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Guidance for Industry

FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

(This version of the guidance replaces the version that was made available on April 15, 1999. This document has been revised to update the contact information, Part 1- Section XI (Other Guides), and minor formatting changes).

This Guidance Document supersedes GUIDELINE 26, "Guidelines for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs."

For questions regarding this document, contact Meg Oeller, Center for Veterinary Medicine, Food and Drug Administration, Office of Minor Use and Minor Species Animal Drug Development, HFV-50, 7500 Standish Place, Rockville, MD 20855, 240-276-9005, email: margaret.oeller@fda.hhs.gov.

Additional or updated copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, 7519 Standish Place, Rockville, MD 20855 and may be viewed on the internet a http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine

May 29, 2008

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FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

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FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

Part 1: Introduction

This guidance represents the agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. PURPOSE OF THIS DOCUMENT

The major purpose of this document is to suggest means of generating effectiveness and safety data to support the approval of minor use animal drugs. A minor animal drug use is defined as use in a minor species OR use in any animal species for a condition that is rare or that occurs in limited geographic areas. Minor species are defined by exclusion, as any species other than major species. Major species are defined as cattle, swine, chickens, turkeys, horses, dogs, and cats. According to current regulations, sheep are a minor species except with respect to human food safety data collection requirements, for which sheep are considered major species. CVM intends to issue a proposed regulation in which sheep would be defined as a minor species for all requirements of the drug approval process. Other guidance addresses issues relating to exotic and wildlife species.

CVM currently considers veal calves separately from cattle for the drug approval process. Thus, portions of this guidance document relating to 'Domestic and Semi-Domestic Minor Ruminants' may prove useful with respect to supporting indications for use in veal calves.

The guidance document, as applied to minor use animal drugs, does not lessen the legal requirements for demonstrating the safety and effectiveness of a new animal drug. Instead, the guidance document suggests possible means of generating safety and effectiveness data to satisfy these requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

This document is intended to reflect the current way that animal drugs are approved for minor species and minor uses. The Animal Drug Availability Act of 1996 required CVM to examine the way that these products are approved and to propose means to facilitate such approvals. In the FEDERAL REGISTER, Vol. 63, No. 209, October 29, 1998, CVM published a notice of the availability of its report proposing several options to encourage animal drug approvals for minor species and for minor uses. It is very likely that additional

policies and programs will be implemented over the next few years to accomplish this goal. Because policies and programs may change, sponsors are encouraged to contact CVM early in project development to determine the most efficient path to approval of their products.

A person may follow the guidance in this document, or may choose to follow alternate procedures or practices. If a person chooses to use alternate procedures or practices, that person may wish to discuss the matter further with the agency to prevent an expenditure of money and effort on activities that may later be determined to be unacceptable to FDA.

This guidance document does not bind the agency or the public, and does not create or confer any rights, privileges, or benefits for or on any person. The document represents FDA's current thinking on means to provide data supporting drug approvals for minor species and minor uses. When a guidance document states a requirement imposed by statute or regulation, the requirement is law and the force and effect of this requirement are not changed in any way by inclusion in the guidance.

II. ORGANIZATION OF THIS DOCUMENT

Part 1 of this document includes general information applicable to all types of minor uses. Part 2 presents specific plans to provide data for various categories of minor uses. These categories include minor uses in major species, minor avian species (gamebirds, semi-domestic waterfowl, and ratites), minor ruminants, rabbits, and aquatic species (finfish, aquatic invertebrates, alligators, etc.).

To use this document effectively, the user need only read this introduction and the section pertinent to the animal of interest. Each section contains information on effectiveness, target animal safety, human food safety, and environmental issues. This organization reflects the major data components of the animal drug approval process exclusive of manufacturing data.

III. APPROVAL PROCESS OVERVIEW

Users of this document may range from those well acquainted with the new animal drug approval process to those who have no experience with this process at all. A brief overview of the technical sections involved in the new animal drug approval process follows. Those already familiar with these components may wish to skip to the next section.

New animal drugs are approved for specific intended uses (indications). To get a drug approved for a new indication, a sponsor submits a new animal drug application (NADA). The application may be original or a supplement to an existing NADA. The following list outlines the types of information submitted to support an NADA.

1) Effectiveness
2) Safety to the target species
5) Chemistry, manufacturing, and controls
6) Environmental Assessment

3) Human food safety (food-producing animal species)
4) Labeling
7) Freedom of Information (FOI) Summary

The effectiveness section of an application may include data from dose titration or other dose determination, dose confirmation, and field studies. The target animal safety section may include studies which identify the toxic syndrome(s) associated with the drug and the margin of safety of use of the product in the treated animal. The human food safety section may include short and long term toxicology studies, total residue and metabolism studies, analytical method validation studies, and tissue residue depletion studies. The chemistry, manufacturing, and controls section includes information which must be supplied by the manufacturer regarding the manufacture of the product. Labeling must be provided by the NADA sponsor. These types of data are supplied to meet requirements set forth in the Federal Food, Drug, and Cosmetic Act (FFD&CA).

Environmental information is submitted to support FDA's need to comply with the National Environmental Policy Act (NEPA). Before approving a new animal drug, the agency must consider potential effects on the environment. In many cases, for a minor use, a categorical exclusion from the need to provide an environmental assessment (EA) will be granted. In other cases, some type of EA will be necessary to support a "finding of no significant impact" (FONSI). The environmental assessment (EA) may include information on the introduction of the drug into the environment through manufacture, use, and disposal, the fate of the drug in the environment, and the effects of the drug in the environment.

The Freedom of Information summary describes the studies which serve as the basis for the drug approval. This summary, along with the EA, must be made available to the public upon approval of the drug. The FOI Summary is the means whereby the agency complies with the Freedom of Information Act (FOIA).

Data needed to support an NADA are collected during an investigational stage, before a new animal drug application is submitted. Studies are conducted at this stage under an investigational new animal drug (INAD) exemption. All correspondence with the FDA's Center for Veterinary Medicine (CVM) regarding the drug is maintained in an INAD file. Although not required, sponsors usually submit study protocols for review before beginning studies to make sure that CVM agrees that study designs are appropriate to obtain the required information.

We strongly recommended that sponsors contact CVM early in the process to plan the development of their NADA. Decisions on the type and number of studies to be conducted and on the designs of those studies can be made in cooperation, and should greatly facilitate the entire process. Such product development planning also puts the sponsor in direct contact with the people at CVM responsible for reviewing each of the technical sections.

IV. MINOR USE APPROVAL PROCESS PROVISIONS--DATA EXTRAPOLATION

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In recognition of the scarcity of approved drugs for minor uses and the lack of resources available for minor use drug research, CVM has included special provisions in this guidance document to encourage and facilitate minor use animal drug approvals. These include increased flexibility and interspecies data extrapolation, which can drastically minimize the amount of new research, expense, and difficulty involved in achieving approval of a minor use new animal drug. The attached species-specific sections of this guidance document suggest ways to fulfill data requirements through use of data extrapolation.

CVM allows interspecies data extrapolation to support minor use applications whenever scientifically justifiable. Minor use applications often derive the greatest benefit from interspecies extrapolation when the drug is already approved for use in a major species and such data already exist in the approved major species application(s). This is especially true for food-producing species; if the drug is approved for use in a related food species, data extrapolation may be utilized in place of some expensive human food safety studies.

It is important to note, however, that minor use applicants who do not have access to proprietary data for a major species must first obtain written permission from the owner of that data to allow CVM to refer to the data on behalf of the minor use applicant.

V. RELATION BETWEEN NADAS AND OTHER FILES

The lack of financial incentive for a pharmaceutical firm to conduct studies needed for a minor use drug approval may lead to the funding, conduct, and submission of effectiveness and safety studies by parties other than a potential NADA sponsor. These studies may be submitted to public master files (PMFs), or, occasionally, to investigational new animal drug (INAD) files or veterinary master files (VMFs).

Once these studies are accepted by CVM as adequate to support an approval, an NADA sponsor may utilize these data by reference to support a minor use NADA (or supplemental NADA) if one of the following conditions has been met:

1) the availability of the data in a PMF has been published in the Federal Register, or

2) the sponsor of a veterinary master file or INAD has provided authorization for CVM to refer to the data on behalf of the NADA sponsor.

VI. WORKING WITH CVM

CVM recognizes that potential participants in the minor use approval process may not have regulatory experience and many need additional guidance. CVM recommends that interested parties initiate contact with CVM early in the process. A meeting or phone conference with CVM to discuss a research plan for the drug is often useful. If needed, CVM can also explain regulatory requirements applicable to investigational use of the drug. Once a plan is developed, CVM strongly suggests that the petitioner submit protocols for CVM's review before initiating the studies. CVM may also provide the petitioner with guidance on compilation of data into an appropriate format for submission.

VII. ASSISTANCE

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If a specific animal or drug indication is not addressed in this document, or if you need additional information, please contact one of the individuals listed below.

General questions:
FDA Liaison to the NRSP-7 Minor Use Animal Drug Program, 301-827-7581

Food/semi-domestic species:
Director, Division of Therapeutic Drugs For Food Animals, 301-827-7580

Non-food species and Wildlife/Exotic Species:
Director, Division of Therapeutic Drugs for Non-Food Animals, 301-827-7543

Production Drugs:
Director, Division of Production Drugs For Food Animals, 301-827-0219

VIII. POLICY ON ANIMAL TESTING

It is the position of the Center for Veterinary Medicine that animal testing should derive the maximum amount of useful scientific information using the minimum number of animals necessary. Consideration should be given to the use of accepted alternative methods to whole animal testing.

Attempts should be made to eliminate or minimize the degree and duration of suffering in the animals that are used. Pain-relieving medication, including anesthetics, should be considered and employed when such drugs will not interfere with the nature and purpose of the testing.

Euthanasia of moribund animals should be considered and employed when the procedure will not interfere with the nature and purpose of the testing. The euthanasia procedure employed should comply with the recommendations of the 1993 Report of the American Veterinary Medical Association (AVMA) Panel on Euthanasia (Journal of the American Veterinary Medical Association, 1993, Vol. 202, No. 2, pp. 229-249).

IX. WILDLIFE AND EXOTIC SPECIES

FDA differentiates wildlife and exotic animals from minor species. "Wildlife" species are those which live in an unconfined free-range environment, are usually under the jurisdiction of a local, state, or federal government, and usually are limited in number. These species may be covered by hunting statutes but they are not routinely farm-or ranch-raised for slaughter for human food.

"Exotic" species are those mammalian or avian species which are rare, not indigenous to the United States, and/or which are confined for educational, reproductive, or aesthetic purposes. Such species include those maintained in zoological parks and private collections.

Contact the Division of Drugs for Non-food Animals (301) 827-7543 for guidance regarding approval of drugs for use in wildlife and exotic animals.

X. DEFINITIONS

The following terms are used throughout this document. While more than one definition may be possible for some terms, the definitions provided are those used by the Center.

ADI - Acceptable Daily Intake; a value calculated for a new animal drug based on the no observable effect level (NOEL) obtained in the human food safety toxicology studies in combination with an appropriate safety factor

Categorical Exclusion - Exclusion from the requirement to prepare an environmental assessment

CFR - Code of Federal Regulations

Dose Confirmation Study - *In vivo* study to confirm the effectiveness of a selected drug dose; may be conducted in the laboratory or in the field

Dose Determination Study - Study used to select an appropriate dose or dose range

Environmental Assessment - Public document that describes evidence and analysis that a federal agency used to determine whether a finding of no significant impact is appropriate or if an environmental impact statement is required

FDA/CVM - U.S. Food and Drug Administration, Center for Veterinary Medicine

Federal Register - Official federal publication containing information such as proposed regulations, notices of public meetings, etc.

Field Trial - *in vivo,* non-laboratory study to determine effectiveness and safety of a product under actual use conditions

GLPs - Good Laboratory Practice Regulations (described in 21 CFR 58), regulations which outline requirements for documentation, quality assurance, and data integrity for safety studies

INAD - Investigational New Animal Drug

INAD Exemption - Exemption which permits the otherwise illegal shipment in interstate commerce of an unapproved animal drug for investigational studies; contact CVM regarding information on how to establish an INAD exemption

INAD File - File which holds data under direct review and correspondence between CVM and sponsors of new animal drugs regarding investigational drug use, including study protocol design and studies submitted for review

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Marker Residue - The residue(s) serving as the analyte for the regulatory method; the ratio of marker residues to total residues is established so that the marker residue serves as an index of the total residues in that tissue

Major Species - Cattle, horses, swine, chickens, turkeys, dogs, and cats

Minor Species - Other than a major species, and distinguished from wildlife/exotic species

Minor Use - Any new animal drug use in a minor species OR a new animal drug use in any animal species for control of an infrequently occurring or geographically limited disease

NADA - New Animal Drug Application; application for approval of a specific drug product, so that the drug may be legally marketed; must be supported by, among other things, effectiveness, animal safety, human safety, and drug manufacturing data

NADA Sponsor - Entity that owns and is responsible for the contents of an NADA and is responsible for compliance with all post-approval requirements such as distribution, advertising, and reporting to FDA

NEPA - National Environmental Policy Act; national charter for protection of the environment. Requires FDA to perform an environmental assessment of an action such as approving an NADA

NRSP-7 - NRSP-7 is the National Research Support Project Number 7; a USDA program promoting minor species drug studies

PMF - Public Master File; file which holds publicly generated or otherwise publicly available data (generally effectiveness, animal safety, residue chemistry, and environmental assessment) that may be referenced by an NADA sponsor to support an original or supplemental NADA approval

Regulatory Method - A method of analysis to monitor drug residues and to establish a withdrawal time in an edible tissue

Safe Concentration - The total residues of the drug (parent drug and all metabolites) that are permitted in edible products

Salt Water Species - For purposes of our discussions, those non-mammalian and non-avian species found in pure seawater or water of intermediate salinity (brackish water)

Semi-Domestic Species (ruminants and waterfowl) - Animals that are otherwise considered wild species that are also reared specifically for slaughter for human consumption

Supplemental NADA - Application for modification of an existing drug approval; this could include the addition of a label indication for a minor species, approval of use in another animal species, changes in conditions of use, or other changes to the original approval

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Target Animal Safety Study - *In vivo* study of the safety of a drug in the animal species for which drug approval is being sought

Target Tissue - May refer to that tissue where a drug is intended to have its effect, or to that edible tissue in which the regulatory method measures the concentration of the marker residue and in which the regulatory tolerance is established

Tolerance - The concentration of the marker residue, as measured by the regulatory method in the target tissue, which corresponds to the safe concentration for total residues of the drug in that tissue

Veal calves - Including , but not limited to, calves fewer than 150 pounds in weight or fewer than 3 weeks of age (bob veal) and calves fed exclusively a formula or all milk diet (formula fed or fancy veal calves)

Withdrawal Period for a drug - The interval between the time of last administration of the drug and the time when the animal can be safely slaughtered for food purposes. This is based on depletion of the marker residue in the target tissue to the tolerance.

XI. OTHER GUIDES

The following guides may be useful to use in conjunction with this document. They are available from CVM by writing to: Food and Drug Administration, Center for Veterinary Medicine, Communications Staff, 7519 Standish Place, HFV-12, Rockville, MD 20855. These documents are also available on the internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm in the on-line library under CVM Guidance documents.

#3 General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals (July 2006)

#33 Target Animal Safety Guidelines for New Animal Drugs (June 1989)

#40 Anticoccidial Guideline

#49 Guidance Document for Target Animal Safety and Drug Effectiveness Studies for Anti-Microbial Bovine Mastitis Products (Lactating and Non-lactating Cow Products) (April 1996)

#56 Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials (July 2001)

90 Guidance for Industry: Effectiveness of Anthelmintics: General Recommendations, Final Guidance, VICH GL7 (October, 2001)

96 Guidance for Industry: Efficacy Of Anthelmintics: Specific Recommendations for Ovines: VICH GL13, Final Guidance (March, 2001)

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97 Guidance for Industry: Efficacy Of Anthelmintics: Specific Recommendations for Caprines: VICH GL14, Final Guidance (March, 2001)

The following document is available from NRSP-7. To get a copy, contact the NRSP-7 Liaison at FDA/CVM/HFV-130, 7500 Standish Place, Rockville, MD 20855.

