

**COVINGTON & BURLING**

1201 PENNSYLVANIA AVENUE, N. W.

P.O. BOX 7566

WASHINGTON, D.C. 20044-7566

(202) 662-6000

FACSIMILE: (202) 662-6291

**EUGENE I. LAMBERT**

DIRECT DIAL NUMBER

(202) 662-5422

DIRECT FACSIMILE NUMBER

(202) 778-5422

ELAMBERT@COV.COM

LECONFIELD HOUSE

CURZON STREET

LONDON W1Y 8AS

ENGLAND

TELEPHONE: 44-171-495-5655

FACSIMILE: 44-171-495-3101

BRUSSELS OFFICE

KUNSTLAAN 44 AVENUE DES ARTS

BRUSSELS 1040 BELGIUM

TELEPHONE: 32-2-549-5230

FACSIMILE: 32-2-502-1598

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February 17, 1998

**Via hand delivery**

Linda M. Wilmot, DVM  
Chair  
ADAA Minor Use/Minor Species Working Group  
Center for Veterinary Medicine (HFV-112)  
Food and Drug Administration  
7500 Standish Place  
Rockville, MD 20855-2773

**Re: Comments of Warner-Lambert Company on FDA's  
Discussion Draft "Proposals to Increase the  
Availability of Approved Animal Drugs for Minor  
Species and Minor Uses"**

Dear Dr. Wilmot:

On behalf of our client, Warner-Lambert Company, we hereby submit comments on the Discussion Draft "Proposals to Increase the Availability of Approved Animal Drugs for Minor Species and Minor Uses" ("the Draft Proposals"). We wish to express our appreciation for allowing these comments to be submitted after the original deadline for submission of comments.

Warner-Lambert, through its Tetra/Second Nature division and subsidiaries, markets feeds and treatments for non-food ornamental fish and reptiles. On behalf of Tetra/Second Nature, Warner-Lambert would like to comment on four specific areas of the Draft Proposals:

1. *The requirements with respect to current Good Manufacturing Practices.*

The manufacturing procedures used in Tetra/Second Nature's government-certified German manufacturing facilities are substantially equivalent to cGMPs, and should be acceptable to FDA.

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2. *The regulation of unapproved medicated products that are already on the market.*

Warner-Lambert submits that these products have established track records for safety and effectiveness, and should be regulated via a "monograph" system rather than individual approvals, using the expert review panel approach discussed in the Draft Proposals.

3. *The composition, use and oversight of expert review panels.*

Expert review panels established by an individual company should include company experts; expert review panels established by outside organizations need to consider conflicts of interest in the operation of such panels.

4. *The regulation of new animal drugs not currently on the market.*

Warner-Lambert proposes that new animal drugs that are not currently on the market should be regulated through the alternate approval standard explained in the Draft Proposals.

All of the comments are specifically limited to the application of the Draft Proposals to medicated feeds or treatments for ornamental fish or reptiles. The comments are not intended to apply to any other segment of the animal feed or animal pharmaceutical industries. As such, they apply only to a very limited range of non-food animals.

### **SECTION III C MANUFACTURING**

#### **Comment 1: Current Good Manufacturing Practices requirements**

The Draft Proposals state that animal drugs for minor uses are to be manufactured in accordance with current Good Manufacturing Practices ("cGMPs") pursuant to 21 C.F.R. Parts 211, 225 and 226. These regulations, particularly Part 225, which relates to the manufacture of Type B and C medicated feeds from Type A medicated articles, and Part 226, which is directed to the manufacture of Type A medicated articles, are different in their application of Good Manufacturing Practices to these types of products compared to "finished pharmaceuticals" under Part 211. The Draft Proposals advise, moreover, that CVM is flexible in its case-by-case determination of what constitutes cGMPs for these products and uses, recognizing that some products may be medicated feeds of original manufacture, rather than subsequent dilution by a third party.

