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UNIVERSITY

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

Dear FDA Officials:

RE: Response to FDA objectives on the FDA Modernization Act of 1997 (Docket No. 98N-0339)

I am responding to the questions that FDA and CVM raised regarding the FDA Modernization Act of 1997 (Docket No. 98N-0339). My comments are based on the drug needs of minor animal species industries, especially the aquaculture industry.

FDA questions:

1. What can FDA do to improve its explanation of the Agency's submission review processes, and make explanations more available to product sponsors and other interested parties?

Answer: The explanation of the submission review processes are not as important as having timely reviews. FDA needs to provide a timetable for reviews of each type of submission in a document that is circulated to all product sponsors, including compassionate INAD sponsors. Then, FDA needs to perform reviews in a timely manner. If that means more reviewers, then FDA should go to Congress to ask for more reviewers on behalf of animal health. Reviews of protocols and technical section submissions to NADAs are not timely, especially for minor species such as aquatic animals. Many submissions have not been reviewed even after 6 to 12 months after they are submitted. Because of the time delay, sponsors do not get feedback on their submissions to determine if they need to change the format, contents, etc. of future submissions and, thus, perpetuate mistakes that continue to increase the time for Agency review.

FDA needs to streamline its review process.

FDA can meet the demands for approval of safe minor species drugs by releasing to Congress the document entitled "Proposals to increase the availability of approved animal drugs for minor species and minor uses" that CVM developed with input from the minor species industries.

2. How can the Agency maximize the availability and clarity of information concerning new products?

98N-0339

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OFFICE OF
**THE NADA
COORDINATOR**

In Cooperation with
Cooperative State Research,
Education and Extension
Service, USDA

3039 Edgewater Lane
La Crosse, WI
54603-1088

(608) 781-2205

FAX: (608) 783-3507

E-mail: rozschnick@aol.com

Answer: FDA needs to ensure that all information on new products is accessible on its Web Page and placed in a timely manner in “FDA Veterinarian”. FDA needs to identify key persons in each industry to provide “alerts” on new products coming through the pipeline to the Federal Register before they are published but after FDA has approved them.

3. How can FDA work with its partners to ensure that products--domestic and foreign-produced and marketed by the regulated industry are of high quality and provide necessary consumer protection; and how can FDA best establish and sustain an effective, timely, and science-based postmarketing surveillance system for reporting, monitoring, evaluating, and correcting problems associated with use/consumption of FDA-regulated products?

Answer: If FDA accepts the tolerances and withdrawal times for the use of certain drugs on animals in other countries, then FDA should allow the use of those same drugs in the U.S. Without this consideration, FDA is creating an uneven playing field for domestic producers. FDA needs to create some kind of interim approval system or conditional approval so that sponsors can meet the data requirements while being allowed to market the very drugs that are allowed by FDA to be used on imported animals. The same withdrawal times and tolerances should apply for foreign and domestic use.

FDA needs to develop a policy for a postmarketing surveillance system that sets priorities for surveillance and compliance for both foreign and domestic products. This means that FDA may not do postmarketing monitoring on certain kinds or classes of products because they are known to be safe for consumption. These decisions should be based on science and the mode of culture. There is no way that FDA can have an effective and timely surveillance program unless the Agency makes some hard decisions through a good risk assessment on which products to monitor before the product is marketed. If the Division of Surveillance and Compliance is to do postmarketing, the Agency needs to ensure that it has sufficient numbers of scientists who are knowledgeable in these areas of expertise. FDA could rely on the domestic industry to assist the Agency in making some of these decisions and help in the review process.

FDA can meet the demands for approval of safe minor species drugs by releasing to Congress the document entitled “Proposals to increase the availability of approved animal drugs for minor species and minor uses” that CVM developed with input from the minor species industries.

4. What approach should FDA use to ensure an appropriate scientific infrastructure with continued access to scientific and technical expertise needed to meet its

statutory obligations and strengthen its science-based decision-making process?

Answer: FDA needs to ensure that the best trained scientists and experts in this field are selected for these positions and that the selection process is based on getting the best person for the position. There is too much at stake for our domestic industry to not get the best scientists available in this area of expertise. FDA needs to ensure that CVM's Division of Therapeutic Drugs for Food Animals performs the animal drug evaluation process (pre-approval evaluation) and the Division of Surveillance and Compliance is involved only in the post-approval process.

FDA can meet the needs for scientific infrastructure for minor species minor use drugs by releasing to Congress the document entitled "Proposals to increase the availability of approved animal drugs for minor species and minor uses" that CVM developed with input from the minor species industries.

5. What do you believe FDA should do to adequately meet the demands that are beginning to burden the application review process, especially for non-user fee products, so that it can meet its statutory obligations to achieve timely product reviews?