NRSP-7: Recommendations for Evaluating Analytical Methods (January 10, 1994)

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FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

Part 2A: Minor Use in a Major Species

A minor animal drug use is a drug use in a minor species, or a drug use in *any* animal species for control of an infrequently occurring or geographically limited disease. "Minor species" means animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats. Wildlife and exotic species not raised for food or fiber use are considered separately by CVM.

I. EFFECTIVENESS

Means for demonstrating effectiveness will be determined on a case-by-case basis. The petitioner is advised to *discuss the plan with CVM early in the development process*. In most cases, at least one dose determination study and some clinical field data will be needed. However, CVM will take into consideration the practical limitations of data collection for an infrequently occurring disease. Literature may be utilized to demonstrate part or all of the effectiveness claim.

II. TARGET ANIMAL SAFETY

A controlled study demonstrating the safety of the drug in the target species will be needed in most cases. The sponsor may choose to conduct a study with an untreated control group and a 10X group for 3X the maximum proposed duration of treatment. If no toxic effects are observed at this dose level, this single study will be sufficient to demonstrate the safety of the drug in the target animal, unless adverse effects are identified in the effectiveness studies.

Assuming the toxic syndrome has been defined, the need for a study conducted at 10X the maximum proposed label dose may be obviated. Standard study design incorporates an untreated control group and a group or groups receiving higher than the maximum proposed label dose for three times the maximum proposed duration. This is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. However, alternative study designs may be considered where appropriate.

III. HUMAN FOOD SAFETY

Before approving a new animal drug for minor use in a major species, the FDA must determine that people will not be exposed to unsafe residues in their food as a result of the approved use. The health risk associated with an animal drug residue equals the hazard (or inherent toxicity of the compound) times exposure. FDA regulates the public health risks associated with animal drug residues by assessing hazard and controlling exposure through the setting of tolerances and withdrawal periods. The risk standard that FDA applies, "reasonable certainty of no harm", ensures that drug residues in edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effects. CVM allows alternative ways to assess the human health risk for

minor use applicants. Please contact the Center to discuss the specific drug, indications, and conditions for minor use.

IV. ENVIRONMENTAL CONSIDERATIONS

The FDA is required under the National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Exemptions and applications to FDA for the investigation and approval of animal drugs must include sufficient environmental information to allow the Agency to assess whether environmental impacts may occur from the manufacture, use and disposal of the drugs.

FDA's regulations for implementing NEPA are contained in Title 21 of the Code of Federal Regulations (CFR), Part 25. These regulations were recently revised and published in the FEDERAL REGISTER on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA.

An EA is not required for most minor use applications. In most cases, a minor use application will be granted a categorical exclusion from the requirement to provide an EA. The regulations under which a categorical exclusion for a minor use can be granted are included in 21 CFR 25.33(d)(4), 25.33(c) and 25.33(d)(5). Section 25.33(d)(4) provides a categorical exclusion for drugs intended for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. FDA believes similar animal management practices generally include dosage, duration of use and concentration of the medication, as well as management style, such as feedlot, pasture or open pens. Although 25.33(d)(4) does not specifically include minor use, for environmental review, FDA will consider this to be equivalent to a minor species. In both cases, minor use and minor species, if the animal drug is already being used under similar animal management practices, then no significant differences from the major use approval are anticipated in the environmental introduction, fate and effects of the drug.

If for some reason an application cannot be excluded under 21 CFR 25.33(d)(4), then it may still be possible to obtain a categorical exclusion under 21 CFR 25.33(c) or 25.33(d)(5). Section 25.33(c) provides for a categorical exclusion for animal drug substances that occur naturally in the environment when the use does not alter significantly the concentration or distribution of the drug, its metabolites or degradation product(s) in the environment.

Section 25.33(d)(5) provides a categorical exclusion for drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species. Although not specifically covered under this regulation, feed additives issued under a veterinary

feed directive (VFD) would be considered equivalent to a prescription use. Because VFDs are issued under a veterinarian's order, they may also be categorically excluded.

For a categorical exclusion from the requirement to prepare an EA to be claimed, the sponsor submitting an exemption or application must state in the submission that the use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to the applicant's knowledge, no extraordinary circumstances exist. Section 21 CFR 25.15(d) can be consulted regarding this requirement. FDA will review the claim and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate that the proposed use may significantly affect the quality of the human environment.

Extraordinary circumstances are described in 21 CFR 25.21 and may include any use where the available data establish that there is potential for serious harm to the environment. This includes uses that adversely affect a species (flora or fauna), or the critical habitat of a species that is entitled to special protection under Federal law, such as the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna. Additional extraordinary circumstances are described in the regulations for implementing the provisions of NEPA contained in 40 CFR 1508.27. These may include uses that are controversial, that result in high uncertainty or unknown risks, that are precedent setting in nature, and uses that threaten a violation of Federal, state or local law or requirements imposed for the protection of the environment.

In some cases, an EA may be necessary. There are no specific guidelines available for the preparation and submission of an EA under the new regulations. Some information on the purpose and scope of an EA is contained in 21 CFR 25.40. In general, the content and format of an EA for veterinary drugs should consist of 11 parts. These are:

1. date, name, and address of the applicant

2. description of the proposed use (including descriptions of what the use is and any anticipated disposal)

3. identification of the substances that are subject of the use

4. description of the ecosystem at the site of introduction (including a conceptual model with assessment endpoints of the potential impacts at exposed sites in the environment)

5. an analysis section (including analysis of the fate and effects of the substances)

6. a risk characterization based upon the exposures and the hazards (derived from the conceptual model and analysis of the fate and effects information)

7. description of any alternatives to the proposed use (including mitigations)

8. preparer's names

9. signature block of responsible individual

10. references

11. appendices

The critical portions of the EA are the formulation of the conceptual model and the risk analysis that are conducted in sections 4, 5, 6, and 7. Data included in these sections may be obtained from the literature and from laboratory studies. The data should follow good laboratory practices or, in the case of literature, be of similar quality and well documented.

Guidance for performing an environmental risk analysis includes the following:

1. Baker, J.L., et al., editiors. 1994. Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. SETAC Press, Pensacola, FL.

2. Cockerham, Lorris and Shane, Barbara, editors. 1994. Basic Environmental Toxicology. CRC, Boca Raton, FL.

3. Environmental Protection Agency. Proposed Guidelines for Ecological Risk Assessment. the FEDERAL REGISTER of September 9, 1996 (61 FR 47552).

4. Suter, G.W. 1993. Ecological Risk Assessment. Lewis Publishers, Boca Raton, FL.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment. If significant effects requiring the preparation of an Environmental Impact Statement (EIS) are identified, FDA will prepare an EIS. If such effects are not identified, FDA will prepare a finding of no significant impact (FONSI).

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FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

Part 2B: Minor Avian Species (Gamebirds, Semi-Domestic Waterfowl, and Ratites)

I. EFFECTIVENESS

A. COCCIDIOSTATS

1. Introduction

Suggested below are some possible approaches, which may be used alone or in combination, to demonstrate the effectiveness of a minor avian coccidiostat.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

Studies should be conducted using the target animal for which the drug is intended. Each coccidial species for which a claim is being made should be confirmed by experimentation with that species. We recommend that a claim include the most pathogenic species occurring in the host minor species. Mixed infections are acceptable, but the predominant species should be documented.

a. Literature

We suggest that the petitioner begin with a literature review. The petitioner should search particularly for carefully controlled experiments using the candidate compound for the intended label claim. Should adequate documentation not exist in the literature, the effectiveness of the compound should be evaluated in a sequence of trials that includes dose confirmation.

b. Method of Infection

Natural infection is ideal; however, induced infection is acceptable for dose determination studies. The history and drug exposure of the isolate used for induced infection should be indicated, if known. Titration studies conducted to determine the number oocysts to be used in the induced infection should be included. Single cell isolation is not required. Virulence studies should be conducted to determine the appropriate number of oocysts to produce an acceptable infection that will allow the therapeutic effects of the compound to be clearly measured. The virulence of the parasite may be characterized by depression in rate of weight gain, total number of excreted fecal oocysts, and increased mortality.

c. Measures of Effectiveness

Parameters for evaluation of the drug effectiveness will depend on the coccidial species and disease being evaluated, as well as what is practicable as an objective measurement in a given species. Potential parameters include mortality due to the coccidial infection, number of excreted fecal oocysts, weight gain, lesion scores (a key should be provided), and/or dropping scores (a key should be provided). If total fecal oocyst numbers are used as one of the parameters to evaluate effectiveness, CVM prefers the measurement of total oocyst counts over a collection period of several days.

All mortality and morbidity, whether resulting from coccidiosis or other pathogens should be diagnosed. For coccidiosis, wet mount examinations should be made and coccidia identified.

d. Product Assays

Feed and/or water must be assayed for drug content. The results of assays should be provided with the final study report.

e. Medication & Induced Infection

The administration of medicated feed and oocysts may be initiated concurrently. However, if the drug exerts its activity during initial stages of the parasite life cycle, the drug may be administered no more than two days prior to the induced infection.

2. Dose Determination

CVM will not require dose determination studies for anticoccidial products. The sponsor may determine the dose without concurrence from CVM. The Center will not review protocols for dose determination studies. The trials conducted or supporting data for the chosen dose or dose range should be submitted as non-pivotal studies only, in accordance with the legal requirements for the sponsor to submit all data relevant to an NADA approval. 21 CFR 514.1(b)(8)(iv).

The non-pivotal studies may provide the rationale for the dose selection, although CVM will not comment on the adequacy of the studies. The sponsor should summarize the rationale for dose selection for inclusion in the FOI Summary.

3. Dose Confirmation

A minimum of two dose confirmation studies should be conducted including the most relevant parasites for the target bird. Dose confirmation trials should be conducted using induced infection. The sponsor should ensure that an adequate coccidiosis model is designed in the protocol which will allow a clear evaluation of the data to support effectiveness of the compound.

B. ANTIMICROBIALS

1. Introduction

Suggested below are some possible approaches, which may be used alone or in combination, to demonstrate the effectiveness of a minor avian antimicrobial. These approaches have been divided into two categories, based on the proposed claim for the minor avian species:

- antimicrobials which have not been approved in another avian species for a similar indication.
- antimicrobials which have been approved in another avian species for a similar indication

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

a. Literature

No matter which of these categories applies, CVM suggests that the petitioner begin with a literature search and review for studies relevant to the proposed claim. Reports of controlled experiments are most useful. CVM suggests that the petitioner discuss, early in the development process, the use of literature to meet some or all of the effectiveness requirements.

b. Other Considerations

Some factors that will influence the approach selected include the nature of the disease condition, the drug, the nature and availability of the animals, and other practical considerations.

2. Drug Which Has NOT Already Been Approved in Another Avian Species for the Same Claim

The following are possible options:

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Dose Determination Via PK/MIC

Dose may be determined by using pharmacokinetic and MIC data in association with a clinical confirmation study in naturally-infected animals.

c. Dose Determination in Animals With Induced Infections

Dose may be determined via a dose determination study in animals with induced infections (generally using 3 non-zero doses and a zero dose control group) with a clinical confirmation study in naturally-infected animals.

d. Dose Determination With Naturally-Infected Animals

Dose may be determined via field dose determination in naturally-infected animals using several doses including a negative control with a clinical confirmation study in naturally-infected animals. If the field dose determination study is large enough, a second confirmation study should not be necessary.

3. Drug Which Has Already Been Approved in Another Avian Species for the Same Claim

The following are possible options:

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Interspecies Data Extrapolation

Data may be extrapolated between a major and a minor species when a comparable host/disease relationship exists. A dose or dose range may be determined by allometric scaling or by direct extrapolation of the already approved dose in the comparable major species, with supportive serum concentration/bioavailability data and minimum inhibitory concentration (MIC) data, and without a clinical confirmation study.

A dose or dose range may also be determined by allometric scaling or by direct extrapolation of the already approved dose in the comparable major species, with a clinical confirmation study in naturally-infected animals.

Allometric scaling of dose may be done using the equation developed by Jim Riviere, D.V.M., Ph.D., at North Carolina State University:

$$d_m = d_M (Bw_M / Bw_m)^{0.25}$$

Where: d_m = Total dose in the minor species (in mg)

d_M = Total dose in the major species (in mg)

Bw_m = Average body weight in the minor species

Bw_M = Average body weight in the major species

Other equations for allometric scaling may be proposed as appropriate.

c. Dose Determination in Animals With Induced Infections

Dose may be determined via a dose determination study in animals with induced infections (generally using 3 non-zero doses and a zero dose control group) with a clinical confirmation study in naturally-infected animals.

d. Dose Determination With Naturally-Infected Animals

Dose may be determined via field dose determination in naturally-infected animals using several doses including a negative control with a clinical confirmation study in naturally-infected animals. If the field dose determination study is large enough, a second confirmation study should not be necessary.

4. Other

The development of alternative approaches to the demonstration of effectiveness should take into account the following questions to which CVM will be seeking answers.

How is effectiveness defined and what is an adequate level of effectiveness, as viewed by the veterinarian and/or producer?

Do the parameters and means of data evaluation used constitute an appropriate measure of effectiveness?

Is effectiveness related to the administered drug? Is there a dose-response relationship? Has the influence of other confounding factors on the study results been minimized?

What is an appropriate dose or dose range by the proposed route of administration, i.e., what dose or dose range achieves an adequate level of effectiveness?

What are the adverse effects of administration of the proposed dose or dose range? Adverse reactions observed in effectiveness studies should always be reported, and birds dying during effectiveness experiments should be necropsied to determine cause of death. See also the next section on target animal safety.

C. PRODUCTION DRUGS

Production drugs are those new animal drugs intended to affect the structure and/or function of an animal's body. Effects claimed for production drugs are normally related to improved animal performance, e.g., increased rate of weight gain, increased milk production, improved feed efficiency, increased carcass leanness, and improved reproductive performance. In the past, the minor species/minor use regulations were not interpreted to apply to production uses of new animal drugs, and the requirements for production uses of new animal drugs in minor species were the same as for major species. The Center will now consider production claims for minor species.

The requirements for approval of production claims for minor species will depend upon whether or not an approval in a similar major species already exists. All requests will be handled on a case-by-case basis and an attempt will be made to make use of all available data that may relate to the request. Thus, sponsors are encouraged to work closely with the Center and to share all available information early in the approval process. Sponsors should be aware that the ability to show effectiveness depends upon the relative size of the response of a drug as well as upon the variability associated with the response.

II. TARGET ANIMAL SAFETY

The type of target animal safety studies needed in the minor avian species will be determined on a case-by-case basis. Requirements will depend upon the available information on the drug's margin of safety in other species and the available information on the safety of the drug in the minor species. This information includes literature reports, adverse reactions reports, and safety information gleaned in effectiveness studies. For example, if a drug is approved and has a wide margin of safety in several other species, including chickens or turkeys, and no adverse effects were found in an effectiveness study and several literature reports, a target animal safety study in the minor avian species may not be required. Rather, the basis for demonstrating animal safety may include interspecies extrapolation and data in the minor species at the proposed use level.

In most cases, a basic target animal safety study will be needed. The target animal safety study may be combined with an effectiveness study, if desired, to minimize the total number of animals required. Such a combination study takes careful planning.

In order to establish safety of drugs intended for use in breeding animals, reproductive data is necessary. Otherwise, a label restriction to non-breeding animals will be required.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. A Target Animal Safety Guideline is available from CVM and provides additional study design information.

A. LITERATURE

CVM suggests that the petitioner search the literature for relevant reports and submit these as soon as possible. CVM will use these reports, in conjunction with its own review of adverse reactions reported to FDA, to make a preliminary determination of remaining animal safety requirements, if any. If adverse effects are discovered in the course of subsequent effectiveness studies, this determination will be reassessed in light of the additional data.

B. TOXICITY TEST

A single study may be conducted using the drug at 10X the recommended dose for 3X the recommended duration. This study may be used as a first step to identify the toxic effects prior to conducting a multiple dose Target Animal Safety study. If no toxic effects are observed at this dose level, this single study will be sufficient to demonstrate the safety of the drug in the target animal unless adverse effects are identified in the effectiveness studies.

C. MULTIPLE DOSE TARGET ANIMAL SAFETY STUDIES

Safety studies should be conducted in apparently normal birds and should demonstrate the margin of safety for the use of the product in the intended species. The treatment groups used in the safety study for each species should generally include a non-medicated control, the proposed use level, an estimated toxic level, and an intermediate level. This approach is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. The drug should be administered for 3 times the recommended maximum use duration.

