



The voice of fish and wildlife agencies

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Attention Docket ID No. FDA-2017-N-5104

Re: Review of Existing Center for Veterinary Medicine Regulatory and Information Collection Requirements

Dear Deputy Commissioner Abram:

The Association of Fish and Wildlife Agencies (AFWA), founded in 1902, is the professional association for the state fish and wildlife agencies, and our membership includes public agencies charged with the protection and management of North America's fish and wildlife resources. AFWA's governmental members include the fish and wildlife agencies of the states, provinces, and federal governments of the U.S. and Canada, and we collaborate with Mexico. All 50 states are members of AFWA and rely heavily on successful propagation of fish species to achieve fisheries resource management objectives for state and federally-listed threatened and endangered fish as well as those that provide for robust recreational opportunities. To achieve these goals our members depend on access to therapeutants regulated by the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) and we sincerely appreciate the opportunity to provide comments intended to facilitate increased collaboration as we work to implement the best available science in an effort to streamline the aquatic drug approval process moving forward.

The availability of a comprehensive suite of therapeutants to effectively and efficiently treat indications in captive and wild fish, induce spawning for key species, and reduce preventable outbreaks is critical to the conservation of our nations fish and aquatic resources and remains a priority for the Association and its members. As you know, prior to 1990, the FDA exercised its authority for Regulatory Discretion and chose not to regulate the use of drugs in aquatic species. FDA's position allowed public and private fisheries professionals' broad access to a wide variety of drugs and other chemicals, and such compounds were routinely utilized to maintain aquatic animal health. However, in the early 1990s the FDA determined that there was a need to regulate drug use in aquatic species. The challenge presented by this policy change to regulate drug use in aquatic species was exacerbated by FDA's broad definition of a drug. A drug as defined by the FDA includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)].

In response to the aforementioned facts, the Association established a cooperative initiative between AFWA (representing all 50 states), U.S. Fish and Wildlife Service (FWS), U.S. Geological Survey (USGS), and U.S. Department of Agriculture (USDA) in an effort to fund, conduct, and coordinate the extensive research required to obtain FDA approval of priority aquaculture drugs as identified by the states. Over

time, this initiative developed into a working group under AFWA's Fisheries & Water Resources Policy Committee and now represents the longest standing working group in the Association where, currently, both federal and state partners (USGS, FWS, and NOAA) come together to work collaboratively on the mutual goal of achieving aquatic animal drug approvals. Although, there have been drugs added to the approval list over the last 20 years, due largely to the collaborative effort of the AFWA Drug Approval Working Group (DAWG), there remains a significant need in the aquatic community for more access to approved drugs.

The successful completion of all "technical section" requirements necessary to obtain FDA approval of a new drug is a time consuming and expensive endeavor. This statement is true for all animal species. It has long been estimated that a single new drug approval requires an investment of 8-10 years and 10-20 million dollars. It is also important to note that in some respects, new drug approvals for fish are even more arduous than those for humans or many terrestrial animal species. As fish are a potential source of food for humans, fish drug approvals require completion of the full tier of studies needed to complete the Human Food Safety (HFS) technical section. Of all the technical sections (5) potentially required for a new animal drug approval, the HFS technical is typically the most expensive, time consuming, and challenging to navigate for the regulated community.

In the pharmaceutical business, FDA approval of a new drug for use in humans is worth billions of dollars in new revenue. Somewhat similarly, FDA approval of a new drug for use in a major terrestrial animal species is worth many millions (or possibly even billions) of dollars in new revenue. Quite conversely, a pharmaceutical company that obtains FDA approval of a new drug for use in an aquatic species may never fully recover the costs of their investment. Based on the relatively small size of the aquaculture industry in the U.S., the economic incentives simply do not exist to entice pharmaceutical companies to pursue aquatic species drug approvals. The bottom line is that few, if any, pharmaceutical sponsors have been willing to pursue such approvals without some assurance of cost-sharing assistance from public sector agencies/entities (e.g., AFWA/DAWG), leaving the aquaculture community with an extremely limited suite of approved drugs to choose from when attempting to grow and maintain healthy fish.