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The manufacturing facility of Warner-Lambert's Tetra/Second nature division for medicated feed and medicinal products sold in the United States is located in Germany. The ISO-9000-compliant facility is certified by the German government as an animal drug manufacturer and holds a separate German government certification as an animal feed and animal premix manufacturer. Tetra/Second nature has held such certifications for over twenty years. The requirements to obtain and maintain Tetra's animal drug certification include thorough inspections of the premises every two to three years and more frequent inspection of Tetra's products, labeling and protocols. Maintenance of the German government certification for the production of animal feeds and animal premixes entails surprise inspections of Tetra's facilities, including its equipment and personnel. Moreover, the German system is similar to the NADA procedure in that the manufacturer is required to report to the authorities all adverse reactions associated with any of the products covered by the certification. Tetra has reported no significant adverse reactions to its products since the inception of its certification in 1974.

Although manufacturing conditions sanctioned by the German government for these types of feeds and other therapeutic products do not precisely match cGMPs in every detail, they are very similar to cGMPs and produce a comparable result. The German-sanctioned manufacturing processes should therefore be considered "equivalent" to cGMPs as required in the United States. In the interest of international harmonization, we submit that manufacturing processes for these types of products that are certified by our World Trade Organization neighbors, such as Germany, should be considered equivalent to cGMPs, and should be deemed to have met FDA requirements in this respect.

#### **SECTION IV B REMOVAL OF DISINCENTIVES**

##### **Comment 2: The regulation of unapproved medicated feed ingredients already on the market**

There are a number of active ingredients used in the treatment of ornamental fish or reptiles that have been on the market for a number of years, but have never been formally approved. Some of these products have been incorporated into medicated feed. Examples of these products include Tetra Medica Medicated Flake Food and Medicated Food Sticks. Other treatments for ornamental fish, such as the anti-parasitic formulation ContraSpot, and the combination anti-parasitic and antibacterial products Marin-Oomed and Gold-Oomed, are marketed separately from feed. These types of products have been used on ornamental fish for many years, and have established track records with respect to their safety and effectiveness. For example, the Contra-Spot and Gold-Oomed products have been sold for a number of years for control of bacterial infections and parasites. These products contain malachite green oxalate and formaldehyde. Literature reports published over the last fifty

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years as well as expert evaluations show that malachite green is an effective antiparasitic agent and formaldehyde is an effective disinfectant. Both chemicals have been used individually and in combination for a substantial period of time, and the company has both acute and chronic toxicity data for these products.

Because treatment products for non-food ornamental fish and reptiles have been used for so many years, and because they have established safety and effectiveness records, we believe that it would be neither necessary nor cost effective for FDA or industry to subject each of these ingredients as used in current or prospective products to the full NADA review process. Rather, we submit that a more appropriate and efficient regulatory scheme would be to issue "monographs" for these ingredients, precisely as was done in the case of historically used human over-the-counter drug products. This approach has two benefits. First, it would allow FDA to promulgate one set of standards for a given ingredient or product, without having to issue separate NADA approvals to each manufacturer. Second, it would allow manufacturers collectively to rely on the safety and effectiveness data that has already been established for the ingredient or product, without having to commit the considerable resources required to conduct individual controlled studies that would be necessary to support an NADA.

For example, the total annual sales for medicated feed for ornamental fish in the United States totals an estimated \$200,000 to \$300,000 at wholesale. Tetra's annual wholesale revenues of any individual product in this market range from \$20,000 to \$50,000. The entire U.S. wholesale market for medicated products for reptiles is estimated to be about \$1 million per year. Annual wholesale revenues from Tetra's largest-selling product in this category are no greater than about \$35,000. Hence, the size of the market and the potential revenues for many of these products that could be used to support individual NADAs are extremely limited.

The use of a monograph-based regulatory framework for existing medicated feed ingredient and treatment products for ornamental fish would not compromise any of the safeguards built into the proposed regulations. Because these products are marketed and used only for non-food ornamental fish or reptiles, they do not raise human health or safety concerns. Nor are there currently any medicated feed ingredients for use in ornamental fish or reptiles that have previously been approved for these applications. Therefore, there are no competitive interests of NADA holders that need to be protected. For all of these reasons, we urge FDA to develop a monograph-based regulatory system for these ingredients and products.

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

**Comment 3: Expert review panels**

Warner-Lambert supports the use of expert review panels (ERPs) as a means of bridging the gap between studies and literature on specific active ingredients, and concluding that the formulated product is safe and effective for its intended use with ornamental fish. In reviewing the concepts presented in the Draft Proposals, however, Warner-Lambert has the following comments.

