November 8, 2016

Report of the CVM Working Group on the Regulation of ADAA Combination Drug Medicated Feeds

In 2014, an FDA Center for Veterinary Medicine working group was formed to address a stated performance goal in the Animal Drug User Fee Amendments of 2013 (ADUFA III) goals letter, specifically to explore, in concert with affected parties, potential changes to procedures and requirements related to the new animal drug application (NADA) approval process for combination drug medicated feeds. A docket to accept public comment was opened in 2014, and a public meeting was held in 2015. Two discussions were held with a working group from the Animal Health Institute, a trade organization representing the animal pharmaceutical industry during the development of this report. Additionally, input was solicited from other affected parties, including animal producers groups, feed mills, veterinary professional groups, and consumers. This report was developed for the discussions with regulated industry for reauthorization of the Animal Drug User Fee Act (ADUFA).

A. Labeling

1. The working group agrees with the publication of approved representative labeling for Type B and Type C medicated feeds (i.e., Blue Bird labels) on the CVM Web page, as the benefits of making these labels available to stakeholders are undeniable. CVM is aware that the Blue Bird labels currently available consist mostly of recently approved labels. CVM represents an important source for approved Blue Bird labels and has the administrative record of the approved Blue Bird labels. In order to identify and post all approved Blue Bird labels, including previously-approved labels that have not yet been posted, we propose that additional resources be obtained or a potential reallocation of resources between and within ONADE and OSC be evaluated in order to permit the publication of all approved Blue Bird labels in a timely fashion and to continue publication of labels as new or revised labeling is approved in order to ensure continued success.

2. The working group proposes that the active pharmaceutical ingredient (API) used to prepare Type B and Type C medicated feeds be identified by the established name(s) of the new animal drug(s) on Blue Bird labels. If, in addition to the established name(s), sponsors would like to include on the Blue Bird labels the proprietary name of the new animal drug (Type A medicated article(s)) used to prepare the medicated feed, the working group proposes that they do so using footnotes. This is consistent with CVM Guidance for Industry (GFI) #181, “Blue Bird Medicated Feed Labels.”

B. Phased Review of ADAA Combination New Animal Drugs

The working group proposes that sponsors pursuing approval of single new animal drugs for use in or on medicated feeds use an investigational new animal drug file (INAD file) and phased review processes for any medicated feed combinations that will contain the single new animal drug and other previously-approved new animal drugs when the combination is eligible for approval under the amendments to the Food, Drug, and Cosmetic Act (FD&C Act) made under the Animal Drug Availability Act of 1996 (ADAA). Such a combination is an ADAA combination new animal drug.

This proposal would not require a modification of the ADAA-based statutory requirement in section 512(d)(4) of the FD&C Act for the individual drugs intended for use in the combination to have previously been separately approved. The current requirement would remain unchanged, and CVM would not approve any combination new animal drugs for use in medicated feed containing the single new animal drug and previously approved drugs until after the single new animal drug has been approved.

The human food safety (HFS) technical section requirements will remain the same (i.e., a non-interference residue depletion study) as under the ADAA amendments. We note, however, that the requirement for a non-interference residue depletion study may be waived on a case-by-case basis when a sponsor can provide scientific justification for why such a study is not needed. Note, section 512(d)(4) does not require a reassessment of toxicology or microbial food safety.

To implement phased review of a technical section submitted to an INAD file, CVM will need to modify existing, or create new, policy and procedures in order to provide consistent administration of practices within ONADE for presubmission conferences where approval requirements for the combination new animal drugs intended for use in or on medicated feed are conveyed to sponsors. This may include identification of submissions that would need to be provided to the INAD file and expected responses to those submissions. New project management best practices will need to be established to: provide a record linking the single new animal drug and associated combination new animal drug(s); provide a record to link all decisions affecting the approval requirements of the single and combination new animal drug(s); and encourage sponsors to use the administrative NADA process for ADAA combination drugs for use in or on medicated feed. Finally, programmatic changes may need to be considered for CVM electronic (IT) systems to accommodate these changes.

When a sponsor and CVM hold a presubmission conference or predevelopment meeting regarding a single new animal drug for use in or on medicated feed, the meeting should include either the sponsor identifying, or CVM requesting, information regarding expected use of the single new animal drug in combination with previously-approved new animal drugs. This will facilitate the establishment of INAD exemptions and files for the combination new animal drugs and early discussion of approval requirements for those combinations.