The Association would like to take the opportunity to extend its appreciation to CVM staff for their willingness to attend the DAWG meetings and greatly appreciates the chance to share our thoughts with CVM on how we can work more collaboratively to identify the opportunities to bolster science and decrease regulatory burden with regard to aquatic animal drug approvals.

If you have any questions regarding the attached commentary, please contact Ms. Devin DeMario at ddemario@fishwildlife.gov or 202-838-2562.

Sincerely,



Virgil Moore
President

These comments are in reference to: **Guidance for Industry 61: FDA Approval of New Animal Drugs for Minor Uses and for Minor Species; Part 2E: Aquatic Species**

Section I. Effectiveness

B. Water Treatments for External Infections

- To date, interactions with CVM on drug approvals have not been supportive of broad label claims and have not been consistent with the language found in Section I.B. stating that “*CVM encourages sponsors and investigators to support label claims which are as broad as possible, covering a variety of pathogens and fish species.*” For example, currently a pathogen causing mortality must be identified to the species level prior to the application of a treatment; if trials show susceptibility to the treatment then the new or expanded label is only applicable for that infectious pathogen species.
- CVM operations currently do not support the statement that, “*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.*” At present, effectiveness, as well as Target Animal Safety (TAS) and residue depletion studies are required on up to six different fish species for freshwater fish (excluding ornamental fish) species. Based on recent interactions with CVM as well as past experience with freshwater fish, it is anticipated that an additional six marine fish species would need to be tested to support a claim for marine fish, a faction of aquaculture that currently has no approved drugs to utilize. Data that were presented at a CVM sponsored seminar on reducing efficacy and Target Animal Safety (TAS) requirements in support of drug approvals (held at FDA CVM Learning Management Institute, Spring 2010 Scientific Seminar Series, March 29 and 30, 2010, Rockville MD) assessed numerous fish species and revealed that there is no evidence of significant variability in biomarkers relative to treatment effectiveness. Additional research presented yielded unequivocally that in TAS studies, lesions were observed across all species included in the study design and were not restricted to one or a few species. With regard to residue depletion studies, research conducted on multiple species showed a relatively tight temporal range for the depletion of drug residue from tissues and the driving factor on residue depletion was temperature dependent and not fish species dependent.
- ***“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).”*** - Based on experience thus far, CVM requires testing on 6 different fish species. To the best of our knowledge, there is little to no evidence that a drug is effective in treating one fish species but is not effective treating another fish species. It is unclear as to why the FDA views fish (as a group of animals) differently than it does other “food animals” or companion animals. With over 100 freshwater fish species currently raised in the U.S., the implications of “species-by-species” data

requirements are significant. While CVM has allowed some “species grouping”, as cited in the italicized text above, with respect to drug approvals for freshwater fish (i.e., data from two or more species within a like grouping of fish are considered sufficient for all group members; e.g., all freshwater salmonid species), data requirements for “all fish” label claims remain significantly greater than similar claims for other animals. The Association would appreciate the opportunity to discuss the potential to further streamline these approval processes and provide more consistency to the regulated community.

Section I. Effectiveness

B. Water Treatments for External Infections

1. Dose Confirmation/Field Trials

- While this section states that, *“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.”* Experience with this process thus far has revealed inconsistencies in the types of documentation that CVM deems acceptable for use in aquatic animal drug approval processes. Additional clarification with respect to what constitutes acceptable unpublished, non-reviewed, or peer-reviewed literature would be beneficial. Consistency and transparency in these requirements will ensure that the limited private and public resources put toward these research efforts are not wasted.