III. HUMAN FOOD SAFETY

A. INTRODUCTION

Before approving a new animal drug for minor use, the FDA must determine that people will not be exposed to unsafe residues in their food as a result of the approved use. The health risk associated with an animal drug residue equals the hazard (or inherent toxicity) of the compound times the exposure. FDA regulates the public health risks associated with animal drug residues by assessing hazard and controlling exposure through the setting of tolerances and withdrawal periods. The risk standard that FDA applies, "reasonable certainty of no harm", ensures that drug residues in edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effects. In making that determination, FDA considers the safe concentration of total residues, the rate of residue depletion under the conditions of minor use, and the probability of a unique metabolite of toxicological concern occurring from the proposed minor use.

In many cases, the new animal drug proposed for minor use will already have a major use approval. The sponsor of the major use approval may authorize the FDA to access the human food safety data contained in the major use approval file on behalf of the minor use approval. Whenever scientifically and legally possible, the FDA intends to extrapolate results obtained from tests demonstrating human safety of major use drugs to support approvals of minor uses of these drugs. In general, data from the approved drug use in poultry (chickens or turkeys) will be used to extrapolate to the minor use avian species. However, it must be recognized that instances will arise when such data extrapolation is not justified. Acceptability of the data extrapolation from major to minor species will be determined on a case-by-case basis by considering a sponsored drug's currently approved use(s), proposed use(s), and all other available relevant information.

In a limited number of instances, an adequate assurance of safety can be achieved without major-use approval. The type and extent of toxicological data required to support the approval will be decided based on the particular use of the drug and the class of compounds to which the drug is related. Sources for these data may include the scientific literature, proprietary data, or original research. Examples of drug uses which may qualify for consideration of approval under this category are drugs for which sufficient toxicological data exist to establish a safe concentration but do not have a major use approval; and cases where drug administration may be limited to a very brief period at early life stages. Consideration will be given for production practices which incorporate a prolonged inherent withdrawal time for the drug. Examples include free-ranging gamebirds held for sport and egg dips for those species in which the egg is not considered edible. For the treatment of wildlife, please consult CVM for guidance.

B. FOOD SAFETY ASSESSMENT

1. Hazard Assessment (Toxicological Considerations)

The hazard associated with an animal drug product is assessed using a standard battery of toxicology tests. Each test is designed to examine a different toxicological endpoint. In determining the toxicological endpoints to be examined, the hazard assessment focuses on the effect of multiple exposures to low levels of the drug. The no effect dose from these toxicology studies is divided by a safety factor to determine an acceptable daily intake (ADI). The ADI represents the total drug residues, parent and all metabolites, that can be safely consumed daily throughout one's lifetime. A safe concentration is then calculated for each edible tissue. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. An Approved NADA Exists for the New Animal Drug.

The safe concentration established for the NADA approved for a major food animal species (or in a minor species where a complete human food safety data package was generated) will be applied, where appropriate, to the minor avian species food animal application.

b. An Approved NADA Does NOT Exist for the New Animal Drug.

If an approved NADA does not exist for the new animal drug, the petitioner will need to provide hazard assessment data appropriate to the assignment of an ADI. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

2. Controlling Exposure (Residue Chemistry Considerations)

Once the ADI and safe concentration have been determined, the risk to consumers is minimized by controlling exposure. The first step in controlling exposure is to determine when the concentration of drug in the edible tissues of the food animal reaches the calculated safe concentration. In some cases, a tolerance (i.e., a legal limit on the amount of drug residues permitted in edible tissue) and a withdrawal period (i.e., a drug-free period prior to slaughter) are established to ensure that consumers are not exposed to harmful drug residues.

The withdrawal period is the time period prior to slaughter during which a drug is not to be used. This period enables the animal's normal metabolism to detoxify the drug and facilitate the drug's depletion by natural excretion. In other cases, the compound's inherent toxicity and the residue levels are such that no tolerance or withdrawal period are necessary to ensure food safety.

The general residue chemistry data required to satisfy questions regarding the human food safety of drugs for use in minor avian species may be found in the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. Tolerance

The tolerance is defined as the concentration of the marker residue, as measured by the regulatory method in the target tissue, which corresponds to the safe concentration for total residues of the drug. The tolerance for monitoring drug residues in the edible tissues of the minor use species will be set, where appropriate, at the level previously established for the approved use in the major species. Sponsors of minor use drugs, however, may have access to the data supporting human safety of the approved major use drug only if the holder of the original approval(s) agrees to such access or if the data are publicly available. In the case where a tolerance has not been established in a major species, the FDA will establish a tolerance appropriate to the risk (hazard and exposure).

b. Metabolism

Drug metabolism in the minor species may, when scientifically justifiable, be examined on the basis of available data concerning the metabolism of the drug in the most closely related species for which the drug is approved or, preferably, in the minor species for which approval is being sought. If the data are not publicly available, the sponsors of minor use drugs may have access to the data supporting human safety of the approved major use drug only if the holders of the original major use approval(s) agree to such access.

If insufficient data exist to determine how an approved major use drug is metabolized in the minor species, the FDA will consider proposals which present known and theoretical metabolic reaction pathways that the drug (and/or drug class of which the parent is a member) could undergo. This information would be used to determine whether or not a unique metabolite(s) of toxicological concern might occur in the minor species.

If a unique metabolite of toxicological concern is suspected to result from the minor use, the alleviation of toxicological concern may begin with either synthesis and *in vitro* testing for mutagenicity or verification of the metabolite *in vivo* in the minor use species. If the findings of such studies demonstrate the presence of the metabolite and/or uphold the toxicological concern, additional testing requirements could be imposed.

c. Analytical Method

A method of analysis will usually be necessary to monitor drug residues and to establish a withdrawal time in edible tissues of the minor species. The most reliable approved method of analysis for drug residues in the major species may be used if the sponsor of the minor use application demonstrates that the method of analysis is reliable in the minor species.

In cases where a previously approved regulatory method is shown to be adequate to monitor the minor use of a sponsored compound, FDA will not require a method validation trial in government laboratories as a condition of minor use approval. See the 1994 guidance document, "NRSP-7: Recommendations for Evaluating Analytical Methods."

d. Withdrawal Period

In most cases, a residue depletion study will be necessary to determine an appropriate withdrawal period for use of a drug in a minor species. The withdrawal period is defined as the interval between the time of last administration of the drug and the time when the animal can be safely slaughtered for food purposes. This determination is based on depletion of the marker residue in the target tissue to the tolerance. Residues of the compound should be measured in the appropriate edible tissues. The edible tissues for minor avian species are discussed below. The FDA will determine the withdrawal period using a statistical tolerance limit procedure.

In any specific case, a residue depletion study may not be necessary if the sponsor can document that no residues of concern will be present in the edible tissues of treated animals when the tissues are made available for human consumption.

3. Edible Tissues in Minor Avian Species

The edible tissues in avian species are considered to be the muscle, liver, and skin with adhering fat. The eggs are also considered an edible tissue if the eggs of the minor avian species are to be available for human consumption.

4. Practical Zero Withdrawal Time for Minor Avian Species

A practical zero withdrawal time of 6 hours after the last treatment is assumed for minor avian species. Tissue residue data collected up to 6 hours after the last treatment with the drug may be used when attempting to determine whether the drug treatment requires a withdrawal time from the cessation of treatment to the time of slaughter for human consumption.

5. Experimental Design for Residue Depletion Studies

Residue depletion studies are conducted under normal use conditions in the field, in the target animal species, at the maximum expected dose for the maximum recommended duration of dosing or until the drug levels have reached a steady state in the edible tissue. Residue data for the drug in the edible tissue(s) are obtained as a function of time after the last treatment with the compound.

The study design should be such that the times chosen for sample collection are in the phase of the depletion curve closest to the established tolerance. The study should be designed to obtain the maximum number of valid non-zero measurements in order to be useful for statistical analysis. For most minor species residue depletion studies, 4 to 5 animals are sampled at 4 to 5 time periods. The animals should be represented by an equal number of males and females. However, it has been found that the use of additional animals (i.e., 8 animals per time period) frequently reduces the impact of animal to animal variability, resulting in a shorter calculated withdrawal time.

The withdrawal time, defined as that period from the last administration of the drug to the time at which the marker depletes to the tolerance, is calculated based on the upper bound of the 99th percentile tolerance limit with a 95% confidence level. The calculation is greatly affected by variability in the depletion data, and the use of fewer animals per time period will probably lead to an increased withdrawal time. See the guideline, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" for withdrawal time calculations and further information regarding assumptions of the statistical analysis of residue data.

IV. ENVIRONMENTAL CONSIDERATIONS

The FDA is required under National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Exemptions and applications to FDA for the investigation and approval of animal drugs must include sufficient environmental information to allow the Agency to assess whether environmental impacts may occur from the manufacture, use and disposal of the drugs.

FDA's regulations for implementing NEPA are contained in Title 21 of the Code of Federal Regulations (CFR), Part 25. These regulations were recently revised and published in the FEDERAL REGISTER on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA.

An EA is not required for most minor use applications. In most cases, an application for use in a minor species will be granted a categorical exclusion from the requirement to provide an EA. The regulations under which a categorical exclusion for a minor species can be granted are included in 21 CFR 25.33(d)(4), 25.33(c), and 25.33(d)(5). Section 25.33(d)(4) provides a categorical exclusion specifically for drugs intended for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. FDA believes similar animal management practices generally include dosage, duration of use and concentration of the medication, as well as management style, such as feedlot, pasture or open pens. A categorical exclusion can be applied to a minor species application when the animal drug is already being used under similar animal management practices, and no significant differences from the major use approval are anticipated in the environmental introduction, fate and effects of the drug.

If for some reason an application cannot be excluded under 21 CFR 25.33(d)(4), then it may still be possible to obtain a categorical exclusion under 21 CFR 25.33(c) or 25.33(d)(5). Section 25.33(c) provides a categorical exclusion for animal drug substances that occur

naturally in the environment when the use does not alter significantly the concentration or distribution of the drug, its metabolites or degradation product(s) in the environment.

Section 25.33(d)(5) provides a categorical exclusion for drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species. Although not specifically covered under this regulation, feed additives issued under a veterinary feed directive (VFD) would be considered equivalent to a prescription use. Because VFDs are issued under a veterinarian's order, they may also be categorically excluded.

For a categorical exclusion from the requirement to prepare an EA to be claimed, the sponsor submitting an exemption or application must state in the submission that the use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to the applicant's knowledge, no extraordinary circumstances exist. Section 21 CFR 25.15(d) can be consulted regarding this requirement. FDA will review the claim and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate that the proposed use may significantly affect the quality of the human environment.

> Extraordinary circumstances are described in 21 CFR 25.21 and may include any use where the available data establish that there is a potential for serious harm to the environment. This includes uses that adversely affect a species (flora or fauna), or the critical habitat of a species that is entitled to special protection under Federal law, such as, the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna. Additional extraordinary circumstances are described in the regulations for implementing the provisions of NEPA contained in 40 CFR 1508.27. These may include uses that are controversial, that result in high uncertainty or unknown risks, that are precedent setting in nature and uses that threaten a violation of Federal, state or local law or requirements imposed for the protection of the environment.

In some cases, an EA may be necessary. There are no specific guidelines available for the preparation and submission of EA under the new regulations. Some information on the purpose and scope of an EA is contained in 21 CFR 25.40. In general, the content and format of an EA for veterinary drugs should consist of 11 parts. These are:

1. date, name, and address of the applicant

2. description of the proposed use (including descriptions of what the use is and any anticipated disposal)

3. identification of the substances that are subject of the use

4. description of the ecosystem at the site of introduction (including a conceptual model with assessment endpoints of the potential impacts at exposed sites in the environment)

5. an analysis section (including analysis of the fate and effects of the substances)

6. a risk characterization based upon the exposures and the hazards (derived from the conceptual model and analysis of the fate and effects information)

7. description of any alternatives to the proposed use (including mitigations)

8. preparer's names

9. signature block of responsible individual

10. references

11. appendices

The critical portions of the EA are the formulation of the conceptual model and the risk analysis that are conducted in sections 4, 5, 6, and 7. Data included in these sections may be obtained from the literature and from laboratory studies. The data should follow good laboratory practices or, in the case of literature, be of similar quality and well documented.

Guidance for performing an environmental risk analysis includes the following:

1. Baker, J.L., et al., editiors. 1994. Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. SETAC Press, Pensacola, FL.

2. Cockerham, Lorris and Shane, Barbara, editors. 1994. Basic Environmental Toxicology. CRC, Boca Raton, FL.

3. Environmental Protection Agency. Proposed Guidelines for Ecological Risk Assessment. the FEDERAL REGISTER of September 9, 1996 (61 FR 47552).

4. Suter, G.W. 1993. Ecological Risk Assessment. Lewis Publishers, Boca Raton, FL.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment. If significant effects requiring the preparation of an Environmental Impact Statement (EIS) are identified, FDA will prepare an EIS. If such effects are not identified, FDA will prepare a finding of no significant impact (FONSI).

Contains Nonbinding Recommendations

FDA Approval of Animal Drugs for Minor Uses and for Minor Species

Part 2C: Domestic and Semi-Domestic Minor Ruminants

I. EFFECTIVENESS

A. ANTIPARASITICS

1. Introduction

CVM will not require dose determination studies for anthelmintic products. The sponsor may determine the dose without concurrence from CVM. Any dose determination studies which are conducted should be submitted as non-pivotal studies only, in accordance with the requirements for the sponsor to submit all data relevant to an NADA approval 21 CFR 514.1 (b)(8)(iv).

The non-pivotal studies may provide the rationale for the dose selection, although CVM will not comment on the adequacy of the studies. The sponsor should summarize the rationale for dose selection for inclusion in the FOI summary.

In cases where doses are extrapolated from major species, at least one adequate and well-controlled dose confirmation trial should be conducted in the minor ruminant species. This trial should consist of two groups of test animals. One group should serve as an unmedicated control group, while the remaining group should be administered the drug. Each group should contain 12 animals.

The sponsor should assure that an adequate model for demonstrating induced or natural infection with the parasite is described in the protocol. The number and genera of parasites required will be determined on a case by case basis. The trial should be conducted in North America.

Field trials for antiparasitic compounds may not be necessary for minor species, however, such trials may be included as supporting data after discussions with CVM.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

2. Method of Infection

The parasitic infection can be experimentally-induced or of natural origin. If induced infections are utilized, the source of the infective larvae should be documented. Parasitic infection in all test animals should be verified by fecal egg counts or other accepted methods prior to initiation of the trial. If the resulting data are acceptable and the effectiveness is similar to that demonstrated in cattle, the remaining parasitic genera for which the test product has approval

can be extrapolated for the minor ruminant species. This approach will be considered on a case-by-case basis.

3. Measures of Effectiveness

Geometric means will be calculated for both the treated and control groups. The sponsor should test for treatment differences using appropriate statistical methodology such as the Wilcoxon signed-rank test. The treated group must be significantly better than the control group ($p<0.05$, one-tailed test), before calculating percentage effectiveness. At least 90% effectiveness is necessary for each parasite claim in the pivotal trials supporting approval. Exception to the 90% effectiveness rule (example, for parasites for which there is no other treatment) should be discussed with CVM prior to conducting the studies supporting such exceptions.

The final results from the trial should be expressed as percent effectiveness using the following formula:

$$\frac{P_{CG} - P_{TG}}{P_{CG}} \times 100 = \% \text{ Effectiveness}$$

Where: P_{CG} = Mean number of parasites in the control group
P_{TG} = Mean number of parasites in the treated group

Field trials for anthelmintics conducted under actual use conditions will not be required for minor ruminant species. If a significant difference in toxicity is observed between the bovine species and the minor ruminant species, additional studies may be required. See also the section on Target Animal Safety.

Additional information concerning the development of a study protocol, suggested aspects for conducting the trial, and preferred necropsy procedures are listed in CVM's "Guideline for Evaluating the Effectiveness of Antiparasitic Compounds in Bovine."

