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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2012-N-1067; Proposed Rule; New Animal Drugs; Updating Tolerances for Residues of New Animal Drugs in Food**

The ANIMAL HEALTH INSTITUTE (“AHI”) submits these comments to Docket No. FDA-2012-N-1067; Proposed Rule; New Animal Drugs; Updating Tolerances for Residues of New Animal Drugs in Food. 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 welcomes the proposal to update the animal drug regulations regarding tolerances for residues of approved and conditionally approved new animal drugs in food. We appreciate the Agency’s efforts in bringing much needed clarity to a complex, critical topic for our industry. We like and agree with many of the proposed changes, however, we offer the following suggestions and comments below.

We suggest the Agency be consistent with VICH terms and definitions. The latest draft of the VICH Acute reference dose guidance has updated terminology regarding the ASDI and defining the toxicological point of departure. Consistent terminology in this proposed rule will avoid confusion, and perhaps changes will not be necessary in the future.

1. Definition of the acceptable single-dose intake (ASDI)

- The proposed definition for the acceptable single-dose intake (ASDI) is “the amount of total residue that may safely be consumed in a single meal.” The latest draft of the VICH acute reference dose guideline defines the acute reference dose (ARfD) as “an estimate of the amount of residues expressed on a body weight basis that can be ingested in a period of 24 hours or less without adverse effects to human health.” We propose that the Agency use the VICH term and definition, excluding the ASDI term, to avoid the confusion of having two terms that mean virtually the same thing.

## 2. Calculation of the ADI

- In the proposal, the ADI is calculated by dividing the no-observed-effect-level (NOEL) (from the most appropriate toxicological study) by a safety factor. We request the Agency use the term Point of Departure (POD) rather than NOEL. The POD or threshold for toxicological effects of concern is then defined as a NOEL, no-observed-adverse-effect-level (NOAEL) or benchmark dose lower confidence limit (BMDL), as appropriate on a case-by-case basis.

A paragraph such as the following could be considered:

“The basic approach for the derivation of an ADI is identification of an appropriate POD, or threshold, for the toxicological endpoint of concern. This is typically identified as a no-observed effect level (NOEL) or no-observed adverse effect level (NOAEL) dose or benchmark dose lower confidence limit (BMDL). The ADI is determined by dividing this POD by an appropriate Uncertainty Factor(s).”

## 3. Definition of “regulatory method”

- In the proposal, the proposed definition for “regulatory method” is “the aggregate of all experimental procedures for measuring and confirming the presence of the marker residue in the target tissue of the target animal.” “Regulatory method” has historically been used to refer specifically to the required determinative and confirmatory procedures for regulatory surveillance of the residue concentrations in meat products entering the food supply for comparison to the tolerance post-commercialization of the product. The context of the Federal Register proposal appears to be the method(s) used to collect data to support the setting of the tolerance pre-approval. What terminology will now distinguish those two? Does this imply that tolerances may be established using analytical procedures other than the determinative procedure? A clarification of the intent of this definition is needed.

## 4. Definition of “not required”

- In the proposal, FDA is proposing to define “not required” with respect to tolerances as indicating that at the time of approval, the drug met one of the following conditions: (1) No withdrawal period (i.e., zero withdrawal) was necessary for residues of the drug to deplete to or below the concentrations considered to be safe or an adequate withdrawal period was inherent in the proposed drug use, and there was no concern about residues resulting from misuse or overdosing; or (2) the drug qualified for a zero withdrawal period because it was poorly absorbed or metabolized rapidly to such an extent as to make selection of an analyte impractical or impossible.

We propose that (1) and (2) should be replaced with: “(1) No withdrawal period (i.e., zero withdrawal) was necessary for residues of the drug to deplete to or below the concentrations considered to be safe, or (2) an adequate withdrawal period was inherent in the proposed drug use, or (3) there was no concern about residues resulting from misuse or overdosing or

(4) the drug was poorly absorbed or metabolized rapidly to such an extent as to make selection of an analyte impractical or impossible.”

5. General Considerations (Proposed § 556.5(d) regarding a “regulatory method”)

- Proposed § 556.5(d) states that FDA “ requires that a drug sponsor develop a regulatory method to measure drug residues in edible tissues of approved target species at concentrations around the tolerance as provided in § 514.1(b)(7) of this chapter. The tolerance is directly tied to the approved regulatory method because FDA determines the tolerance using data collected with that method.” With reference to our comments in 3. above, it should be clarified if “regulatory method” is referring to method(s) used pre-approval for setting the tolerance vs. a finite method(s) used for determining post-commercialization residue to compare to the tolerance. As stated in 3. above, perhaps different terms are needed for the two cases.

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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