DRAFT

FEED AND LIVESTOCK DRUGS INSPECTION PROGRAM (FLDIP)
TECHNICAL ADVISORY SUBCOMMITTEE (TASC)

California Department of Food and Agriculture (CDFA)
HYBRID CONFERENCE MEETING

OCTOBER 3, 2024
1:00 PM- 3:00 PM
MINUTES

TASC Members	**CDFA Staff**	**Interested Parties**
Dr. Marit Arana, Chair	Rachelle Kennedy	Dan Rice
Jennifer Heguy	KC Gutenberger	Jeremy Banducci
Dr. Chel Moore	Jenna Leal	Alejandro Hernandez
Dr. Xixi Chen	Ted Bert	Ryan Boehler
Dr. Noelia Del Silva Rio	Samantha Moran-Defty	Dr. Allen Bridges
Dr. Robert Poppenga	Erika Lewis-Ortega	Dr. Doug Miller
David Isen	Ashley James	Eric Benziger
	Valerie White	Gary Fuller
	Killeen Sanders	Jed Asmus
	Lindsey Collier	
	Mike Davidson	
	Shelly King	
	Kelly Leon	
	Amber Hayter	
	Natalie Krout-Greenberg	
	Cathryn McCandless	

CALL TO ORDER

Dr. Marit Arana, Chair, called the meeting to order at 1:01 pm.

ROLL CALL/INTRODUCTIONS-ESTABLISH QUORUM

Self-introductions were made, and a quorum was established.

APPROVE MEETING MINUTES FROM March 27, 2024

Chair Arana requested the committee review the minutes from the previous meeting.

MOTION: David Isen moved to approve the meeting minutes from March 27, 2024. Dr. Robert Poppenga seconded, and the motion passed. Jennifer Hegy abstained from voting as she was not present for the last meeting.

BRANCH AND PROGRAM UPDATES

Natalie Krout-Greenberg provided an update on Branch discussions with United States Food and Drug Administration (FDA) and the completion of FDA's reorganization, resulting in the changing of names and acronyms of several departments within FDA.

Jenna Leal announced two upcoming vacancies to the TASC with the intention of a Feed Inspection Advisory Board vote for appointments in November 2024. Leal memorialized previous instances of TASC advice on labeling and use of various feed ingredients, as stated in the bylaws of TASC, and noted the importance of formalizing a process today. Leal continued with commending the work of Elanco Animal Health, Inc. in completing safety and efficacy review of Bovaer® 10 by FDA and the resulting letter of discretionary enforcement. Leal emphasized that CDFA will not be evaluating the safety and efficacy of Bovaer®10 and will defer to FDA for that process, but will be regulating proper labeling, use, and applicability of Bovaer®10 in California. Leal further elaborated with a timeline of the steps taken between Elanco Animal Health, Inc. and CDFA to date.

PROCESS TO EVALUATE PRODUCTS UNDER FDA ENFORCEMENT DISCRETION FOR SAFE AND EFFECTIVE USE IN CALIFORNIA

KC Gutenberger provided a background of FDA's various federal pathways of feed ingredient and animal drug approvals and discussed how FDA is currently evaluating and potentially changing these processes, including the withdrawal of Policies and Procedure Manual 1240.3605; Regulating Animal Foods with Drug Claims, and pending in Congress is the Innovative Feed Enhancement and Economic Development (IFEED) Act of 2023.

Dr. Poppenga asked if there is a known timeframe for any such changes from FDA. Leal responded that CDFA is not aware of a designated timeline, noting some of the changes are dependent on acts of Congress during an election year.

Gutenberger emphasized the status of FDA pathways has prompted the importance of formalizing the process for TASC involvement in evaluating the application of new feed products and ingredients regarding labeling and use in California. Gutenberger outlined a proposed five step formal process.

1. Evaluation by FDA including safety and efficacy review and issuance of an enforcement discretion letter, or equivalent.
2. CDFA evaluation including review of the product label and data as necessary to support decisions regarding proper labeling and use.
3. TASC evaluation providing expertise regarding proper labeling and use in making recommendations to the FIAB.
4. Feed Inspection Advisory Board (FIAB) evaluation of TASC recommendations and making recommendations to the Secretary.
5. Secretary designation of any requirements regarding labeling and use of the product in California.

Chair Arana advised the TASC that a motion and discussion was appropriate.

MOTION: David Isen moved to recommend the FIAB support the proposed five step process to evaluate products/ingredients under FDA enforcement discretion for safe and effective labeling and use in California. Xixi Chen seconded the motion, and the motion passed unanimously.