Sponsors seeking approval of single new animal drug(s) and ADAA combination new animal drugs containing the single new animal drug that use the phased review process will need to communicate with CVM regarding the timing of submissions and will need to be prepared to monitor for changes within one technical section or application that may impact other technical sections, requirements, or applications. Effective communication with CVM, including sharing and discussing comprehensive information regarding the timing of submissions, will permit CVM to predict and possibly temporarily reallocate resources to meet the anticipated review demand for both the technical sections and NADAs. Additional human resources for CVM will likely be needed to ensure success of the program.

Finally, additional contingency language will need to be included in technical section complete letters or, alternatively, be part of a new type of letter used for an ADAA combination new animal drug to convey the relevant administrative requirements. For example, a technical section complete letter for the combination new animal drug will need to state that it is contingent upon the approval of the single new animal drug before CVM approves the combination new animal drug containing the single new animal drug.

C. Reducing Time Between Parent Type A Medicated Article Approval and Combination Approval

The working group proposes that CVM consider modifications to review time frames for certain types of submissions and applications made to CVM for ADAA combination new animal drugs used in or on animal feeds. The proposals in this section are intended to provide processes which may shorten the time between approval of a single new animal drug and the ADAA combination new animal drug application to something less than the minimum 180-day time frame typical of the current process. The exact reduction in time will be addressed during ADUFA IV negotiations. This action applies only to a subset of new animal drugs, their phased review submissions, and applications filed under section 512(b)(1) which have met the following conditions:

1. The ADAA combination will be for previously and separately approved drugs for use in or on animal feed.
2. All major technical section requirements under the FD&C Act have been met for the ADAA combination drug NADA. The major technical sections under the FD&C Act include: Human Food Safety; Effectiveness; Target Animal Safety; and Chemistry, Manufacturing, and Controls.
3. All minor technical section requirements under the FD&C Act have been met. The minor technical sections include Labeling and All Other Information.
4. The sponsor intends to claim a categorical exclusion under 21 CFR 25.33(a)(2) and state that no extraordinary circumstances exist.

   There are two ways that a sponsor could claim a categorical exclusion for an ADAA combination product with potential modifications to the current review processes. These modifications will meet the requirements of each drug in the combination being previously separately approved[1] and will result in a reduction in review time when these conditions have been met:

   - Modified review time for a non-administrative (traditional) application.

     The NADA for applications meeting the above conditions (ADAA combination drug NADA) is submitted as a non-administrative NADA containing a request for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.33(a)(2). This NADA is then reviewed and processed in a time frame less than 180 days, but not less than 60 days as currently allowed for administrative NADAs.

     or, alternatively

- Modified review time for an environmental impact technical section under phased review. Where the request for a categorical exclusion is submitted as a technical section under the INAD (as part of the phased review process), CVM will review the Environmental Impact technical section in less than the statutory time frame of 180 days, and the exact time frame will be determined as part of the ADUFA IV negotiations. After the Environmental Impact technical section complete letter is issued, an application for use of the ADAA combination drug in medicated feed is submitted as an administrative NADA.

D. Development of a Guidance for Industry to Address Content and Process for Approving ADAA Combinations

Instead of drafting a new guidance for industry (GFI) to address the content and approval process for applications for ADAA combinations, the working group proposes that CVM first examine whether language regarding this issue could be added to an existing guidance document. The working group suggests that GFI #132, "Administrative Applications and the Phased Review Process," may be an appropriate document in which to include such additional language if it is determined that such language would be helpful for the regulated industry. Such language may include use of the phased review process for approval as it relates to certain ADAA combinations and the requirements for each technical section, including Human Food Safety. The working group proposes that the feasibility of adding language to a current GFI be examined once Congress has reauthorized the collection of animal drug user fees.

[1] Because the categorical exclusion would not apply unless each drug in the combination has been previously approved, a sponsor may not submit a claim for a categorical exclusion (and state that no extraordinary circumstances exist) for an animal drug to be used in animal feed in combination with other previously-approved animal drugs until the single drug also has been approved. See 21 CFR 25.33(a)(2).