B. ANTIMICROBIALS

1. Introduction

Suggested below are some possible approaches, which may be used alone or in combination, for demonstrating the effectiveness of a minor ruminant antimicrobial. These approaches have been divided into two categories, based on the proposed claim for the minor ruminant species:

- antimicrobials which have been approved in another ruminant species for a similar indication; and

- antimicrobials which have not been approved in another ruminant species for a similar indication.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

a. Literature

No matter which of these categories applies, CVM suggests that the petitioner begin with a literature search and review for studies relevant to the proposed claim. Reports of controlled experiments are most useful. CVM suggests that the petitioner discuss, early in the development process, the use of literature to meet some or all of the effectiveness requirements.

b. Other Considerations

Some factors that will influence the approach selected may include the nature of the disease condition, the drug, the nature and availability of the animals, and other practical considerations

2. Drug Which Has NOT Already Been Approved in Another Ruminant Species for the Same Claim

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Dose Determination Via PK/MIC

Dose may be determined by using pharmacokinetic and MIC data in association with a clinical confirmation study in naturally-infected animals.

c. Dose Determination in Animals With Induced Infections

Dose may be determined via a dose determination study in animals with induced infections (generally using 3 non-zero doses and a zero dose control group) with a clinical confirmation study in naturally-infected animals.

d. Dose Determination With Naturally-Infected Animals

Dose may be determined via field dose determination in naturally-infected animals using several non-zero doses with a clinical confirmation study in naturally-infected animals. If the field dose determination study is large enough, a second confirmation study should not be necessary.

3. Drug Which Has Already Been Approved in Another Ruminant Species for the Same Claim

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Interspecies Data Extrapolation

Data may be extrapolated between a major and a minor species when a comparable host/disease relationship exists. A dose or dose range may be determined by allometric scaling or by direct extrapolation of the already approved dose in the comparable major species with supportive serum concentration/bioavailability data and minimum inhibitory (MIC) data, and without a clinical confirmation study.

A dose or dose range may also be determined by allometric scaling or by direct extrapolation of the already approved dose in the comparable major species, with a clinical confirmation study in naturally-infected animals.

Allometric scaling of dose may be done using the equation developed by Jim Riviere, D.V.M., Ph.D., at North Carolina State University:

$$d_m = d_M (Bw_M / Bw_m)^{0.25}$$

Where: d_m = Total dose in the minor species

d_M = Total dose in the major species

Bw_m = Average body weight in the minor species

Bw_M = Average body weight in the major species

Other equations for allometric scaling may be proposed as appropriate.

c. Dose Determination in Animals With Induced Infections

Dose may be determined via a dose determination study in animals with induced infections (generally using 3 non-zero doses and a zero dose control group) with a clinical confirmation study in naturally-infected animals.

d. Dose Determination With Naturally-Infected Animals

Dose may be determined via field dose determination in naturally-infected animals using several non-zero doses with a clinical confirmation study in naturally-infected animals. If the field dose determination study is large enough, a second confirmation study should not be necessary.

4. Other

The development of alternative approaches to the demonstration of effectiveness should take into account the following questions to which CVM will be seeking answers.

How is effectiveness defined and what is an adequate level of effectiveness, as viewed by the veterinarian and/or producer?

Do the parameters and means of data evaluation used constitute an appropriate measure of effectiveness?

Is effectiveness related to the administered drug? Is there a dose-response relationship? Has the influence of other confounding factors on the study results been minimized?

What is an appropriate dose or dose range by the proposed route of administration, i.e., what dose or dose range achieves an adequate level of effectiveness?

What are the adverse effects of administration of the proposed dose or dose range? Adverse reactions observed in effectiveness studies should always be reported, and animals dying during effectiveness experiments should be necropsied to determine cause of death. See also the section on target animal safety.

C. ANTIMICROBIAL DRUGS FOR INTRAMAMMARY INFUSION IN GOATS AND SHEEP

1. Introduction

Suggested below are some possible approaches for demonstrating the effectiveness of intramammary antimicrobials for minor ruminants. These approaches have been divided into two categories, based on the proposed claim for the minor ruminant species:

- antimicrobials which have been approved in cattle for the same indication
- antimicrobials which have not been approved in cattle for the same indication.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. The CVM Mastitis guideline should be consulted for further study design suggestions.

a. Literature

No matter which of these categories applies, CVM suggests that the petitioner begin with a literature search and review for studies relevant to the proposed claim. Reports of controlled experiments are most useful. CVM suggests that the petitioner discuss, early in the development process, the use of literature to meet some or all of the effectiveness requirements.

b. Other Considerations

CVM is willing to consider alternative approaches. However, the utility of pharmacokinetic data to document the effectiveness of mastitis drug products has not yet been well defined.

2. Drug Which Has NOT Been Approved in Cattle for the Same Claim

Three intramammary infusions at 12-hour intervals are considered the maximum practical duration of administration. For dosage regimens of less than three doses at 12-hour intervals, the petitioner should document that the shorter regimen provides comparable effectiveness to a three dose, 12-hour regimen for mastitis therapy.

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Other Considerations

Dose may be determined via a dose determination study conducted in the minor species using a control and at least three non-zero drug levels and at least one controlled field trial conducted with the effective dosage regimen selected from the dose determination study. The infectious mastitis case may be characterized by signs including:

a) grossly abnormal milk and presence of flakes, clots, and/or discoloration;

b) evidence of inflammation with apparent clinical tissue changes, swelling, heat and/or pain in the affected quarters;

c) evidence of leukocytosis in milk;

d) isolation of pathogenic microorganism in pure culture from fresh plating of milk sample;

e) drop in milk production;

f) fever (especially in cases of peracute mastitis).

In addition, the MIC of the dairy pathogens in the minor species should be established using 30 to 50 isolates of each pathogen. Isolates should be collected from a variety of genera/species and serotypes. These data should be collected by more than one laboratory. No one laboratory should be responsible for a disproportionate number of claimed pathogen isolates.

3. Drug Which Has Already Been Approved in Cattle for the Same Claim

a. Literature

As noted in Section 1a above, literature may be used to meet some or all of the effectiveness requirements.

b. Interspecies Data Extrapolation

Data may be extrapolated between the major and minor species when a comparable host/disease relationship exists. Dose may be determined via direct extrapolation of the dosage regimen approved for cattle and at least one controlled field trial conducted in the minor species. The most prevalent minor species pathogen should be the primary pathogen in the clinical field trial, with a sufficient number of animals to provide sufficient confidence. The MIC of mastitis pathogens from the minor species should be comparable to that of the MIC of mastitis pathogens of cattle. Where the pathogen MIC data differ, more MIC data should be collected in the minor species sufficient to demonstrate that most of the population of that pathogen will respond to the drug. See also CVM's Mastitits Guideline.

D. PRODUCTION DRUGS

Production drugs are those new animal drugs intended to affect the structure and/or function of an animal's body. Effects claimed for production drugs are normally related to improved animal performance, e.g., increased rate of weight gain, increased milk production, improved feed efficiency, increased carcass leanness, and improved reproductive performance. In the past, the minor species/minor use regulations were not interpreted to apply to production uses of new animal drugs, and the requirements for production uses of new animal drugs in minor species were the same as for major species. The Center will now consider production claims for minor species.

The requirements for approval of production claims for minor species will depend upon whether or not an approval in a similar major species already exists. All requests will be handled on a case-by-case basis and an attempt will be made to make use of all available data that may relate to the request. Thus, sponsors are encouraged to work closely with the Center and to share all available information early in the approval process. Sponsors should be aware that the ability to show effectiveness depends upon the relative size of the response of a drug as well as upon the variability associated with the response.

II. TARGET ANIMAL SAFETY

The type of target animal safety studies needed in the minor ruminant species will be determined on a case-by-case basis. Requirements will depend upon the available information on the drug's margin of safety in other species and the available information on the safety of the drug in the minor species. This information includes literature reports, adverse reactions reports, and safety information gleaned in effectiveness studies. For example, if a drug is approved and has a wide margin of safety in several other species, including cattle, and no adverse effects were found in an effectiveness study and several literature reports, a target animal safety study in the minor ruminant species may not be required. Rather, the basis for demonstrating animal safety may include interspecies extrapolation and data in the minor species at the proposed use level.

In most cases, a basic target animal safety study will be needed. The target animal safety study may be combined with an effectiveness study, if desired, to minimize the total number of animals required. Such a combination study takes careful planning.

Contains Nonbinding Recommendations

In order to establish safety of drugs intended for use in breeding animals, reproductive data are necessary. Otherwise, a label restriction to non-breeding animals will be required.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. The CVM Mastitis guideline should be consulted for further study design suggestions.

A. LITERATURE

CVM suggests that the petitioner search the literature for relevant reports and submit these as soon as possible. CVM will use these reports, in conjunction with its own review of adverse reactions reported to FDA, to make a preliminary determination of remaining animal safety requirements, if any. If adverse effects are discovered in the course of subsequent effectiveness studies, this determination will be reassessed in light of the additional data.

B. TOXICITY TEST

A single study may be conducted using the drug at 10X the recommended dose for 3X the recommended duration. This study may be used as a first step to identify the toxic effects prior to conducting a multiple dose Target Animal Safety study. If no toxic effects are observed at this dose level, this single study will be sufficient to demonstrate the safety of the drug in the target animal, unless adverse effects are identified in the effectiveness studies.

C. MULTIPLE DOSE TARGET ANIMAL SAFETY STUDIES

Safety studies should be conducted in apparently normal animals and should demonstrate the margin of safety for the use of the product in the intended species. The treatment groups used in the safety study should generally include a non-medicated control, the proposed use level, an estimated toxic level, and an intermediate level. This approach is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. The drug should be administered for 3 times the recommended maximum use duration.

D. IRRITATION STUDY

An irritation study may be required for antimicrobial drugs for mammary infusion in goats. CVM suggests that six normal lactating goats, a majority of which are first kid does, be selected for this study. The age, stage of lactation, milk production, and California Mastitis Test (CMT) observation should be recorded at the start of the study. Parameters to be measured twice daily for each half of the udder include palpation results and quantitative somatic cell counts (QSCCs). Data sheets should include a copy of the laboratory's analyses (QSCCs) with the technician's signature for each doe. Duplicate milk samples for QSCCs are recommended.

The pre-treatment period includes four milkings (two days) before the drug is administered. This period is the time span when baseline observations are made to establish normalcy in all test animals. During this period, it is recommended that duplicate milk samples for culturing be taken from each half. This optional procedure

helps identify a pathogenic organism as a possible cause of QSCCs. The treatment period begins at the fifth milking after the initiation of the test period. The labeled dose schedule should be followed, and both halves should be treated. The post-treatment period lasts for twelve milkings (six days) after the labeled milk discard time.

III. HUMAN FOOD SAFETY

A. INTRODUCTION

Before approving a new animal drug for minor use, the FDA must determine that people will not be exposed to unsafe residues in their food as a result of the approved use. The health risk associated with an animal drug residue equals the hazard (or inherent toxicity of the compound) times the exposure. FDA regulates the public health risks associated with animal drug residues by assessing hazard and controlling exposure through the setting of tolerances and withdrawal periods. The risk standard that FDA applies, "reasonable certainty of no harm", ensures that drug residues in edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effects. In making that determination, FDA considers the safe concentration of total residues, the rate of residue depletion under the conditions of minor use, and the probability of a unique metabolite of toxicological concern occurring from the proposed minor use.

In many cases, the new animal drug proposed for minor use will already have a major use approval. The sponsor of the major use approval may authorize the FDA to access the human food safety data contained in the major use approval file on behalf of the minor use approval. Whenever scientifically and legally possible, the FDA intends to extrapolate results obtained from tests demonstrating human safety of major use drugs to support approvals of minor uses of these drugs. In general, data from the approved drug use in cattle will be used to extrapolate to the minor use ruminant species. However, it must be recognized that instances will arise when such data extrapolation is not justified. Acceptability of the data extrapolation from major to minor species will be determined on a case-by-case basis by considering a sponsored drug's currently approved use(s), proposed use(s), and all other available relevant information.

In a limited number of instances, an adequate assurance of safety can be achieved without major-use approval. The type and extent of toxicological data required to support the approval will be decided based on the particular use of the drug and the class of compounds to which the drug is related. Sources for these data may include the scientific literature, proprietary data, or original research. Examples of drug uses which may qualify for consideration of approval under this category are drugs for which sufficient toxicological data exist to establish a safe concentration but do not have a major use approval; and cases where drug administration may be limited to a very brief period at early life stages. Consideration will be given for production practices which incorporate a prolonged inherent withdrawal time for the drug.

B. FOOD SAFETY ASSESSMENT

1. Hazard Assessment (Toxicological Considerations)

The hazard associated with an animal drug product is assessed using a standard battery of toxicology tests. Each test is designed to examine a different toxicological endpoint. In determining the toxicological endpoints to be examined, the hazard assessment focuses on the effect of multiple exposures to low levels of the drug.

The no effect dose from these toxicology studies is divided by a safety factor to determine an acceptable daily intake (ADI). The ADI represents the total drug residues, parent and all metabolites, that can be safely consumed daily throughout one's lifetime. A safe concentration is then calculated for each edible tissue. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. An Approved NADA Exists for the New Animal Drug.

   The safe concentration established for the NADA approved for a major food animal species (or in a minor species where a complete human food safety data package was generated) will be applied, where appropriate, to the minor ruminant species food animal application.

b. An Approved NADA Does NOT Exist for the New Animal Drug.

   If an approved NADA does not exist for the new animal drug, the petitioner will need to provide hazard assessment data appropriate to the assignment of an ADI. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

2. Controlling Exposure (Residue Chemistry Considerations)

Once the ADI and safe concentration have been determined, the risk to consumers is minimized by controlling exposure. The first step in controlling exposure is to determine when the concentration of drug in the edible tissues of the food animal reaches the calculated safe concentration. In some cases, a tolerance (i.e., a legal limit on the amount of drug residues permitted in edible tissue) and a withdrawal period (i.e., a drug-free period prior to slaughter) are established to ensure that consumers are not exposed to harmful drug residues.

The withdrawal period is the time period prior to slaughter during which a drug is not to be used. This period enables the animal's normal metabolism to detoxify the drug and facilitate the drug's depletion by natural excretion. In other cases, the compound's inherent toxicity and the residue levels are such that no tolerance or withdrawal period are necessary to ensure food safety.

The general residue chemistry data required to satisfy questions regarding the human food safety of drugs for use in minor ruminant species may be found in the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. Tolerance

The tolerance is defined as the concentration of the marker residue, as measured by the regulatory method in the target tissue, which corresponds to the safe concentration for total residues of the drug. The tolerance for monitoring drug residues in the edible tissues of the minor use species will be set, where appropriate, at the level previously established for the approved use in the major species. Sponsors of minor use drugs, however, may have access to the data supporting human safety of the approved major use drug only if the holder of the original approval(s) agrees or if the data are publicly available. In the case where a tolerance has not been established in a major species, the FDA will establish a tolerance appropriate to the risk (hazard and exposure).

b. Metabolism

Drug metabolism in the minor species may, when scientifically justifiable, be examined on the basis of available data concerning the metabolism of the drug in the most closely related species for which the drug is approved or, preferably, in the minor species for which approval is being sought. If the data are not publicly available, the sponsors of minor use drugs may have access to the data supporting human safety of the approved major use drug only if the holders of the original major use approval(s) agree to such access.

If insufficient data exist to determine how an approved major use drug is metabolized in the minor species, the FDA would consider proposals which present known and theoretical metabolic reaction pathways that the drug (and/or drug class of which the parent is a member) could undergo. This information would be used to determine whether or not a unique metabolite(s) of toxicological concern might occur in the minor species.

If a unique metabolite of toxicological concern is suspected to result from the minor use, the alleviation of toxicological concern may begin with either synthesis and *in vitro* testing for mutagenicity or verification of the metabolite *in vivo* in the minor use species. If the findings of such studies demonstrate the presence of the metabolite and/or uphold the toxicological concern, additional testing requirements could be imposed.

c. Analytical Method

A method of analysis will usually be necessary to monitor drug residues and to establish a withdrawal time in edible tissues of the minor species. The most reliable approved method of analysis for drug residues in the major species may be used if the sponsor of the minor use application demonstrates that the method of analysis is reliable in the minor species.