PRESENTATION FROM ELANCO REGARDING BOVAER®10: PRESENTED BY ALLEN BRIDGES AND DOUG MILLER

Dr. Allen Bridges provided an in-depth explanation of the federal review process for Bovaer®10 to receive an enforcement discretion letter from FDA. Bridges outlined Elanco's work with FDA Center for Veterinary Medicine (CVM) beginning in 2022 and noted that FDA has since put forth guidance on this pathway for others to follow in the future. Office of New Animal Drug Evaluation (ONADE) reviewed the Bovaer®10 product for food safety, including toxicology, residue data, tolerance, antimicrobial resistance risk and withdrawals. FDA determined the product had zero-day withdrawal time in tissue and milk. Bovaer®10 went through an Environmental Risk Assessment and it was concluded that Bovaer®10 showed no evidence of passing into the environment because it is highly metabolized. The CVM Division of Animal Food Ingredients (DAFI) also evaluated Bovaer®10 for target animal safety, effectiveness, and manufacturing. It was determined that in overdosing studies of feeding twice the dose there may be a decrease in dry matter intake. Elanco is continuing to gather data regarding stability and mixability. Bridges stated unique aspects to the FDA enforcement discretion letter for Bovaer®10 are that it does not have a New Animal Drug Application number, is required to be produced under current good manufacturing practices (CGMPs) for animal food rather than animal drugs, will not be listed in the Code of Federal Regulations (CFR) as an animal drug, is not required to be labeled as a medicated feed, and there are no requirements for use in combination with any animal drugs. Elanco has proceeded with state registrations as a food additive. Of the 39 states which have registered or otherwise allowed Bovaer® 10, some states have registered as a food additive, some states which have remedy laws have registered as a livestock remedy, and some states have issued their own enforcement discretion.

Leal noted that Elanco sought registration for Bovaer®10; however California does not register feed products.

Members of TASC had several questions, which were addressed by Dr. Bridges and Dr. Doug Miller.

Dr. Noelia Del Silva Rio asked how long was Bovaer®10 fed to animals. Bridges and Miller responded that, relevant to residue and withdrawal data, the requirements for the study are to feed the product until the substance reaches steady state in the animal, which was five days for 3-nitrooxypropanol (3-NOP). The pilot and pivotal studies for this data were five days, and it was concluded that 3-NOP is metabolized.

Poppenga commented that ONADE looks at the literature including much longer trials than five days. Bridges responded yes, Elanco was required to submit all other information (AOI) including additional literature and studies around the product.

Poppenga was curious what FDA considered effective reduction in methane. Bridges and Miller responded that it was based on a significant difference from the control. FDA did not establish a threshold or quantity. However, studies have demonstrated a 20-30% reduction in methane.

Chen asked if there is a difference between FDA and the European Union (EU) in terms of the stage of the cattle. Bridges responded that the EU approval is far broader including dry cows and beef. FDA required specific studies for each class of animal conducted in the U.S. for consideration. Since most of the studies available were in lactating dairy cattle, that is all that has been considered by FDA at this time.

Poppenga asked about the origin of the actual chemical. Bridges responded 3-NOP is currently made in Switzerland, sent to Germany for making Bovaer®10, bagged in Germany, sent to Elanco's warehouse in Switzerland and shipped to the U.S.

Chen asked about impurities conclusions. Bridges responded that it is required to be less than 2% total impurities; however, they are well below that as the recent batch had less than 0.67% total impurities. Chen asked if Bovaer® 10 is 10% 3-NOP, and Bridges clarified that Bovaer® 10 is guaranteed to be a minimum of 10% 3-NOP. Chair Arana asked if the rest is a silicon dioxide carrier, and Bridges clarified it is silicon dioxide and propylene glycol.

Poppenga asked if FDA is going to go through the process again to classify this ingredient. Bridges responded yes, if the IFEED Act passes it will have a permanent home as a Zootechnical Animal Food Substance.

Following questions, Chair Arana prompted the TASC to consider regulation of labeling and use for Bovaer® 10 in California. Leal read Food and Agricultural Code (FAC) Sections 14902.1 and 15011.

MOTION: Dr. Poppenga moved to recommend to the FIAB, to recommend to the Secretary, that Bovaer®10 falls under Feed Program authority as prescribed in Food and Agricultural Code Sections 14902.1 and 15011. Chen seconded the motion. The motion passed unanimously, except that Dr. Chel Moore recused himself from voting.

LABEL REQUIREMENTS OF COMMERCIAL FEEDS CONTAINING BOVAER®10

Gutenberger introduced proposed labeling requirements for commercial feeds containing Bovaer®10 and provided the TASC a visual example of a premix label containing Bovaer®10 for discussion and evaluation. The example premix label was developed by Elanco in collaboration with feedback from the CDFA Safe Animal Feed Education (SAFE) Program. Gutenberger stated the suggested necessary elements that should be present on any feed label containing Bovaer®10 include: all guarantees, indications for use, limitations, warnings, caution statements and other statements that appear on the Bovaer®10 label, concentration of 3NOP in mg/lb, and adequate directions for use which are likely to be followed in usual feeding practices to achieve a rate of 27.2mg – 36.3mg 3-NOP per pound (reflective of the FDA reviewed label for Bovaer® 10. TASC members had several questions and comments.