Section I. Effectiveness

B. Water Treatments for External Infections

1. Dose Confirmation/Field Trials

3. Dose Determination/Dose Confirmation Field Trials

- Text in this section outlines that, *“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”* – Based on numerous rejected alternatives that have been provided thus far it remains unclear as to what criteria an alternative approach would need to meet in order for CVM to accept it as a science based alternative consistent with the text found in Section 1. Part C. This lack of clarity results in researchers and drug sponsors investing valuable time, expertise, and resources into the development of an experimental design to address the known variabilities and challenges in Dose Confirmation Field Trials only for those resources to be lost upon a rejection from CVM, often resulting in loss of interest from the sponsor and the cessation of the endeavor. For example, suggestions that included the use of disease challenge trials and use of pharmacokinetic data + minimum inhibitory concentration data were rejected although research has found similar methods to be acceptable for ascertaining immune response and rates of compound biometabolism. It is also unclear as to

what the definition of a “site” is within this section. Meeting the requirements within this section to conduct field trials at a minimum of two sites has been shown to be difficult to achieve due to the challenges surrounding conducting “controlled” field trials on sites that are often not owned by the sponsor or the researcher. Further refining the acceptable criteria for “alternative approaches” with those conducting the studies and sponsors investing in the drug approval process in a clear and transparent manner is desirable.

Section I. Effectiveness

C. Systemically active drugs

- As mentioned in the previous section, it is unclear as to what the definition of a “site” is within this section. Further, meeting the similar requirements within this section to conduct field trials at a minimum of two sites has been shown to be difficult to achieve due to the challenges surrounding conducting “controlled” field trials on sites that are often not owned by the sponsor or the researcher. Please also see bullet three under Section I.B. in relation to species groupings.

Section II. Target Animal Safety

A. Water Treatments for External Infections,

2. Multiple Dose Target Animal Safety Studies.

- To date, the research supporting the need to test individual fish species at one or two different doses as outlined in this section has not been presented. Over the last two decades of research it has been the common toxicological practice within the field of aquatic therapeutants to identify one effective treatment dose and conduct all testing at that specific dose in a controlled setting. The current exception to this approach is when the endpoint of the therapeutant varies based on the unique objectives of the research being conducted. For example, fisheries professionals utilize sedatives to handle fish in a non-invasive manner, to immobilize fish for – surgical procedures, and, in some cases, to efficiently euthanize individuals. Therefore, fisheries professionals sedate fish to a desired end point and not for a defined period time and call on their training to effectively reach these objectives. The Association respectfully requests the opportunity to discuss these recommendations in more detail in an effort to better understand the rationale for multiple species testing in relation to the best available science as well as the ability to pragmatically incorporate varying therapeutant end points in the TAS requirements.
- It should be further noted that although not stated in this Guidance for Industry document, it has been made clear that TAS studies for Minor Species have to be conducted in compliance with the Good Laboratory Practice (GLP) regulation (21 CFR 58) and should only be required of sponsors who are conducting their own research in support of drug approvals. We offer that for aquatic Minor Species, more common QA practices, like ISO9000 certification should be used. Although many programs operate under strict quality assurance and quality control practices,

very few programs are technically GLP compliant and this severely constrains studies that can be done by otherwise extremely competent researchers, further limiting the ability to conduct the many needed studies to achieve a drug approval. If FDA CVM is going to require GLP's for aquatic Minor Species, they should only be required of the Study Director's facility which would allow studies to be conducted under the Study Director's supervision at sites that are not set up to do GLP studies.

Section II. Target Animal Safety

B. Systemic treatments

- While the Association appreciates the language encouraging interaction with CVM prior to the initiation of any studies, we feel that this interaction along with more refined standards would provide both consistency and certainty to the sponsors and researchers when seeking to develop studies to inform much needed aquatic animal drug approvals. Aforementioned comments regarding TAS studies, Field Trials and Acceptable literature and data are also applicable to this section.