Answer: FDA needs to go to Congress and ask that it provide the funds to support the Food Quality Protection Act that they passed. This is another unfunded mandate at a time when Congress has been downsizing FDA budgets. FDA can not meet these requirements without proper funding and staffing of good scientists. The animal health industries would support FDA in this effort. If user fees are required, Congress will kill the animal health industry, especially minor species. FDA can meet the demands for approval of safe minor species drugs by releasing to Congress the document entitled "Proposals to increase the availability of approved animal drugs for minor species and minor uses" that CVM developed with input from the minor species industries. Those provisions that FDA can enact without Congressional approval, the Agency should do immediately.

6. What suggestions do you have for the Agency to eliminate backlogs in the review process?

Answer: FDA needs to request additional funds from Congress to hire more reviewers and send to Congress the document entitled "Proposals to increase the availability of approved animal drugs for minor species and minor uses" that CVM developed with input from the minor species industries. FDA needs to work more closely with sponsors to ensure that submissions are in the proper format and supply the information that FDA is seeking. One way to do that would be to

develop sample submissions as a guide for sponsors. Consideration should be made for drugs that are not human health hazards (based on other long uses, etc.) whereby FDA would not require a whole set of mammalian safety studies. FDA should do more calculations and extrapolations from other uses and the culture systems used. Any drug that has a “Generally Recognized As Safe” ruling for any use should have that status applied to any use. FDA should accept the reviews by regulatory agencies from other countries that have a good review program.

All these suggestions would decrease the time it takes for reviews and still provide for human food safety.

7. What other objectives related to the Agency’s statutory obligations or public expectations, beyond the six objectives, should be included in the FDA plan?

Answer: FDA needs to be proactive regarding funding requirements to get the job done. The Agency needs to get the animal industries involved in the process and keep them informed of its needs.

CVM questions:

1. Thinking of the many consumer protection functions performed by CVM (a listing of the functional activities performed by each of the offices in the Center was included in the information package mailed to you), are there some that should be changed? If so, how? Are there some that could be deleted? Are there functions not included that you would add?

Answer:

A. All functions of the Division of Manufacturing Technologies should be changed to help the minor species industries, especially the aquaculture industry where bulk drugs are extensively used. There should be different standards for manufacturing of drugs for minor species and minor uses, especially for water borne drugs that are used in large quantities as compared to drugs administered in medicated feed or injected. These standards should be determined by a panel of manufacturers and CVM and these standards should be reflected on the product label.

B. Changes should be made in the Statutory Authority of CVM as follows:

The standards should be different for target animal safety and effectiveness of new animal drugs intended for use in minor species or for minor uses. The human food safety standards for drugs intended for minor species or for minor uses must provide data that demonstrates that the food is safe for human consumption;

however, the methods and tests used to provide this assurance may be different from those required for major food species.

In the case of target animal safety and effectiveness standards, the principle should be “Let the marketplace decide.” If a product is proven safe and effective for use in one species to control a certain disease, the producers will buy the product. Thus, minimal data should be required. The principles of flexibility should apply to labeling, study design, and number of studies for determining efficacy. “Flexible labeling” should be used to allow for the broadest listing of species and diseases, where groups of animals (e.g., classes of fish) and diseases can be placed on the label and where a range of doses or concentrations is acceptable to one dose or concentration. In addition, there should be no need to establish an “optimum dose or concentration” since the labeling would allow a range based on a variety of sources of data and information.

CVM should offer conditional approvals and postmarket surveillance as a tradeoff for requiring less in the way of premarket target animal safety and effectiveness studies for new animal drugs for minor species and minor uses.

Sufficient target animal safety data and information may be available in the literature even though the studies may not have been done under “Good Laboratory Practices” provisions. If there are no acceptable data available in the literature, one target animal safety study should be sufficient to cover “all fish” by using a flexible study design with the most sensitive representative species that has been determined by a pilot study or historical information.

Concerning human food safety, there is a need to accept the definition and concept of non-food fish for all early life stages (eggs, fry, fingerlings) and broodstock, and not on a case-by-case basis of early life stages. The public and private aquaculture industry needs to define the size of fingerlings for each species so that CVM can incorporate this life stage into the definition. Inclusion of broodstock in the non-food definition would mean that no broodstock would ever enter to human food supply.

The human food safety standards should have a consumption factor in its calculations in which only consumption data for the domestically farmed animals is used. In addition, CVM, who has encouraged crop grouping research, needs to review the research data on the concept, accept a range of variations in response to the drugs researched in pharmacokinetic studies, and require only one set of residue chemistry studies per drug. The use of surrogate species to reduce costs and, at the same time, providing for human food safety is extremely important to increasing the number of approved drugs for aquaculture. There is a need for CVM to

recognize the safety of those drugs that have a long history of safe use, especially those drugs that are considered to be Generally Recognized as Safe (GRAS); no additional safety studies should be required to add aquaculture drug uses to GRAS drugs.

If there is a concern for human food safety (e.g., drug resistance in humans) from the use of drugs in minor species, then FDA should accept risk assessments by experts that factor in culture practices, consumption figures, and built-in controls (e.g., post-approval monitoring).

