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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
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**Re: Docket No. FDA–2011–D–0784; Guidance for Industry on Evaluating the Effectiveness of Anticoccidial Drugs in Food-Producing Animals; Availability**

The ANIMAL HEALTH INSTITUTE (“AHI”) submits these comments to Docket No. FDA–2011–D–0784; Guidance for Industry on Evaluating the Effectiveness of Anticoccidial Drugs in Food-Producing Animals (GFI #217). AHI is the national trade association representing manufacturers of animal health products -- the pharmaceuticals, biological products and feed additives used in modern food production, and the medicines that keep livestock and pets healthy. AHI member companies represent the majority of animal pharmaceuticals and animal insecticides, as well as serving a significant segment of the world market.

AHI provided minor comments on the draft guidance on January 23, 2012 which did not affect the finalization of the guidance, and the final guidance was published in the Federal Register on November 20, 2012. Since then, AHI has identified inconsistency in the statistical approach used with other statistical guidance at both CVM and EMA and with certain portions of the guidance itself, which was overlooked the first time the draft guidance was out for review. We would like to point out the following experimental design issues which could lead to incorrect conclusions:

**Page 7 (Section I.D.) states:**

*D. Masking*

*In order to minimize bias, you should mask all personnel responsible for day-to-day management of the animals, including those making and recording observations.*

AHI agrees with this approach.

**Page 13 (Section II.B.2.) states:**

*2. Housing*

*You should give special consideration to the placement of birds within the battery. You should place non-inoculated, non-medicated control groups in the uppermost battery tier to prevent coccidial contamination of these birds.*

This is in direct contradiction to the masking section on Page 7. No one can be masked if the top row of the battery is always the same treatment. And, if cross-contamination is a concern, why not be concerned about cross-contaminating all the other treatment groups instead of just this one?

**Page 20 (Section II.B.8.a.) states:**

*a. Evaluation of an acceptable level of virulence*

*You should compare the inoculated, non-medicated control group to the non-inoculated, non-medicated control group to verify an acceptable level of virulence. The differences between these groups should be clinically relevant and statistically significant at  $\alpha = 0.05$  using a two-sided test. (See section II.B.5 for a discussion of differences CVM considers clinically relevant).*

If Page 13, Section II.B.2. is followed regarding the housing of this group, an analysis and corresponding p-value that is generated is not appropriate (or doable) given the experimental unit for that treatment (the row of non-inoculated, non-medicated birds is the experimental unit) is different from inoculated, non-medicated treatment (the cage is the experimental unit). There is not an appropriate way to model the analysis that is asked for if Page 13, Section II.B.2.

The main problem is the contradiction of Page 13, Section II.B.2. with the other two sections on Pages 7 and Pages 20 mentioned above. If we are to analyze that data and generate a p-value, we have to be able to randomize (which corresponds to what is mentioned in Page 7, Section I.D. above) and have to be able to appropriately identify and replicate the experimental unit (the cage, if randomized appropriately). If this treatment group is always kept on the top of the battery, there could be other things going on that are only effecting that treatment (e.g. AC/heat vents could be pointed directly on them from the ceiling, the techs could observe those birds first when the tech is most awake and taking his/her time when rushing to get finished at the end of the battery, lighting is an issue with chickens, etc.).

If that treatment is not replicated, or randomized, any analysis containing that group is not appropriate. There is no valid statistical model to account for this scenario.

**Additionally, Page 15 (Section II.B.6.) states:**

*6. Battery Study Design*

*We recommend a randomized complete block design for battery studies to account for heterogeneous environmental effects, such as temperature or humidity, which may exist within a facility. Efforts should be made to ensure homogeneous distribution of cages within each block; however, you should place the non-inoculated, non-medicated control groups in the top cages to prevent cross contamination. The cages used in the study should be identical in size. Male and female birds should be caged separately.*

It would seem that there is a conflict within this paragraph. In the first line, a randomized complete block design is recommended, but then it is recommended to place the non-inoculated, non-medicated control groups in the top cages. By doing so, the design would no longer be a randomized complete block.

The aim of an anticoccidial trial is to prove that the drug is effective. Therefore, a medicated, infected group (MI) must be compared against an unmedicated, infected group (UI).

Our opinion is that unmedicated, uninfected birds (UU) should not be part of the statistical analysis and should not be part of the randomization procedure. If these birds are caged in the top row, they would obviously not be part of the randomization process. The UU birds would be used as sentinels to determine if other infections that could confound the results are occurring.

Regarding comingling the UU group vs. moving the group to the top:

- First, keep in mind that these are not new studies; they have been conducted for years, with the UU group at the top. The idea is to try to keep the UU group from getting infected by the coccidia with which the other groups are artificially infected.
- The UU group has been used as a sentinel group to demonstrate that no other (non-coccidia) infection, that may affect the outcome of the study, is present.
- The other groups (MI - medicated, infected & UI - unmedicated, infected) are purposely infected with a known coccidia. If other infections occur, they could confound the outcome of the study and could lead to the study being discounted.

Thank you in advance for your consideration of these comments. Should you have any questions, please do not hesitate to contact AHI at (202) 637-2440.

Sincerely,



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