In cases where a previously approved regulatory method is shown to be adequate to monitor the minor use of a sponsored compound, FDA will not require a method validation trial in government laboratories as a condition of minor use approval. See the guidance document, "NRSP-7: Recommendations for Evaluating Analytical Methods."

d. Withdrawal Period

In most cases, a residue depletion study will be necessary to determine an appropriate withdrawal period for use of a drug in a minor species. The withdrawal period is defined as the interval between the time of last administration of the drug and the time when the animal can be safely slaughtered for food purposes. This determination is based on depletion of the marker residue in the target tissue to the tolerance. Residues of the compound should be measured in the appropriate edible tissues. The edible tissues for minor ruminant species are discussed below. The FDA will determine the withdrawal period using a statistical tolerance limit procedure.

In any specific case, a residue depletion study may not be necessary if the sponsor can document that no residues of concern will be present in the edible tissues of treated animals when the tissues are made available for human consumption.

3. Edible Tissues in Minor Ruminant Species

   The edible tissues in ruminant species are considered to be the muscle, liver, kidney, and fat. The milk is also considered an edible tissue if the milk of the minor ruminant species is to be available for human consumption.

4. Practical Zero Withdrawal Time for Minor Ruminant Species

   A practical zero withdrawal time of 8 to 12 hours after the last treatment is assumed for minor ruminant species. Tissue residue data collected up to 8 to 12 hours after the last treatment with the drug may be used when attempting to determine whether the drug treatment requires a withdrawal time from the cessation of treatment to the time of slaughter for human consumption .

5. Experimental Design for Residue Depletion Studies

   Residue depletion studies are conducted under normal use conditions in the field, in the target animal species, at the maximum expected dose for the maximum recommended duration of dosing or until the drug levels have reached a steady state in the edible tissue. Residue data for the drug in the edible tissue(s) is obtained as a function of time after the last treatment with the compound.

   The study design should be such that the times chosen for sample collection are in the phase of the depletion curve closest to the established tolerance. The study should be designed to obtain the maximum number of valid non-zero measurements in order to be useful for statistical analysis. For most minor species residue depletion studies 4 to 5 animals are sampled at 4 to 5 time periods.

   The animals should be represented by an equal number of males and females. However, it has been found that the use of additional animals (i.e., 8 animals per time period) frequently reduces the impact of animal to animal variability, resulting in a shorter calculated withdrawal time.

   The withdrawal time, defined as that period from the last administration of the drug to the time at which the marker residue depletes to the tolerance, is calculated based on the upper bound of the 99th percentile tolerance limit with a 95% confidence

level. The calculation is greatly affected by variability in the depletion data, and the use of fewer animals per time period will probably lead to an increased withdrawal time. See the guideline, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" for withdrawal time calculations and further information regarding assumptions of the statistical analysis of residue data.

IV. ENVIRONMENTAL CONSIDERATIONS

The FDA is required under National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Exemptions and applications to FDA for the investigation and approval of animal drugs must include sufficient environmental information to allow the Agency to assess whether environmental impacts may occur from the manufacture, use and disposal of the drugs.

FDA's regulations for implementing NEPA are contained in Title 21 of the Code of Federal Regulations (CFR), Part 25. These regulations were recently revised and published in the FEDERAL REGISTER on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA.

An EA is not required for most minor use applications. In most cases, an application for use in a minor species will be granted a categorical exclusion from the requirement to provide an EA. The regulations under which a categorical exclusion for a minor species can be granted are included in 21 CFR 25.33(d)(4), 25.33(c), and 25.33(d)(5). Section 25.33(d)(4) provides a categorical exclusion specifically for drugs intended for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. FDA believes similar animal management practices generally include dosage, duration of use and concentration of the medication, as well as management style, such as feedlot, pasture or open pens. A categorical exclusion can be applied to a minor species application when the animal drug is already being used under similar animal management practices, and no significant differences from the major use approval are anticipated in the environmental introduction, fate and effects of the drug.

If for some reason an application cannot be excluded under 21 CFR 25.33(d)(4), then it may still be possible to obtain a categorical exclusion under 21 CFR 25.33(c) or 25.33(d)(5). Section 25.33(c) provides a categorical exclusion for animal drug substances that occur naturally in the environment when the use does not alter significantly the concentration or distribution of the drug, its metabolites or degradation product(s) in the environment.

Section 25.33(d)(5) provides a categorical exclusion for drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species. Although not specifically covered under this regulation, feed additives issued under a veterinary feed

directive (VFD) would be considered equivalent to a prescription use. Because VFDs are issued under a veterinarian's order, they may also be categorically excluded.

For a categorical exclusion from the requirement to prepare an EA to be claimed, the sponsor submitting an exemption or application must state in the submission that the use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to the applicant's knowledge, no extraordinary circumstances exist. Section 21 CFR 25.15(d) can be consulted regarding this requirement. FDA will review the claim and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate that the proposed use may significantly affect the quality of the human environment.

> Extraordinary circumstances are described in 21 CFR 25.21 and may include any use where the available data establish that there is a potential for serious harm to the environment. This includes uses that adversely affect a species (flora or fauna), or the critical habitat of a species that is entitled to special protection under Federal law, such as, the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna. Additional extraordinary circumstances are described in the regulations for implementing the provisions of NEPA contained in 40 CFR 1508.27. These may include uses that are controversial, that result in high uncertainty or unknown risks, that are precedent setting in nature and uses that threaten a violation of Federal, state or local law or requirements imposed for the protection of the environment.

In some cases, an EA may be necessary. There are no specific guidelines available for the preparation and submission of EA under the new regulations. Some information on the purpose and scope of an EA is contained in 21 CFR 25.40. In general, the content and format of an EA for veterinary drugs should consist of 11 parts. These are:

1. date, name, and address of the applicant

2. description of the proposed use (including descriptions of what the use is and any anticipated disposal)

3. identification of the substances that are subject of the use

4. description of the ecosystem at the site of introduction (including a conceptual model with assessment endpoints of the potential impacts at exposed sites in the environment)

5. an analysis section (including analysis of the fate and effects of the substances)

6. a risk characterization based upon the exposures and the hazards (derived from the conceptual model and analysis of the fate and effects information)

7. description of any alternatives to the proposed use (including mitigations)

8. preparer's names

9. signature block of responsible individual

10. references

11. appendices

The critical portions of the EA are the formulation of the conceptual model and the risk analysis that are conducted in sections 4, 5, 6, and 7. Data included in these sections may be obtained from the literature and from laboratory studies. The data should follow good laboratory practices or, in the case of literature, be of similar quality and well documented.

Guidance for performing an environmental risk analysis includes the following:

1. Baker, J.L., et al., editiors. 1994. Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. SETAC Press, Pensacola, FL.

2. Cockerham, Lorris and Shane, Barbara, editors. 1994. Basic Environmental Toxicology. CRC, Boca Raton, FL.

3. Environmental Protection Agency. Proposed Guidelines for Ecological Risk Assessment. the FEDERAL REGISTER of September 9, 1996 (61 FR 47552).

4. Suter, G.W. 1993. Ecological Risk Assessment. Lewis Publishers, Boca Raton, FL.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment. If significant effects requiring the preparation of an Environmental Impact Statement (EIS) are identified, FDA will prepare an EIS. If such effects are not identified, FDA will prepare a finding of no significant impact (FONSI).

FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

Part 2D: Rabbits

I. EFFECTIVENESS

A. ANTICOCCIDIALS

1. Introduction

Suggested below are some possible approaches, which may be used alone or in combination, to demonstrate the effectiveness of a coccidiostat for use in rabbits.

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

Each coccidial species for which a claim is being made should be confirmed by induced infection. We recommend that a sponsor file a claim including the most pathogenic parasite: *Eimeria stiedae,* infecting the bile duct epithelium of rabbits (members of the genera *Oryctolagus, Sylvilagus,* and *Lepus*). Mixed infections are acceptable and encouraged.

a. Literature

We suggest that the petitioner begin with a literature review. The petitioner should search particularly for controlled experiments using the candidate compound for the intended label claim. Should adequate studies not exist in the literature, the effectiveness may be evaluated in a sequence of trials that includes dose confirmation.

b. Method of Infection

The sponsor should ensure that an adequate model is included in the protocol which will allow a clear interpretation of the drug's effectiveness (number of oocysts, history of *E. stiedae* and virulence test).

Natural infection is ideal; however, induced infection is acceptable for dose determination studies. The history and drug exposure of the isolate used for induced infection should be indicated, if known. Titration studies conducted to determine the number oocysts to be used in the induced infection should be included. Single cell isolation is not required.

Virulence studies should be conducted to determine the appropriate number of oocysts to produce an acceptable infection that will allow the therapeutic effects of the compound to be clearly measured. The virulence of the parasite may be characterized by depression in rate of weight gain, total number of excreted fecal oocysts, and increased mortality.

c. Measures of Effectiveness

E. stiedae infection produces enlargement of the liver and yellowish-white lesions of varying size. Intestinal coccidial lesions are seen in the small and large intestines. For *E. stiedae,* it is recommended that liver weight be used as an index to liver enlargement (ratio liver weight/body weight) and liver lesions (with key provided). Morbidity, mortality, and weekly weight gain should be measured. Wet mounts should be used for coccidia identification. All mortality and morbidity, whether resulting from coccidiosis or other pathogens should be diagnosed.

Parameters for evaluation of the drug effectiveness will depend on the coccidial species and disease being evaluated, as well as what is practicable as an objective measurement. Potential parameters include mortality due to the coccidial infection, number of excreted fecal oocysts, weight gain, lesion scores (a key should be provided), and/or dropping scores (a key should be provided). If total fecal oocyst numbers are used as one of the parameters to evaluate effectiveness, CVM prefers the measurement of total oocyst counts over a collection period of several days.

d. Product Assays

Feed and/or water must be assayed for drug content. The results of assays should be provided with the final study report.

e. Drug Administration

All rabbits in the medicated group should be started on the drug two to seven days prior to oocysts challenge.

2. Dose Determination

The sponsor may determine the dose or dose range without concurrence from CVM. The Center will not review protocols for dose determination studies. The trials conducted or supporting data for the chosen dose or range should be submitted as non-pivotal studies only, in accordance with the legal requirement that the sponsor submit all data relevant to an NADA, 21 CFR 514.1(b)(8)(iv).

The non-pivotal studies may provide the rationale for dose selection, though CVM will not comment on the adequacy of the studies. The sponsor should summarize the rationale for dose selection for inclusion in the FOI Summary.

3. Dose Confirmation

In dose confirmation trials, rabbits may be infected using feed, water, litter, or seeder animals. A minimum of two experimental groups should be represented:

- infected non-medicated
- infected medicated

Additional field trials may be conducted, if desired, to better evaluate the performance of the compound under natural exposure to the parasite and commercial use conditions.

B. ANTIMICROBIALS

1. Introduction

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

a. Literature

We suggest that the petitioner begin with a literature review. The petitioner should search particularly for carefully controlled experiments against diseases for the intended label claim. Next, the petitioner should check the published literature for data of the drug use which could support the claim being made. Also, the petitioner should submit reprints or photostats as part of the new animal drug application. Literature can be used to satisfy some or all of the effectiveness requirements, which will be established on a case-by-case basis. We suggest that the petitioner discuss with the Agency the use of literature to meet requirements early in the development process.

Pharmacokinetic and metabolic data cannot be extrapolated from any of the major species to rabbits because there is no major species comparable to rabbits.

The following discussion applies if the literature does not meet all requirements for demonstrating drug effectiveness.

b. Other Considerations

Pharmacokinetic and MIC data may be used to determine dose. Pharmacokinetic data collected from rabbits during human drug studies may be appropriate. Alternatively, a uniform infection that is experimentally-induced in clinical studies with a control and two or three non-zero drug levels may be used to determine the dose.

The dose or dosages should then be confirmed with at least one adequate and well controlled field trial. Clinical field trials should include an infected unmedicated control group or an infected acceptable positive control group and an infected medicated group. The intent of the field trial is to confirm the minimum dose under use conditions. CVM recommends pre-selection (blocking) rather than random selection in field trials.

With regard to the environmental conditions, it is recommended that rabbits be individually caged and that environmental factors be kept similar in the field trial(s).

Appropriate parameters should be established for objectively evaluating field trial therapy. The cause of death should be determined by necropsy and reported for any animals dying during therapy. If animals die due to apparent drug related toxicity, an additional study should be conducted to meet target animal safety study requirements.

C. PRODUCTION DRUGS

Production drugs are those new animal drugs intended to affect the structure and/or function of an animal's body. Effects claimed for production drugs are normally related to improved animal performance, e.g., increased rate of weight gain, increased milk production, improved feed efficiency, increased carcass leanness, and improved reproductive performance. In the past, the minor species/minor use regulations were not interpreted to apply to production uses of new animal drugs, and the requirements

for production uses of new animal drugs in minor species were the same as for major species. The Center will now consider production claims for minor species.

The requirements for approval of production claims for minor species will depend upon whether or not an approval in a similar major species already exists. All requests will be handled on a case-by-case basis and an attempt will be made to make use of all available data that may relate to the request. Thus, sponsors are encouraged to work closely with the Center and to share all available information early in the approval process. Sponsors should be aware that the ability to show effectiveness depends upon the relative size of the response of a drug as well as upon the variability associated with the response.

II. TARGET ANIMAL SAFETY

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. A Target Animal Safety Guideline is available from CVM and provides additional study design information.

The need for target animal safety studies in rabbits will be determined on a case-by-case basis and will depend mostly upon:

a) available information on the drug's margin of safety in other species;

b) available information on the safety of the drug in rabbits (including literature reports, adverse reactions reports, and safety information gleaned in effectiveness studies).

Data originally generated to support human safety of a drug may also be relevant to safety of the drug in rabbits.

In order to establish safety of drugs intended for use in breeding animals, reproductive data is necessary. Otherwise a label restriction to non-breeding animals will be required.

In most cases, a basic target animal safety study will be needed. The study should include a placebo or untreated control group, and at least one other group dosed at a higher dose than the proposed dose. The target animal safety study may be combined with an effectiveness study, if desired, to minimize the total number of animals required. Such a combination study takes careful planning.

A. TOXICITY TEST

A single study may be conducted using the drug at 10X the recommended dose for 3X the recommended duration. This study may be used as a first step to identify the toxic effects prior to conducting a multiple dose Target Animal Safety study. If no toxic effects are observed at this dose level, this single study, will be sufficient to demonstrate the safety of the drug in the target animal, unless adverse effects are identified in the effectiveness studies.

B. MULTIPLE DOSE TARGET ANIMAL SAFETY STUDIES

Safety studies should be conducted in apparently normal rabbits and should demonstrate the margin of safety for the use of the product. The treatment groups used in the safety study should generally include a non-medicated control, the proposed use level, an estimated toxic level, and an intermediate level. This approach is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. The drug should be administered for 3 times the recommended maximum use duration.

III. HUMAN FOOD SAFETY

A. INTRODUCTION

Before approving a new animal drug for minor use, the FDA must determine that people will not be exposed to unsafe residues in their food as a result of the approved use. The health risk associated with an animal drug residue equals the hazard (or inherent toxicity of the compound) times the exposure. FDA regulates the public health risks associated with animal drug residues by assessing hazard and controlling exposure through the setting of tolerances and withdrawal periods. The risk standard that FDA applies, "reasonable certainty of no harm", ensures that drug residues in edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effects. In making that determination, FDA considers the safe concentration of total residues, the rate of residue depletion under the conditions of minor use, and the probability of a unique metabolite of toxicological concern occurring from the proposed minor use.

In many cases, the new animal drug proposed for minor use will already have a major use approval. The sponsor of the major use approval may authorize the FDA to access the human food safety data contained in the major use approval file on behalf of the minor use approval. Whenever scientifically and legally possible, the FDA intends to extrapolate results obtained from tests demonstrating human safety of major use drugs to support approvals of minor uses of these drugs.

There are, however, no major food animal species from which residue metabolism data are routinely extrapolated to rabbits. Acceptability of the data extrapolation from major to minor species will be determined on a case-by-case basis by considering a sponsored drug's currently approved use(s), proposed use(s), and all other available relevant information.

In a limited number of instances, an adequate assurance of safety can be achieved without major-use approval. The type and extent of toxicological data required to support the approval will be decided based on the particular use of the drug and the class of compounds to which the drug is related. Sources for these data may include the scientific literature, proprietary data, or original research. Examples of drug uses which may qualify for consideration of approval under this category are drugs for which sufficient toxicological data exist to establish a safe concentration but do not have a major use approval; and cases where drug administration may be limited to a

very brief period at early life stages. Consideration will be given for production practices which incorporate a prolonged inherent withdrawal time for the drug.