Section III. Human Food Safety

B. Special Conditions for Consideration with Aquatic Species

1. Life Stage Considerations: Food Fish Status of the Inedible Life Stages of Edible Species.

- The Association respectfully requests that CVM reconsider its policy that, "*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.*" Consideration should first be given to the fact that eggs in a propagation setting are not to be consumed. Further, the volume and concentration of drug administered in this environment for treatment purposes of eggs or fry is miniscule and there is no practical reason why residues should be measured in eggs or resultant fry when these stocks are not available for potential human consumption for numerous growing seasons, during which therapeutic tissue residues deplete significantly in light of both metabolism and dilution due to increased biomass. Similar to fish and fry, it is also not appropriate to require residue depletion studies on broodfish that will be euthanized and discarded as part of standard propagation practices and cannot enter the human food chain. It appears that the consideration of eggs, fry, and broodfish, that are known by FDA to not be marketed for Human Consumption, as "food fish", and thus subject to rigorous and costly depletion studies, is an imposed cost on the public and private sector that exceeds benefit.

Section III. Human Food Safety

B. Special Conditions for Consideration with Aquatic Species

Part 3. a. Temperature Considerations: Effects of Temperature on Nature, Disposition, and Depletion of Residues

- In this section, CVM states that “*residue depletion studies should be conducted at the minimum water temperature for which an approval is sought.*” It is unclear if this statement applies to coldwater fish or for each temperature classification of fish. There is ample evidence that has been submitted to CVM that residue depletion is correlated to water temperature and not fish species. Given the results of these studies, it appears that the CVM can significantly streamline the process in accordance with the best available science by requiring one residue depletion study on a coldwater fish at the lowest temperature possible. The data yielded from that study can then representatively serve as the benchmark to establish the withdrawal period. Based on our interactions with drug sponsors when attempting to navigate the approval process, it appears that there are concerns with the CVM requirement to conduct multiple residue depletion trials and have subsequent multiple withdrawal periods for different fish groups. These requirements ultimately act as a barrier to the progression of needed drug approvals. For more information supporting this approach please see data submitted to CVM re: “Oxytetracycline residue depletion for data to support the statement that residues deplete slower at lower water temperature.” In the event this research is not readily accessible, we would be happy to provide it for your review.

Section III. Human Food Safety

B. Special Conditions for Consideration with Aquatic Species

4. Grouping of Species

- The Association would appreciate the opportunity to discuss the scientific evidence supporting the policy that fish species need to be grouped based on “differences in physiologies.” Further, we would like to work with CVM to investigate the potential for an alternative approach that provides a science informed framework to conduct effective and comprehensive studies while also removing barriers to sponsors and researchers.

Section III. Human Food Safety

C. Food Safety Assessment

1. Hazard Assessment (Toxicological Considerations)

- The Association requests that further consideration be given to drugs that are considered Generally Recognized as Safe (GRAS) by the FDA for purposes that constitute ingestion. If FDA has classified the active ingredient in a drug (e.g., eugenol) as GRAS for human consumption, then the results of that decision, and accompanying research, should be incorporated readily into the aquatic animal drug approval and serve to streamline the Human Food Safety portion of the drug approval process.

Unidentified GFI.

- Although, not included in the language of GFI 61, it is important to take this opportunity to note that CVM currently does not have an appropriate framework to manage certain situations as they relate to Manufacturing Control. For example, we feel that a pharmaceutical grade active ingredient (e.g., eugenol) should be able to be used in the manufacturing of a drug (e.g., AQUIS20E). Based on our interactions with CVM on this topic thus far, it appears that the only official language governing manufacturing control of pharmaceutical grade ingredients is in relation to the use of crude products in the formulation of human medicinals. The products in question are not considered a human medicinal, but are strictly for fish, and the associated regulatory requirements and processes should reflect such.

In addition, due to the increased interest in the use of crude products such as carp pituitary or catfish pituitary to support spawning in aquaculture settings, it is recommended that CVM develop a system to address these crude products in an efficient manner.