

Liability is a complicated legal issue which is beyond the scope of this document. However, it is a valid concern which will need to be addressed. Some of the public comments on this issue included proposals limiting liability through indemnification, establishing a means whereby a minor use applicant could sign an agreement to release the pioneer from liability, and the development of liability coverage as has been developed in the field of minor use crop pesticide approval in some states.

### **CONGRESSIONAL ACTION:**

Amend the 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:**

Promulgate regulations to implement the statutory change.

**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.

**FDA/CVM ACTION:**

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

**F. OTHER CHANGES IN REGULATION OR POLICY**

**1. Minor Use Advocate for Enforcement**

Resources should be increased and earmarked for additional enforcement activities. Increased resources in CVM would be used to 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 or product inclusion in the Index is contingent upon an Agency commitment to protecting the resource commitment of the companies that seek NADA approval or inclusion in the Index.

**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.

**2. Assurance that an Existing Approval Would Not Be at Risk**

A 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 should 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.

This assurance would not exempt a product from examination if problems with safety should be discovered at any time. It simply allows the old approval to stand separately from the new data supporting the supplemental claim.

**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.

**3. Minor Use in International Harmonization**

It has been suggested that providing prospective pharmaceutical sponsors with more international harmonization in the review 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 U.S. 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.

CVM currently reviews foreign data submitted by individual product sponsors. Efforts are underway to facilitate the sharing of reviews of such data between national regulatory agencies. Such reviews would be used as part of the evaluation of a product. They would not have to be accepted as definitive by themselves.

The Agency should develop a system to assess the equivalency of approval systems in other countries and could then use reviews from equivalent systems as a part of the U.S. evaluation. This is similar to the process being proposed by FDA's Center for Food Safety and Applied Nutrition (CFSAN) in pending food import legislation. Such evaluation should be part of the ongoing international harmonization efforts.

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

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. Some existing data from the foreign approval(s) could be submitted to support an approval in the U.S.

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.

**AGENCY/CVM ACTION:**

1. Establish a system, similar to that proposed by CFSAN in its pending food import legislation, to determine that a foreign country's requirements and systems for approving animal drugs are comparable to the U.S. requirements and systems.
2. Establish a program to identify minor use drugs approved in other countries and work with sponsors to submit data in support of approvals in the U.S.
3. Add minor use component to current harmonization activities.

**4. 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 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 approved products, 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.fda.gov/cvm>).

**FDA/CVM ACTION:**

Establish and maintain the minor use database.

**V. CONCLUSIONS**

Passage of the ADAA was an acknowledgment of the existence of a general problem regarding animal drug availability. The specific provision directing the FDA to propose *additional* legislative or regulatory changes to the process for approving new animal drugs for minor species or minor uses is an acknowledgment of a particular problem regarding the availability of animal drugs for these purposes.

The Agency agrees that the lack of legally available drugs for minor species or minor uses is a significant problem. The scope of the problem caused by the insufficient legal availability of animal drugs is confirmed by the spectrum of individuals and organizations (see section II. B., paragraph 3 of this document) that attested to the problem in response to the FEDERAL REGISTER Request for Comments on Development of Options to Encourage Animal Drug Approvals for Minor Species and for Minor Uses, Docket No. 97N-0217.

The Agency recognizes that increased availability of drugs is not the only solution to all disease or management-related problems facing caretakers of minor species, and the Agency supports non-drug-dependent solutions to such problems whenever possible. The Agency has no desire to foster drug-dependent animal care systems at the expense of other options. However, it is clear that there are innumerable situations involving minor species in which no viable alternatives to drug use exist, and in which animals may suffer and die, or their caretakers may be required to violate Federal law or otherwise expose themselves to liability to prevent such suffering and death, as a result of the shortage of legally marketable animal drugs.

In responding to Congress' charge to propose changes that would facilitate the approval of new animal drugs for minor species or minor uses, the Agency has proposed a broad array of proposals, one of which involves an alternative to NADA approval to allow the legal marketing of drugs for minor species. This multi-faceted approach is due, in large part, to the Agency's perception that neither the current animal drug approval process nor any other single approval process can adequately address the enormous diversity of minor species for which drugs are needed. Each of the proposals has utility with respect to certain groups or classes of minor species or minor uses. The relative merits of the proposals change depending upon the class or group of minor species with respect to which they are assessed. For example, one would expect that the process for making drugs legally available for use in food-producing minor species would not be very different from the process for approving drugs for major food-producing species, while the process for making drugs legally available for use in zoo species or aquarium fish might be quite different.

FDA stands ready to work with Congress and other concerned parties to further characterize any proposed statutory changes which are considered worthy of further pursuit, and to subsequently work diligently toward their passage. Should the statute be amended as a result of these proposals, the Agency will devote significant attention to promulgating any necessary regulations or otherwise implementing the statutory changes. Increasing the availability of drugs for minor species and minor uses is, and will continue to be, an important issue for the FDA.