C. Additional function to add to Division of Therapeutic Drugs for Food Animals: Create incentives to encourage the pursuit of approvals or supplemental approvals for minor species and minor uses.

Economic incentives would attract more pharmaceutical and chemical companies to the aquaculture industry. Delayed taxation on profits for a period of years, creation of a classification of “orphan drugs” for minor species or minor uses, extensions of the current periods of exclusivity, and criteria for determining how exclusivity is granted, should be implemented by Congress. The periods of time should be at least 10 years for a new animal drug and seven years for a supplemental NADA. The more minor of the minor use drugs (i.e., those species that have a very low consumption rate or are classified as non-food fish) should be treated differently from food fish that are consumed in greater quantities.

Changing the criteria for qualifying for exclusivity would be one incentive that would encourage sponsors to pursue approval of minor species drugs using a Public Master File. This would involve allowing the company to qualify for exclusivity without having to perform or fund an efficacy study as they currently do; if a company is willing to step forward and become an NADA sponsor, they should have to do it with minimal effort. There may be other criteria for qualifying for exclusivity that could be changed to attract sponsors.

One of the concerns of the pharmaceutical companies is liability. If companies could somehow be protected from litigation via labeling, then sponsors would be more willing to use the data from Public Master Files. Placing a warning on the label that the use of this drug on species with little or no data is done at the risk of the user would be one way of removing the concerns of the sponsor.

Some of the other items mentioned above should offer incentives to sponsors. These would include broad labels that include all fish and more than one disease claim, target animal safety and residue chemistry studies on one surrogate species, and minimal product chemistry requirements.

2. Which of these functions do you believe, it would be acceptable for CVM to charge fees?

Answer: None. If fees are charged, no more minor use minor species drugs will gain approval. Industry needs to help CVM gain additional funding from Congress for these unfunded mandates so that CVM can perform its functions properly and timely.

3. Which of these functions could, and should, CVM rely more on the efforts of third parties, such as testing laboratories, veterinary organizations, standards (domestic or international) setting organizations, states, or regulated industry?

Answer: Review of data by all CVM divisions with that authority. The primary review process could be accomplished by a panel of industry and government participants external to the agency. CVM should pay for these reviews, but industry would have to support increased funding for CVM to do so. In fact, there is a need for expedited reviews of current drug applications that could benefit from a system such as this. Currently, every time new information is requested, CVM has another 180 days to respond. This situation is most discouraging to the pharmaceutical companies. Again, if there could be a guarantee that the review process would be accelerated, the industry would support increased funding for CVM to do so through earmarking the funds for that purpose. If funding is not increased for CVM, then the users would have to come up with the needed funds through user fees or some form of funding mechanism to guarantee that reviews are accelerated.

4. Which of these functions do you see as having the best potential for CVM to collaborate with its external stakeholders? Please be specific and name both the functions and the collaborating stakeholder.

Answer: Division of Therapeutic Drugs for Food Animals' function: Evaluates, for animal safety and effectiveness, new animal drug applications for therapeutic drugs. Expert panels made up of knowledgeable animal industry experts should be used to determine efficacy and animal safety for approvals of drugs for minor species and minor uses. Information from the literature and expert opinion could serve for such determinations. Monographs could be written by industry experts who have the background in that area of expertise. In the early 1970's, CVM considered this approach under "Not New Drug Monographs" but the agency never followed up on this approach. This mechanism would work today if CVM offered guidance in the preparation of the documents.

5. Which of these functions do you believe offers the greatest opportunities for CVM

to place more emphasis on non-regulatory approaches--such as education, technical assistance, and collaborative problem solving--to protect and promote public health?

Answer: Office of Surveillance and Compliance's function: develops and evaluates surveillance and monitoring programs to ensure the safety and effectiveness of animal drugs and to detect emerging resistance to antimicrobials among zoonotic enteric pathogens. The Office needs to educate and problem solve together on these issues so that scientifically defensible policies can be developed and supported by sponsors, users, and consumers.

6. In the international arena, CVM is faced with similar questions on the allocation of its resources. Currently, the Center's international resources are split between international standard setting, such as the establishment of veterinary drug residue standards; efforts to internationally harmonize veterinary drug registration requirements; involvement in Agency efforts to develop mutual recognition agreements between the U.S. and other nations; offering technical assistance to foreign regulatory officials; and providing technical support to U.S. trade agencies. Would you maintain the current mix of effort, or change it? If you would change it, how?

Answer: CVM is playing a very key role in its interaction on international issues. The Agency needs to put most of its efforts on harmonizing veterinary drug requirements worldwide so that data are not being generated again and again for the same purpose. The second area of emphasis should be development of mutual agreements regarding veterinary drug usage and approvals so that the U.S. animal industries have a level playing field. Third, CVM should work with foreign regulatory authorities to share in reviews of submissions so that CVM does not have to review everything is depth itself.

Please keep me informed of developments regarding the "Proposals to increase the availability of approved animal drugs for minor species and minor uses" and its release to Congress.

Sincerely



Rosalie A. Schnick