B. FOOD SAFETY ASSESSMENT

1. Hazard Assessment (Toxicological Considerations)

The hazard associated with an animal drug product is assessed using a standard battery of toxicology tests. Each test is designed to examine a different toxicological endpoint. In determining the toxicological endpoints to be examined, the hazard assessment focuses on the effect of multiple exposures to low levels of the drug. The no effect dose from these toxicology studies is divided by a safety factor to determine an acceptable daily intake (ADI). The ADI represents the total drug residues, parent and all metabolites, that can be safely consumed daily throughout one's lifetime. A safe concentration is then calculated for each edible tissue. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. An Approved NADA Exists for the New Animal Drug.

The safe concentration established for the NADA approved for a major food animal species (or in a minor species where a complete human food safety data package was generated) will be applied, where appropriate, to the minor species food animal application.

b. An Approved NADA Does NOT Exist for the New Animal Drug.

If an approved NADA does not exist for the new animal drug, the petitioner will need to provide hazard assessment data appropriate to the assignment of an ADI. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

2. Controlling Exposure (Residue Chemistry Considerations)

Once the ADI and safe concentration have been determined, the risk to consumers is minimized by controlling exposure. The first step in controlling exposure is to determine when the concentration of drug in the edible tissues of the food animal reaches the calculated safe concentration. In some cases, a tolerance (i.e., a legal limit on the amount of drug residues permitted in edible tissue) and a withdrawal period (i.e., a drug-free period prior to slaughter) are established to ensure that consumers are not exposed to harmful drug residues. The withdrawal period is the time period prior to slaughter during which a drug is not to be used. This period enables the animal's normal metabolism to detoxify the drug and facilitate the drug's depletion by natural excretion. In other cases, the compound's inherent toxicity and the residue levels are such that no tolerance or withdrawal period are necessary to ensure food safety.

The general residue chemistry data required to satisfy questions regarding the human food safety of drugs for use in minor species may be found in the guideline "General Principles for Evaluating the safety of Compounds Used in Food-Producing Animals".

a. Tolerance

The tolerance is defined as the concentration of the marker residue, as measured by the regulatory method in the target tissue, which corresponds to the safe concentration for total residues of the drug. The tolerance for monitoring drug residues in the edible tissues of the minor use species will be set, where appropriate, at the level previously established for the approved use in the major species. Sponsors of minor use drugs, however, may have access to the data supporting human safety of the approved major use drug only if the holder of the original approval(s) agrees to such access, or if the data are publicly available. In the case where a tolerance has not been established in a major species, the FDA will establish a tolerance appropriate to the risk (hazard and exposure).

b. Metabolism

Drug metabolism in the minor species may , when scientifically justifiable, be examined on the basis of available data concerning the metabolism of the drug in the most closely related species for which the drug is approved or, preferably, in the minor species for which approval is being sought. If the data are not publicly available, the sponsors of minor use drugs may have access to the data supporting human safety of the approved major use drug only if the holders of the original major use approval(s) agree to such access.

If insufficient data exist to determine how an approved major use drug is metabolized in the minor species, the FDA may consider proposals which present known and theoretical metabolic reaction pathways that the drug (and/or drug class of which the parent is a member) could undergo. This information would be used to determine whether or not a unique metabolite(s) of toxicological concern might occur in the minor species.

If a unique metabolite of toxicological concern is suspected to result from the minor use, the alleviation of toxicological concern may begin with either synthesis and *in vitro* testing for mutagenicity or verification of the metabolite *in vivo* in the minor use species. If the findings of such studies demonstrate the presence of the metabolite and/or uphold the toxicological concern, additional testing requirements could be imposed.

c. Analytical Method

A method of analysis will usually be necessary to monitor drug residues and to establish a withdrawal time in edible tissues of the minor species. The most reliable approved method of analysis for drug residues in the major species may be used if the sponsor of the minor use application demonstrates that the method of analysis is reliable in the minor species.

In cases where a previously approved regulatory method is shown to be adequate to monitor the minor use of a sponsored compound, FDA will not require a method validation trial in government laboratories as a condition of minor use approval. See the guidance document "NRSP-7: Recommendations for Evaluating Analytical Methods".

d. Withdrawal Period

In most cases, a residue depletion study will be necessary to determine an appropriate withdrawal period for use of a drug in a minor species. The withdrawal period is defined as the interval between the time of last administration of the drug and the time when the animal can be safely slaughtered for food purposes. This determination is based on depletion of the marker residue in the target tissue to the tolerance.. Residues of the compound should be measured in the appropriate edible tissues. The FDA will determine the withdrawal period using a statistical tolerance limit procedure.

In any specific case, a residue depletion study may not be necessary if the sponsor can document that no residues of concern will be present in the edible tissues of treated animals when the tissues are made available for human consumption.

3. Edible Tissues in Rabbits

The edible tissues in rabbits are considered to be the muscle, liver, and kidney.

4. Practical Zero Withdrawal Time for Rabbits

A practical zero withdrawal time of 6 hours after the last treatment is assumed for rabbits. Tissue residue data collected up to 6 hours after the last treatment with the drug may be used when attempting to determine whether the drug treatment requires a withdrawal time from the cessation of treatment to the time of slaughter for human consumption.

5. Experimental Design for Residue Depletion Studies

Residue depletion studies are conducted under normal use conditions in the field, in the target animal species, at the maximum expected dose for the maximum recommended duration of dosing or until the drug levels have reached a steady state in the edible tissue. Residue data for the drug in the edible tissue(s) is obtained as a function of time after the last treatment with the compound.

The study design should be such that the times chosen for sample collection are in the phase of the depletion curve closest to the established tolerance. The study should be designed to obtain the maximum number of valid non-zero measurements in order to be useful for statistical analysis. For most minor species residue depletion studies, 4 to 5 animals are sampled at 4 to 5 time periods. The

animals should be represented by an equal number of males and females. However, it has been found that the use of additional animals (i.e., 8 animals per sex per time period) frequently reduces the impact of animal to animal variability, resulting in a shorter calculated withdrawal time.

The withdrawal time, defined as that period from the last administration of the drug to the time at which the marker depletes to the tolerance, is calculated based on the upper bound of the 99th percentile tolerance limit with a 95% confidence level. The calculation is greatly affected by variability in the depletion data, and the use of fewer animals per time period will probably lead to an increased withdrawal time. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" for withdrawal time calculations and further information regarding assumptions of the statistical analysis of residue data.

IV. ENVIRONMENTAL CONSIDERATIONS

The FDA is required under National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Exemptions and applications to FDA for the investigation and approval of animal drugs must include sufficient environmental information to allow the Agency to assess whether environmental impacts may occur from the manufacture, use and disposal of the drugs.

FDA's regulations for implementing NEPA are contained in Title 21 of the Code of Federal Regulations (CFR), Part 25. These regulations were recently revised and published in the FEDERAL REGISTER on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA.

An EA is not required for most minor use applications. In most cases, an application for use in a minor species will be granted a categorical exclusion from the requirement to provide an EA. The regulations under which a categorical exclusion for a minor species can be granted are included in 21 CFR 25.33(d)(4), 25.33(c), and 25.33(d)(5). Section 25.33(d)(4) provides a categorical exclusion specifically for drugs intended for minor species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. FDA believes similar animal management practices generally include dosage, duration of use and concentration of the medication, as well as management style, such as feedlot, pasture or open pens. A categorical exclusion can be applied to a minor species application when the animal drug is already being used under similar animal management practices, and no significant differences from the major use approval are anticipated in the environmental introduction, fate and effects of the drug.

If for some reason an application cannot be excluded under 21 CFR 25.33(d)(4), then it may still be possible to obtain a categorical exclusion under 21 CFR 25.33(c) or 25.33(d)(5). Section 25.33(c) provides a categorical exclusion for animal drug substances that occur naturally in the environment when the use does not alter significantly the concentration or distribution of the drug, its metabolites or degradation product(s) in the environment.

Section 25.33(d)(5) provides a categorical exclusion for drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species. Although not specifically covered under this regulation, feed additives issued under a veterinary feed directive (VFD) would be considered equivalent to a prescription use. Because VFDs are issued under a veterinarian's order, they may also be categorically excluded.

For a categorical exclusion from the requirement to prepare an EA to be claimed, the sponsor submitting an exemption or application must state in the submission that the use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to the applicant's knowledge, no extraordinary circumstances exist. Section 21 CFR 25.15(d) can be consulted regarding this requirement. FDA will review the claim and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate that the proposed use may significantly affect the quality of the human environment.

Extraordinary circumstances are described in 21 CFR 25.21 and may include any use where the available data establish that there is a potential for serious harm to the environment. This includes uses that adversely affect a species (flora or fauna), or the critical habitat of a species that is entitled to special protection under Federal law, such as, the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna. Additional extraordinary circumstances are described in the regulations for implementing the provisions of NEPA contained in 40 CFR 1508.27. These may include uses that are controversial, that result in high uncertainty or unknown risks, that are precedent setting in nature and uses that threaten a violation of Federal, state or local law or requirements imposed for the protection of the environment.

In some cases, an EA may be necessary. There are no specific guidelines available for the preparation and submission of EA under the new regulations. Some information on the purpose and scope of an EA is contained in 21 CFR 25.40. In general, the content and format of an EA for veterinary drugs should consist of 11 parts. These are:

1. date, name, and address of the applicant

2. description of the proposed use (including descriptions of what the use is and any anticipated disposal)

3. identification of the substances that are subject of the use

4. description of the ecosystem at the site of introduction (including a conceptual model with assessment endpoints of the potential impacts at exposed sites in the environment)

5. an analysis section (including analysis of the fate and effects of the substances)

6. a risk characterization based upon the exposures and the hazards (derived from the conceptual model and analysis of the fate and effects information)

7. description of any alternatives to the proposed use (including mitigations)

8. preparer's names

9. signature block of responsible individual

10. references

11. appendices

The critical portions of the EA are the formulation of the conceptual model and the risk analysis that are conducted in sections 4, 5, 6, and 7. Data included in these sections may be obtained from the literature and from laboratory studies. The data should follow good laboratory practices or, in the case of literature, be of similar quality and well documented.

Guidance for performing an environmental risk analysis includes the following:

1. Baker, J.L., et al., editiors. 1994. Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. SETAC Press, Pensacola, FL.

2. Cockerham, Lorris and Shane, Barbara, editors. 1994. Basic Environmental Toxicology. CRC, Boca Raton, FL.

3. Environmental Protection Agency. Proposed Guidelines for Ecological Risk Assessment. the FEDERAL REGISTER of September 9, 1996 (61 FR 47552).

4. Suter, G.W. 1993. Ecological Risk Assessment. Lewis Publishers, Boca Raton, FL.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment. If significant effects requiring the preparation of an Environmental Impact Statement (EIS) are identified, FDA will prepare an EIS. If such effects are not identified, FDA will prepare a finding of no significant impact (FONSI).

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FDA Approval of New Animal Drugs for Minor Uses and for Minor Species
Part 2E: Aquatic Species

I. EFFECTIVENESS

A. INTRODUCTION

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. The following are recommendations only. Alternate science-based proposals will be considered.

B. WATER TREATMENTS FOR EXTERNAL INFECTIONS

In this delivery system, a drug is added to the water containing fish, or fish are treated by immersion in a solution containing the drug. Exposure may be for a specified length of time or for an indefinite period (e.g., in ponds).

For the purpose of this document, external infections are considered to be infections of the skin and gills. We recognize that external infections may sometimes become systemic, and thus require systemic treatment. The data requirements discussed in this section pertain only to external infections which have not become systemic.

CVM encourages sponsors and investigators to support label claims which are as broad as possible, covering a variety of pathogens and fish species. The guidance below addresses ways, other than testing every fish species, to obtain approval of the drug for groups of fish species. One possible approach to species grouping and its rationale are described below.

This section pertains to water treatments where the primary effect results from localized action at the topical site of administration. The concentration of active drug at the topical site is a function of the administered concentration and water conditions. Although the drug may be slightly absorbed, systemic absorption is not believed to play a significant role in the drug's effectiveness at the topical site. Thus, drug concentration and the effects on the pathogen are considered to be the primary determinants of effectiveness, while differences in immune response among species are considered to be an insignificant factor. This approach allows a greater latitude in the extent of interspecies effectiveness data extrapolation.

Demonstration of effectiveness in one species from any of four broad groupings (cold freshwater, warm freshwater, cold salt water, warm salt water) will ordinarily be considered sufficient evidence of effectiveness against the same pathogens in all other species within that particular group. Demonstration of effectiveness in one species from each group will ordinarily be considered sufficient evidence of effectiveness against the same pathogen in all fish (if such a pathogen occurs in such a broad spectrum of environments). Species may be

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grouped differently, where appropriate, for studies providing data for other sections of the approval package.

1. Dose Determination

   The following options, alone or in combination, may be used to determine the most appropriate effective dose regimen(s).

   a. Literature

      Acceptable literature may include peer-reviewed literature, and in many cases, non-reviewed or unpublished literature. Information on the physicochemical behavior of the drug in water, as well as information on *in vitro* and *in vivo* effectiveness against the predominant pathogens and safety of the drug to fish, may be useful for selecting the dose(s).

   b. *In vitro* Laboratory Tests

      Such tests may be appropriate for opportunistic pathogens, but may not be feasible for obligate parasites that are difficult to culture *in vitro*. The petitioner should demonstrate the effective concentration(s) and times to kill or inhibit the predominant pathogens *in vitro* and should compare these results to drug concentrations in fish production systems and the latter's relationship to target animal safety. The petitioner should also determine the effect of various water conditions (reflecting those expected in the field) on the effective drug concentrations.

   c. Laboratory Dose Determination Studies

      Severe uniform infections should be induced, and the effectiveness of three non-zero therapeutic concentrations for various durations should be compared to a non-medicated control group, and as a non-medicated uninfected control group. The effect of water parameters expected to influence effectiveness should be examined to the extent possible.

   d. Field Dose Determination Studies

      Field type dose determination studies should examine the effectiveness of various therapeutic concentrations and durations against natural infections under a variety of water conditions.

   e. Interspecies Data Extrapolation

      Interspecies data extrapolation from another fish species, for which the drug is already approved, may be used to support effectiveness.

2. Dose Confirmation/Field Trials

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The following options, alone or in combination, may be used to confirm the effectiveness of the proposed claim under field conditions.

a. Literature

Literature should describe well-controlled field trials that provide the information listed below under "Dose Confirmation/Field Trials". Acceptable literature may include unpublished or non-reviewed literature, as well as peer-reviewed literature.

b. Dose Confirmation/Field Trials

These field trials should be controlled and should be conducted at a minimum of two sites. More sites should be used if particular water quality parameters affect the effectiveness of the drug and/or if the label claim will include multiple pathogens. The trials should reflect at least the extremes of the limiting water parameter(s).

3. Dose Determination/Dose Confirmation Field Trials

A combination study may be conducted in those situations where laboratory studies are not possible. One study with 3 non-zero concentrations plus a non-medicated infected treatment group and a non-medicated non-infected treatment group should be conducted at a minimum of two sites. The petitioner should include all other requirements from the individual studies.

Science-based alternative approaches to those approaches listed above will also be considered by CVM.

C. SYSTEMICALLY ACTIVE DRUGS

Systemically active drugs include those drugs that are administered to treat systemic conditions and/or require absorption and distribution throughout the body for their effect.

CVM encourages sponsors and investigators to support label claims that are as broad as possible, covering a variety of pathogens and fish species. The guidance below addresses ways, other than testing every fish species, to obtain approval of the drug for groups of fish species. One possible approach to species grouping and its rationale are described below.

Demonstration of effectiveness in one species from any of four broad groupings (cold freshwater, warm freshwater, cold salt water, warm salt water) could be considered sufficient evidence of effectiveness against the same pathogens in all other species within that particular group. The applicant should present a sufficient scientific justification for such extrapolation. Furthermore, with such a scientific justification, demonstration of effectiveness in one species from each group could be considered sufficient evidence of effectiveness against the same

pathogen in all fish (if such a pathogen occurs in such a broad spectrum of environments).