We believe that there is a difference between panels created by a company and by a third party (whether a science-based organization such as the American Society for Animal Science, or a trade group such the APPMA). Particularly in the case of ornamental fish and reptiles maintained as pets, there are few experts who have not, or are not, consulting for various interested manufacturers. Where a manufacturer creates a panel, it should be able to consist of both outside experts, whose current or prior work for a company is disclosed, and inside experts who have not been responsible for the particular product under review. Such an *ad hoc* panel, whose members were reviewed with FDA before their appointment, would maximize the number of available experts to review various products. If, on the other hand, inside experts were not permitted on such panels, the pool would be smaller, and a drug sponsor should be able to empanel a standing ERP whose members were previously reviewed with FDA, rather than establish a new panel for each new product.

In the case of a third-party-empanelled ERP, the principal problem would be the avoidance of either actual or perceived conflicts of interest on the part of panel members. This problem arises from the relatively small pool of experts and the likelihood that most if not all of them have a history of consulting for manufacturers. The nature of the empanelling entity is less important: While science-based groups such as FASEB have a proven track record in creating and using such panels, trade groups such the Flavor and Extract Manufacturers Association and the Cosmetic, Toiletry and Fragrance Association equally have an established program of expert panel reviews. What becomes important is that the panel process be "transparent," i.e., that how panel members are chosen and their consulting affiliations be evident, and that persons using the panel be able to challenge the use of a particular panel member if the consulting affiliations of that panel member present too much of the appearance of a conflict of interest.

We appreciate that CVM will be reviewing the report of each ERP, and will ultimately decide whether the sponsored article should be approved. It remains important, especially in the case of ERPs created by third parties, that the process and use of panel

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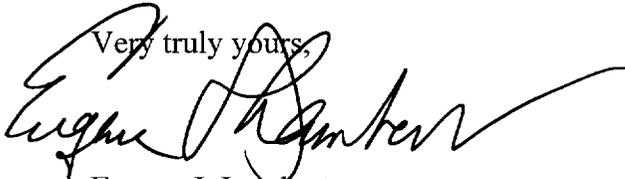
members be consistent with the standards that FDA would follow if the ERP were FDA created.

**Comment 4: The regulation of new drugs for use in ornamental fish**

In contrast to the type of regulatory treatment that should be applied to those medicated feed ingredients and other ornamental fish or reptile treatments that have been on the market for some time, we suggest that the NADA system, and specifically pursuant to the alternate approval standard outlined in the Draft Proposals, would be appropriate for newly developed new animal drugs for use in ornamental fish or reptiles. Unlike the existing products, these new products do not have track records establishing their safety or effectiveness. Hence, Warner-Lambert supports the use of the alternate approval standard of the NADA process for such products. Given the likely size of any market for new products, however, they will remain ones for minor species and uses. Accordingly, the CVM concepts for the use of expert panel reviews and the acceptance of data other than clinically based evidence of safety and effectiveness should be used in the NADA review process.

Warner-Lambert disagrees, however, with the concept that approvals under this system should carry some crepe label suggesting that the conclusion of the agency that the products are safe and effective for their intended (and labeled) use(s) is somehow tainted or made with fingers crossed behind the back. The expertise of the ERP members, based on their experience and training, is the fundamental basis of approval. Even under the current statute, the study requirements are designed to provide a basis upon which adequately trained and experienced experts can conclude that the drug is safe and effective for its intended uses. Although not all the data might be of the rigorous quality for a traditional NADA, it would have to be of sufficient quality that it will be accepted as adequate for experts to act upon. If it is so accepted, then the decision of the expert panel should be deemed to meet the requirements of the statute without denigration.

We believe implementation of the foregoing comments would significantly enhance the application of the Draft Proposals to the ornamental fish feed and treatment industry. Again, we appreciate FDA's agreement to accept these comments following the date set for their submission.

Very truly yours,  
  
Eugene I. Lambert

cc: Marcia Uriu, Esq.

**ROUTING AND TRANSMITTAL SLIP**

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2/19/98

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**REMARKS**

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