Chen asked if the product would be sold stand-alone or go through a feed manufacturer first. Bridges and Miller, with further input from Elanco staff Gary Fuller and Chel Moore,

responded that Bovaer® 10 will be sold to feed distributers, not directly to dairies. The feed distributor may manufacture a premix or may sell to a dairy which has the capability to manufacture their own premix. Elanco will not have a premix product available for sale.

Poppenga asked that the guaranteed analysis does not include propylene glycol. Bridges responded that 3-NOP and silicon dioxide must be guaranteed on the label, and propylene glycol must only be listed in the listing of ingredients. The concentration of propylene glycol would be what remains after considering 3-NOP and silicon dioxide. Arana asked if there is a methodology for silicon dioxide. Poppenga stated he will look into this; however, it may not be easy.

Leal asked for an explanation of the requirements for personal protective equipment (PPE) which are stated on the label. Bridges responded that the safety data sheet (SDS) for this product does require PPE; however, it is no different than the PPE requirements for monensin, which is commonly used in feed mills and dairies. Arana commented that the monensin label does not mention male infertility. Bridges responded that was true, and he can speak to that statement as well. Elanco has already submitted an amendment to FDA to request the removal of that statement because male infertility was only found in rats and the highest dose in the toxicological study. Studies in dogs and monkeys never found an effect on male fertility.

Dan Rice asked about a premix label which includes Bovaer®10, monensin, selenium, and a larvicide. Arana commented that the required warnings statement would not fit on both sides of a label, and the font would need to be very small. Bridges concurred that example label they have developed is consistent with FDA ‘blue bird’ labels, and much of the space is due to the table providing mixing directions. Gutenberger commented that the example shown was a catch-all, and the label for a specific feed would only need to provide applicable directions for mixing and use specific to that formulation. SAFE is working on developing further example labels, such as those including 3-NOP, monensin, selenium, and larvicide.

Silva Del Rio asked how new information, such as from current studies, is going to be used. Bridges stated new data would be used in various ways. As with all products Elanco is looking to expand and modify, for example, the dosage and adding dry cows. After submission and revision by FDA, Elanco will communicate any changes and/or updates to CDFA. Arana asked what level of 3-NOP was being used in a current study ongoing at UC Davis. Miller responded it is at 40 mg/kg- 80 mg/kg and will need to be conducted with an investigational authorization from CVM as off label.

Leal asked the TASC “Should the label change with FDA, do we want to go through this entire process again, or do we want to evaluate that label as it changes? “Arana responded that the whole process is not needed, but the TASC should re-evaluate the suggestions or latest findings.

Poppenga stated that diet can influence the effectiveness of methane reduction, and

asked how that could change. Bridges responded that this is due to CVM's review of certain studies which were conducted in the US which did not evaluate a level of effectiveness of Bovaer®10 when fed outside that range of neutral detergent fiber (NDF) and fat. Bridges clarified that diets outside that range of NDF and fat may impact the magnitude of effectiveness but does not affect the efficacy of methane reduction. The hope is that the range will be removed from the label when more data is reviewed. Arana asked if these values were in terms of dry matter or as-fed, as it was not stated. It was clarified that the values are on a dry matter basis.

Alejandro Hernandez asked if the best used by date is based on when 3-NOP is manufactured or when it is further processed into Bovaer®10. Miller stated the best by date is established after the final product has met all requirements and has 36 months timeframe. Arana commented that is only when kept under 77ºF, which is not going to happen here in California. Miller added that they do have data to show that at 40ºC at 12 months the product is stable in a closed bag.

MOTION: Dr. Poppenga moved to recommend the FIAB, to recommend to the Secretary, requirements for labeling of commercial feeds containing Bovaer®10 to be in compliance with FDA and California Commercial Feed Laws and Regulations and must include, at minimum; all guarantees, indications for use, limitations, warnings, caution statements and other statements which appear on the Bovaer®10 label; a statement of the concentration of 3-NOP in the commercial feed in units of mg/lb; and adequate directions for use which are capable of being followed and likely to be followed in usual feeding practices including, at minimum, directions to further manufacture the feed to achieve a rate of 27.2-36.3 mg 3-NOP per pound (60-80 mg per kilogram) of dry matter in the total mixed ration. Chen seconded the motion. The motion passed unanimously, except that Dr. Chel Moore recused himself from voting.

PUBLIC COMMENTS

No public comments were made.

NEXT MEETING/AGENDA ITEMS

It was decided to wait on scheduling the next TASC meeting to after the November 5, 2024Feed Inspection Advisory Board meeting and appointments of new TASC members.

ADJOURNMENT

The agenda was addressed and completed in totality. The meeting was adjourned at 3:03 pm.

Respectfully Submitted By:

ORIGINAL SIGNED BY JENNA LEAL October 3, 2024
Jenna Leal, Program Manager Date
Feed and Livestock Drugs Program