However, these groupings may not be appropriate for all drugs. Acceptability of data extrapolation from one group to another will be determined on a case-by-case basis by considering a sponsored drug's currently approved use(s), proposed use(s), and all other relevant information. CVM is willing to consider other species groups and encourages the submission of data which support the grouping of aquatic animal species. Species may be grouped differently, where appropriate, for studies providing data for other sections of the approval package.

1. Dose Determination

   The following options, alone or in combination, may be used to determine the most appropriate effective dose regimen(s).

   a. Literature

      Acceptable literature may include peer-reviewed literature, as well as unpublished or non-reviewed literature. Information on the physicochemical behavior of the drug in water, if the drug is administered via water immersion, as well as information on *in vitro* and *in vivo* effectiveness against the predominant pathogens and safety of the drug to fish, may be useful for selecting the dose(s).

   b. *In vitro* Laboratory Tests

      Such tests are appropriate for opportunistic pathogens, but may not be feasible for obligate parasites that are difficult to culture *in vitro*. The petitioner should demonstrate the effective concentration(s) and times to kill or inhibit the predominant pathogens.

   c. Laboratory Dose Determination Studies

      Severe uniform infections should be induced, and the effectiveness of three non-zero therapeutic concentrations for various durations should be compared to a non-medicated control group, and a non-medicated uninfected control group.

   d. Field Dose Determination Studies

      Field type dose determination studies should examine the effectiveness of various therapeutic concentrations and durations against natural infections.

   e. Interspecies Data Extrapolation

      Interspecies data may be extrapolated from another (preferably closely related) fish species for which the drug is already approved, or for which the dose of a drug in the development process has been accepted by CVM. Further discussion with CVM is advised to determine the extent and acceptability of such extrapolation.

2. Dose Confirmation/Field Trials

   The following options, alone or in combination may be used to confirm the effectiveness of the proposed under field conditions.

   a. Literature

      Literature should describe well-controlled field trials that provide the information listed below under "Dose Confirmation/Field Trials". Acceptable literature may include unpublished or non-reviewed literature, as well as peer-reviewed literature.

   b. Dose Confirmation/Field Trials

      These trials should be controlled and should be conducted at a minimum of two sites. More may be necessary if the label claim will include multiple pathogens. The trials should reflect at least the extremes of the limiting water parameter(s).

   c. Other Considerations

      Some factors that will influence the approach selected include the nature of the disease condition, the drug, the nature and availability of the animals, and other practical considerations.

D. PRODUCTION DRUGS

Production drugs are those new animal drugs intended to affect the structure and/or function of an animal's body. Effects claimed for production drugs are normally related to improved animal performance, e.g., increased rate of weight gain, increased milk production, improved feed efficiency, increased carcass leanness, and improved reproductive performance. In the past, the minor species/minor use regulations were not interpreted to apply to production uses of new animal drugs, and the requirements for production uses of new animal drugs in minor species were the same as for major species. The Center will now consider production claims for minor species.

The requirements for approval of production claims for minor species will depend upon whether or not an approval in a similar major species already exists. All requests will be handled on a case-by-case basis and an attempt will be made to make use of all available data that may relate to the request. Thus, sponsors are encouraged to work closely with the Center and to share all available information early in the approval process. Sponsors should be aware that the ability to show effectiveness depends upon the relative size of the response of a drug as well as upon the variability associated with the response.

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II. TARGET ANIMAL SAFETY

Target animal safety studies should be conducted using the life stage or species that will be treated with the compound being studied. In cases where multiple life stages or species will be treated, the drug should be tested on the most sensitive life stage and/or species.

A. WATER TREATMENTS FOR EXTERNAL INFECTIONS

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies. A Target Animal Safety Guideline is available from CVM and provides additional study design information.

1. Toxicity Test

   A single study may be conducted using the drug at 10X the recommended dose for 3X the recommended duration. This study may be used as a first step to identify the toxic effects prior to conducting a multiple dose Target Animal Safety study. If no toxic effects are observed at this dose level, this single study will be sufficient to demonstrate the safety of the drug in the target animal, unless adverse effects are identified in the effectiveness studies. For compounds that are known to be too toxic for this test, a multiple dose target animal safety study should be conducted instead.

2. Multiple Dose Target Animal Safety Studies

   Safety studies should be conducted in apparently normal fish and should demonstrate the margin of safety for the use of the product in the intended species or species groups. The number of species needed for testing will vary with the number of groups for which drug approval is sought. An example of a possible approach to species grouping is described below.

   Suggested groups are cold freshwater (normally <15 °C, 0 ppt salinity), warm freshwater, cold salt water, and warm salt water (normally > 15 °C and > 0 ppt salinity). If approval for more than one group is sought, and the effective dose (concentration) is the same for all of these groups, then one species from each group should be tested. If the margin of safety is similar for all of the tested species, it may be assumed that this margin of safety is representative of all the species in those groups.

   If the effective dose is different between groups, or if approval is sought for a single dose within a single group, two species, as distantly related as possible, per group should be tested. If the margin of safety of each of the two species representing a particular group is similar, the margin of safety may be extrapolated to the rest of that group.

   These extrapolations are based on the assumption that if the toxicity of the drug in very different fish species is similar, then the toxicity in more closely-related species under more similar water conditions should also be similar.

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If the margin of safety is quite different between species, additional species may need to be studied. The number of species to be tested initially is summarized below.

Claim	Number of species
Multiple species groups, same dose	
all 4 groups	4 (1 sp. from each group)
3 groups	3 (1 sp. from each group)
2 groups	2 (1 sp. from each group)

Claim	Number of species
Multiple species groups, different doses	
all 4 groups	8 (2 spp. from each group)
3 groups	6 (2 spp. from each group)
2 groups	4 (2 spp. from each group)
Single group	2 (both from that group)

The treatment groups used in the safety study for each species should include a non-medicated control, the proposed use level, an estimated toxic level, and an intermediate level. This is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. The drug should be administered for 3 times the recommended maximum use duration.

Parameters for evaluation of safety in each treatment group may include:

- clinical observations (e.g. of behavior, appearance, and eating patterns)
- mortality
- weight gain
- necropsy findings (gross and histopathologic abnormalities)

3. Field Trials

   Any adverse effects occurring in effectiveness field trials should be documented. Field trials, as described under the effectiveness section, should include at least one species from each species group for which approval is sought.

4. Literature

   Literature providing any of the data listed in Sections 1 or 2 above may be used to address all or part of these requirements.

B. SYSTEMIC TREATMENTS

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to

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the initiation of any studies. A Target Animal Safety Guideline is available from CVM and provides additional study design information.

1. Toxicity Test

   A single study may be conducted using the drug at 10X the recommended dose for 3X the recommended duration. This study may be used as a first step to identify the toxic effects prior to conducting multiple dose Target Animal Safety study. If no toxic effects are observed at this dose level, this single study will be sufficient to demonstrate the safety of the drug in the target animal, unless adverse effects are identified in the effectiveness studies.

2. Multiple Dose Target Animal Safety Studies

   Safety studies should be conducted in apparently normal fish and should demonstrate the margin of safety for the use of the product in the intended species or species groups. The treatment groups used in the safety study for each species should generally include a non-medicated control, the proposed use level, an estimated toxic level, and an intermediate level. This is generally accomplished by the use of 1X, 3X, and 5X the highest proposed dose. The drug should generally be administered for 3 times the recommended maximum use duration. The number of species needed for testing will vary with the drug, available toxicity information, and the number and types of species for which drug approval is sought. Consultation with CVM on species to be tested is advised.

3. Field Trials

   Any adverse effects occurring in effectiveness field trials should be documented. Field trials, as described under the effectiveness section, should include at least one species from each species group for which approval is sought.

4. Literature

   Literature providing any of the data listed in Sections 1 or 2 above may be used to address all or part of these requirements.

III. HUMAN FOOD SAFETY

The petitioner is advised to discuss the plan with CVM early in the development process. It is also advisable to come to protocol agreement with CVM prior to the initiation of any studies.

A. INTRODUCTION

All drug use in aquatic food animals such as fish or shell fish is considered a minor use for ensuring human food safety. Before approving a new animal drug for minor use, the FDA must determine that people will not be exposed to unsafe residues in their food as a result of the approved use. The health risk associated with an animal

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drug residue equals the hazard (or inherent toxicity of the compound) times the exposure.

FDA regulates the public health risks associated with animal drug residues by assessing hazard and controlling exposure through the setting of tolerances and withdrawal periods. The risk standard that FDA applies, "reasonable certainty of no harm", ensures that drug residues in edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effects. In making that determination, FDA considers the safe concentration of total residues, the rate of residue depletion under the conditions of minor use, and the probability of a unique metabolite of toxicological concern occurring from the proposed minor use.

In many cases, the new animal drug proposed for minor use will already have a major use approval. The sponsor of the major use approval may authorize the FDA to access the human food safety data contained in the major use approval file on behalf of the minor use approval. Whenever scientifically and legally possible, the FDA intends to extrapolate results obtained from tests demonstrating human safety of major use drugs to support approvals of minor uses of these drugs. In general, data from an approved drug use in a major terrestrial species may be used to extrapolate to the aquatic species when there is no existing aquatic animal approval. However, it must be recognized that instances may arise when such data extrapolation is not justified. Acceptability of the data extrapolation from major to minor species will be determined on a case-by-case basis by considering a sponsored drug's currently approved use(s), proposed use(s), and all other available relevant information.

In a limited number of instances, an adequate assurance of safety can be achieved without major-use approval. The type and extent of toxicological data required to support the approval will be decided based on the particular use of the drug and the class of compounds to which the drug is related. Sources for these data may include the scientific literature, proprietary data, or original research.

Examples of drug uses which may qualify for consideration of approval under this category are drugs for which sufficient toxicological data exist to establish a safe concentration but do not have a major use approval; and cases where drug administration may be limited to a very brief period at early life stages. Consideration will be given for production practices which incorporate a prolonged inherent withdrawal time for the drug. For the treatment of wildlife, please consult the CVM guideline for wildlife and exotic species.

B. SPECIAL CONDITIONS FOR CONSIDERATION WITH AQUATIC SPECIES

1. Life Stage Considerations

a. Food Fish Status of the Inedible Life Stages of Edible Species

The Center does not currently classify as a non-food animal the normally inedible life stages of an animal which may be available for human

consumption at a later life stage. Thus, life stages of a food fish such as eggs, sac-fry, fry, juveniles, or brood fish, which are not normally marketed for human consumption, are still considered food fish.

b. Consideration of Withdrawal Time Inherent in a Life Stage

The Center will consider, on a drug and indication basis, the amount of human food safety data required for the approval of a new animal drug proposed for use in an inedible life stage. Depending upon the drug proposed, circumstances of use, and available human food safety information, the data requirements may range from the standard human food safety requirements to essentially the same as for a non-food fish. However, the fish would still be considered a food animal. Sufficient toxicological and residue chemistry data must be available to assure that the consumption of the edible tissues of the medicated fish will not exceed an acceptable daily intake for the drug. A specific alternative is provided for the submission of toxicological and residue chemistry data in the section, Broodstock "Not Intended for Food Use".

A specific drug and drug claim 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, CVM will generally consider the human food safety data requirements to be satisfied. An applicant may petition CVM to take such action. Considering a specific drug and drug claim to be of low risk for human food safety allows the Agency to reassess the human food safety concerns to address new information regarding the toxicity of the drug or changes in the conditions of use.

The use of a drug, which is chemically and toxicologically well characterized, and intended for use on fish eggs, may be a specific instance where the life stage (eggs) can have a significant impact on the amount of human food safety data that will be required. In addition, it may be possible to use the life stage consideration for eggs to permit crop grouping across species (see the section, Grouping of Species, below). Studies done in a limited number of species following treatment of the eggs may provide adequate human food safety data to assure that there are no unsafe residues in the edible tissues of fish at the time of human consumption.

2. Broodstock "Not Intended for Food Use"

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It is recognized that the broodstock of some aquatic species are not routinely slaughtered for human consumption. *Injectable drugs* containing a suitable indelible marking agent may be proposed with an indication of "For Broodstock Not Intended for Food Use". There would be no food safety data requirements for the approval of an NADA for such a drug under the following conditions:

- Incorporation of a suitable indelible marking agent (possible examples may include india ink or tattoo ink) in the injectable formulation which clearly identifies the edible tissues of the medicated fish as "not for food use" and effectively assures removal of treated broodstock from human consumption.

- Implementation of this approach will require generation or submission of tissue studies which confirm the suitability of the selected marking agent to identify the edible tissues of medicated broodstock as "not for food use".

There would be no human food safety limitations for the edible offspring resulting from the medicated broodstock for those fish species in which the offspring are consumed as juvenile or mature fish.

Fish species with edible (marketed) eggs would not be immediately eligible for "not for food use" status *unless* the indelible marking agent administered to the broodstock also clearly marks the eggs of the medicated broodstock.

3. Temperature Considerations

   a. Effects of Temperature on Nature, Disposition, and Depletion of Residues

      It is commonly recognized that ambient water temperature may alter the nature of the drug residues in tissue, the relative disposition of residue among body tissues, and the depletion of these residues. In general, it is assumed that the principal effect will be an increase in the required withdrawal time with decreasing temperature. Because of this, residue depletion studies should be conducted at the minimum water temperature for which an approval is sought. Multiple depletion studies may be conducted at a range of temperatures in order to determine the minimum withdrawal time required for a given temperature range.

      It is sometimes desirable to compare residue depletion data between species which have different temperature ranges, or to compare strains of the same species across temperature ranges. It may be difficult or impossible to determine whether differences in the depletion (or metabolic) characteristics of a drug are the result of differences in water temperature or due to inherent species or strain differences.

   b. Considerations of Temperature and Dietary Interactions

      There can be an interaction between temperature and diet which may affect the nature and distribution of residues. For example, temperature

and dietary lipid saturation have been shown to alter minor components of the metabolic profile.

There are no data currently available to suggest that the interaction between temperature and diet significantly affects the marker to total residue ratio, or otherwise alters a calculated tolerance. However, as dietary constituents continue to be manipulated in attempts to maximize the production characteristics of the aquacultural product, possible effects on drug metabolism should be considered.

4. Grouping of Species

Species grouping (or crop grouping) refers to the use of one or more representative species in the conduct of the safety and effectiveness studies for a new animal drug approval. The data collected for the representative species would then permit inclusion on the label of all species for which those species are considered representative. For example, CVM accepts data collected in Holstein cattle for all breeds of dairy cattle.

There are no definitive crop groups of aquatic species for human food safety data at this time. CVM has traditionally considered salmonids to be a crop group with Atlantic salmon, Pacific salmon or rainbow trout serving to represent all salmonids. This crop group may not be appropriate for all drugs. CVM is willing to consider other crop groups and encourages the submission of data that support the grouping of aquatic food animal species.

a. Acceptable Grouping of Species for Human Food Safety Data

Factors considered in establishing a crop group for human food safety data would include, in addition to drug-specific information, the period of time from cessation of treatment to possible consumption of the medicated fish (typically months to years) and the dilution of the drug concentration in the edible tissue simply due to growth of the animal. It may be possible to group aquatic species by family, water temperature, life stage, or other characteristics across which the human food safety data may be demonstrated to be similar. Other possible crop groupings may be identified on a case-by-case basis depending upon the drug, indication, and conditions of use.

b. Data Requirements for Grouping Species for Human Food Safety Data

Data must be available to support the hypothesis that the selected representative species is typical of the larger group. The members of the selected crop group must be sufficiently alike so that drug absorption, distribution, metabolism, and excretion would not be anticipated to be significantly different for any species within the represented group. The nature of the studies conducted to support a crop group are anticipated to be driven by the particular drug and the species grouping that is being evaluated. A combination of studies may be necessary to address a

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particular "crop grouping". A full human food safety data package (metabolism and residue chemistry) may be collected in one or more representative species and some combination of bridging studies should be conducted to verify the appropriateness of the proposed grouping in other representative species.

The following kinds of studies may be conducted to support the homogeneity of a proposed group for a given drug (or class of drugs):

1) Pharmacokinetic Studies

   Pharmacokinetic studies would be anticipated to serve as bridging studies where existing residue and metabolism data collected in one or more species are shown to be applicable to other members of the crop group. Pharmacokinetic studies may range from classical evaluations of absorption, distribution, metabolism, and excretion (ADME), to bioavailability studies. The design of the appropriate study will need to be evaluated in consideration of the proposed drug, its proposed use, and the proposed species grouping. The extent to which pharmacokinetic studies may substitute for metabolism and/or residue studies is not clear at the present time, and will be considered on a case-by-case basis.

