Recommendations on the Regulation of Combination Drug Medicated Feeds

A. Labeling

1. The working group recommends the posting of approved Blue Bird labeling on the CVM web page, as the benefits of making the labels available to stakeholders are undeniable. CVM is aware that the Blue Bird labels that have been posted so far consist mostly of more recently approved labels. CVM represents an important source for approved Blue Bird labels and has the administrative record of the approved Blue Bird labeling. In order to identify and post all approved Blue Bird labels, including previously-approved labels that have not yet been posted, we recommend that additional resources be obtained or a potential reallocation of resources between and within ONADE and OSC be evaluated in order to permit the posting of all approved Blue Bird labels in a timely fashion and to continue posting labels as new or revised labeling is approved in order to ensure continued success.
2. The working group recommends that on Blue Bird labels, the active drug ingredient used to prepare the medicated feeds be identified by the established names of the new animal drug(s). 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, they may do that by 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 recommends that CVM and sponsors pursuing approval of single-ingredient new animal drugs for use in or on medicated feeds employ the INAD file and phased review processes for any medicated feed combinations that will contain the single new animal drug and previously-approved new animal drugs where the combination is eligible for approval under the streamlined approval process established under the ADAA. This recommendation would not require a modification of the statutory requirement in section 512(d)(4) of the FD&C Act for the individual drugs intended for use in the combination to have been previously 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 already been approved.

The human food safety (HFS) technical section requirements will remain the same (i.e., a noninterference residue depletion study) as under the ADAA. We note, however, that the requirement for a noninterference 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 this recommendation, 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 recommends that CVM consider modifications to review timeframes for certain types of submissions and applications made to CVM for ADAA combination new animal drugs used in or on animal feeds. The recommendations 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 timeframe 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 timeframe 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 timeframe of 180 days, and the exact timeframe 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 recommends 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 recommends 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).