2) Metabolism Studies in the Edible Tissues

   Metabolism studies may range from definitive radiolabel metabolism studies such as are typically required to satisfy human food safety to more limited "cold" analytical method studies conducted to verify a particular residue profile in representative species in the proposed crop grouping.

3) Residue Depletion Studies in the Edible Tissues

   Residue depletion studies may be conducted in some or all of the members of a particular crop grouping. Sufficient metabolism data must be available to assure that the marker residue is appropriate (or at least sufficiently conservative to assure that human food safety is maintained) for each member of the crop group. Testing is generally conducted using market-size fish.

C. FOOD SAFETY ASSESSMENT

1. Hazard Assessment (Toxicological Considerations)

   The hazard associated with an animal drug product is assessed using a standard battery of toxicology tests. Each test is designed to examine a different toxicological endpoint. In determining the toxicological endpoints to

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be examined, the hazard assessment focuses on the effect of multiple exposures to low levels of the drug. The no effect dose from these toxicology studies is divided by a safety factor to determine an acceptable daily intake (ADI). The ADI represents the total drug residues, parent and all metabolites, that can be safely consumed daily throughout one's lifetime. A safe concentration is then calculated for each edible tissue. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. An Approved NADA Exists for the New Animal Drug.

The safe concentration established for the NADA approved for a major food animal species (or in a minor species where a complete human food safety data package was generated) will be applied, where appropriate, to the minor aquatic species food animal application.

b. An Approved NADA Does NOT Exist for the New Animal Drug.

If an approved NADA does not exist for the new animal drug, the petitioner will need to provide hazard assessment data appropriate to the assignment of an ADI. See the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

2. Controlling Exposure (Residue Chemistry Considerations)

Once the ADI and safe concentration have been determined, the risk to consumers is minimized by controlling exposure. The first step in controlling exposure is to determine when the concentration of drug in the edible tissues of the food animal reaches the calculated safe concentration. In some cases, a tolerance (i.e., a legal limit on the amount of drug residues permitted in edible tissue) and a withdrawal period (i.e., a drug-free period prior to slaughter) are established to ensure that consumers are not exposed to harmful drug residues. The withdrawal period is the time period prior to slaughter during which a drug is not to be used. This period enables the animal's normal metabolism to detoxify the drug and facilitate the drug's depletion by natural excretion. In other cases, the compound's inherent toxicity and the residue levels are such that no tolerance or withdrawal period are necessary to ensure food safety.

The general residue chemistry data required to satisfy questions regarding the human food safety of drugs for use in aquatic species may be found in the guideline "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals".

a. Tolerance

The tolerance is defined as the concentration of the marker residue, as measured by the regulatory method in the target tissue, which corresponds to the safe concentration for total residues of the drug. The tolerance for monitoring drug residues in the edible tissues of the minor use species will be

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set, where appropriate, at the level previously established for the approved use in the major species. Sponsors of minor use drugs, however, may have access to the data supporting human safety of the approved major use drug only if the holder of the original approval(s) agrees to such access or if the data are publicly available. In the case where a tolerance has not been established in a major species, the FDA will establish a tolerance appropriate to the risk (hazard and exposure).

b. Metabolism

Drug metabolism in the minor species may, when scientifically justifiable, be examined on the basis of available data concerning the metabolism of the drug in the most closely related species for which the drug is approved or, preferably, in the minor species for which approval is being sought. If the data are not publicly available, the sponsors of minor use drugs may have access to data supporting human safety of the approved major use drug only if the holders of the original major use approval(s) agree to such access.

If insufficient data exist to determine how an approved major use drug is metabolized in the minor species, the FDA would consider proposals which present known and theoretical metabolic reaction pathways that the drug (and/or drug class of which the parent is a member) could undergo. This information would be used to determine whether or not a unique metabolite(s) of toxicological concern might occur in the minor species.

If a unique metabolite of toxicological concern is suspected to result from the minor use, the alleviation of toxicological concern may begin with either synthesis and *in vitro* testing for mutagenicity or verification of the metabolite *in vivo* in the minor use species. If the findings of such studies demonstrate the presence of the metabolite and/or uphold the toxicological concern, additional testing requirements could be required**.**

c. Analytical Method

A method of analysis will usually be necessary to monitor drug residues and to establish a withdrawal time in edible tissues of the minor species. The most reliable approved method of analysis for drug residues in the major species may be used if the sponsor of the minor use application demonstrates that the method of analysis is reliable in the minor species.

In cases where a previously approved regulatory method is shown to be adequate to monitor the minor use of a sponsored compound, FDA will not require a method validation trial in government laboratories as a condition of minor use approval. See the CVM document, "NRSP-7: Recommendations for Evaluating Analytical Methods."

d. Withdrawal Period

In most cases, a residue depletion study (see following sections for study design) will be necessary to determine an appropriate withdrawal period

for use of a drug in a minor species. The withdrawal period is defined as the interval between the time of last administration of the drug and the time when the animal can be safely slaughtered for food purposes. This determination is based on depletion of the marker residue in the target tissue to the tolerance. Residues of the compound should be measured in the appropriate edible tissues. The edible tissues for specific aquatic species are discussed below. For other species, sponsors should consult the Center. The FDA will determine the withdrawal period using a statistical tolerance limit procedure.

In any specific case, a residue depletion study may not be necessary if the sponsor can document that no residues of concern will be present in the edible tissues of treated animals when the tissues are made available for human consumption.

3. Edible Tissues in Aquatic Species

   a. Finfish

      The edible tissues in finfish are considered to be the muscle with adhering skin. For those species for which the skin is inedible (such as catfish or eel) the edible tissue is considered to be muscle.

      Residue depletion studies for those fish with edible skin should be conducted using muscle fillet with adhering skin as the tissue sample. Alternatively, skin and muscle samples may be collected and analyzed separately. The relative contribution by weight of each portion (muscle and skin) should be reported in addition to the residue concentrations so that a calculated value for the concentration of the analyte in muscle with adhering skin may be determined.

      In addition, the eggs of some finfish species are considered edible. Currently, the species with edible eggs are recognized to be shad, salmon, paddlefish, herring, and sturgeon.

   b. Shellfish

      1) Mollusks

         The entire soft tissue mass of hard shell clams, soft shell clams and oysters is considered to be the edible tissue. Muscle is considered to be the edible tissue in scallops and giant clams.

      2) Crustaceans

         The edible tissue for crustacea is considered to be muscle. The internal organs (the "gob") need not be included as an edible tissue at this time. For those species which are marketed as "soft shell" (such as soft shell crabs or soft shell crawfish), the entire animal including the unhardened shell is also considered an edible tissue.

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The edible tissue for shrimp is considered to be the shrimp with the head, tail fan, and shell removed. The midgut should be left intact (i.e., the shrimp should not be "de-veined").

4. Practical Zero Withdrawal Time for Aquatic Species

It is not possible at this time to establish a practical zero withdrawal time for aquatic food animals. Industry processing practices from harvest of the fish to time of slaughter for finfish appear to range from 1 to 6 hrs. As a result, considerations relating to a zero withdrawal time must begin with measurements determined while the animal is on the drug.

5. Selection of Water Quality Conditions for Conduct of Studies

a. Temperature

Water temperature may alter the absorption, distribution, metabolism, and elimination of drugs in poikilothermic animals. In general, the lower end of the species temperature range is recommended for studies in aquatic food animals intended to generate metabolism and residue chemistry information. It is therefore recommended that:

(1) residue depletion studies be conducted at temperatures at the lower end of the species temperature range, and

(2) the resulting calculated withdrawal time not be extrapolated for temperatures colder than actually tested.

While it is recognized that temperature may significantly affect the amount of drug which is absorbed and distributed to the tissues, the information currently available suggests that the depletion of the drug is the rate limiting step. It is recognized that studies for purposes other than human food safety data generation, such as target animal safety, may be more appropriately conducted at higher water temperatures. Thus, it may be necessary to conduct the human food safety studies in the warmer temperatures necessitated by the therapeutic indications associated with the drug claim. In these instances, residue depletion data will not be extrapolated for temperatures below that found in the withdrawal study.

b. Salinity

The salt concentration in the aquatic environment is recognized to have a potential impact on the bioavailability of drugs to the aquatic organism. Thus, it cannot be assumed that tissue residue data collected for drugs administered through the feed or water in freshwater conditions will be the same as the data collected in saline conditions. Studies may be required to show that the salinity of the aquatic environment does not affect the total bioavailability of the drug or the nature of the bioavailable products absorbed by the aquatic food animal. For example, a drug for use in feed for salmon may need to address the bioavailability of the drug in those

salmon cultured for release into the Great Lakes (fresh-water) and those salmon of the same species cultured in saltwater for net pens or sea farming.

c. Other factors

As with water temperature and salinity, other factors in the aquatic environment may alter the manner in which the aquatic animal handles the drug. The conditions of the experiment, including temperature, dissolved solids, pH, alkalinity, and hardness should be standardized as much as possible. In addition, this information should be recorded and readily available for comparison between studies. Differences in dissolved solids, for instance, may offer an explanation for discrepancies in drug concentrations between studies or replicates due to effects on the relative bioavailability of the drug.

6. Nutritional Status

The current scientific literature indicates that the nutritional status of several species of fish can affect the uptake of various trace metals and chemical compounds. In many cases, nutritionally compromised fish take up more substance than those fish on a nutritionally adequate diet. Hence, studies should be conducted in settings closely approximating or in actual production settings. Fish should not be used that were starved immediately prior to studies, without a thorough understanding of the potential effects of fasting on drug uptake and/or depletion.

7. Experimental Design for Residue Depletion Studies

A residue depletion study is conducted under normal use conditions in the field in the target animal species, at the maximum expected dose for the maximum recommended duration of dosing or until the drug levels have reached a steady state in the edible tissue. Residue data for the drug in the edible tissue(s) is obtained as a function of time after the last treatment with the compound. The study design should be such that the times chosen for sample collection are in the phase of the depletion curve closest to the established tolerance. The study should be designed to obtain the maximum number of valid non-zero measurements in order to be useful for statistical analysis.

For cattle, swine, and poultry, 5 animals per time period, and 4 time periods, are typically recommended for collection. The variability associated with residue samples collected from aquatic animals is much larger; therefore, the number of animals per time period should be increased to at least 15 to 20 animals per time period. The withdrawal time, defined as that period from the last administration of the drug to the time at which the marker residue depletes to the tolerance, is calculated based on the upper bound of the 99th percentile tolerance limit with a 95% confidence level. The calculation is greatly affected by variability in the depletion data, and the use of fewer animals per time period may lead to an increased withdrawal time. See the

guideline, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals" for withdrawal time calculations and further information regarding assumptions of the statistical analysis of residue data.

8. Sampling of Edible Tissue

   It is recommended, in general, that the entire tissue of interest be homogenized, and an aliquot of the homogenate be used for the actual analysis. For instance, in salmonids, the edible tissue is considered to be muscle with adhering skin. A whole fillet of one side of the fish should be obtained with adhering skin. This whole fillet may then be homogenized, and an aliquot of the homogenate taken for the actual chemical analysis. The remaining homogenate may be stored in reserve as appropriate. This approach reduces sample variability and helps to assure that the drug concentration in the analyzed sample is representative of the entire edible tissue.

IV. ENVIRONMENTAL CONSIDERATIONS

The FDA is required under National Environmental Policy Act of 1969 (NEPA) to consider the environmental impact of investigating and approving new animal drugs as an integral part of its regulatory process. Exemptions and applications to FDA for the investigation and approval of animal drugs must include sufficient environmental information to allow the Agency to assess whether environmental impacts may occur from the use and disposal of the drugs.

FDA's regulations for implementing NEPA are contained in Title 21 of the Code of Federal Regulations (CFR), Part 25. These regulations were recently revised and published in the FEDERAL REGISTER on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997. Under these regulations, sponsors filing investigational exemptions or new animal drug applications must submit an environmental assessment (EA) unless the exemption or application qualifies for a categorical exclusion from the requirement to prepare an EA.

An EA is not required for most minor use or minor species exemptions or applications. However, this is not the case for exemptions and applications for investigating and approving new animal drugs for use in aquatic species. In many cases, a categorical exclusion can be obtained for the investigations under 21 CFR 25.33(e), but in most cases, the approval of a new animal drug in a minor aquatic species or new aquatic use will require an EA. This is because the regulations under which a categorical exclusion for a minor species or use can usually be granted [i.e., 21 CFR 25.33(d)(4) or 25.33(d)(5)] do not usually apply to aquatic uses. Section 25.33(d)(4) provides a categorical exclusion for drugs intended for minor species or use, when the drug has been previously approved for use in another or the same species where similar animal management practices are used. For aquatic species, it is rare that the drug has already been approved for use in another or the same species where similar management practices are used. Aquatic use usually represents a new

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management style. Section 25.33(d)(5) provides a categorical exclusion for drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species. As stated, this categorical exclusion applies only to terrestrial species. The reason that these exclusions were not made to apply to aquatic species is the concern for new and potentially more direct exposures of the drug to nontarget organisms from the use of animal drugs in an aquatic environment.

If a categorical exclusion could be granted for a minor aquatic species or use it would most likely occur under 21 CFR 25.33(c). Section 25.33(c) provides for a categorical exclusion for animal drug substances that occur naturally in the environment when the use does not alter significantly the concentration or distribution of the drug, its metabolites or degradation product(s) in the environment.

For a categorical exclusion from the requirement to prepare an EA to be claimed, the sponsor submitting an exemption or application must state in the submission that the use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to the applicant's knowledge, no extraordinary circumstances exist. Section 21 CFR 25.15(d) can be consulted regarding this requirement. FDA will review the claim and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate that the proposed use may significantly affect the quality of the human environment.

Extraordinary circumstances are described in 21 CFR 25.21 and may include any use where the available data establish that there is potential for serious harm to the environment. This includes uses that adversely affect a species (flora or fauna), or the critical habitat of a species that is entitled to special protection under Federal law, such as, the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna. Additional extraordinary circumstances are described in the regulations for implementing the provisions of NEPA contained in 40 CFR 1508.27. These may include uses that are controversial, that result in high uncertainty or unknown risks, that are precedent setting in nature, and uses that threaten a violation of Federal, state or local law or requirements imposed for the protection of the environment.

There are no specific guidelines available for the preparation and submission of EA under the new regulations. Some information on the purpose and scope of an EA is contained in 21 CFR 25.40. In general, the content and format of an EA for veterinary drugs should consist of 11 parts. These are:

1. date, name, and address of the applicant
2. description of the proposed use (including descriptions of what the use is and any anticipated disposal)
3. identification of the substances that are subject of the use

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4. description of the ecosystem at the site of introduction (including a conceptual model with assessment endpoints of the potential impacts at exposed sites in the environment)
5. an analysis section (including analysis of the fate and effects of the substances)
6. a risk characterization based upon the exposures and the hazards (derived from the conceptual model and analysis of the fate and effects information)
7. description of any alternatives to the proposed use (including mitigations)
8. preparers names
9. signature block of responsible individual
10. references
11. appendices

The critical portions of the EA are the formulation of the conceptual model and the risk analysis that are conducted in sections 4, 5, 6, and 7. Data included in these sections may be obtained from the literature and from laboratory studies. The data should follow good laboratory practices or, in the case of literature, be of similar quality and well documented.

Guidance for performing an environmental risk analysis include the following:

1. Baker, J.L., et al., editiors. 1994. Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. SETAC Press, Pensacola, FL.

2. Cockerham, Lorris and Shane, Barbara, editors. 1994. Basic Environmental Toxicology. CRC, Boca Raton, FL.

3. Environmental Protection Agency. Proposed Guidelines for Ecological Risk Assessment. the FEDERAL REGISTER of September 9, 1996 (61 FR 47552).

4. Suter, G.W. 1993. Ecological Risk Assessment. Lewis Publishers, Boca Raton, FL.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment. If significant effects requiring the preparation of an Environmental Impact Statement (EIS) are identified, FDA will prepare an EIS. If such effects are not identified, FDA will prepare a finding of no significant impact (FONSI).