ANIMAL HEALTH INSTITUTE
Representing manufacturers of animal health products

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Manager, Regulatory Affairs

May 25, 2012

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

Re: Docket No. FDA–2012–D–0288; International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH); Draft Guidance for Industry on Statistical Evaluation of Stability Data, VICH GL51

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments to Docket No. FDA–2012–D–0288; International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH); Draft Guidance for Industry on Statistical Evaluation of Stability Data, VICH GL51**.** AHI is the national trade association representing manufacturers of animal health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. As such, we have a tremendous interest in initiatives that promote the international harmonization of regulatory requirements.

AHI would like to emphasize that "application of this draft guidance is entirely optional and it is up to the applicant to decide whether or not to use statistical analysis to support the claimed retest period/shelf-life," as stated on page 4 of the guidance. Additional, specific comments on Draft Guidance for Industry #219/VICH GL51 are provided in the attached table.

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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				Document: Draft Guidance for Industry on Statistical Evaluation of Stability Data, VICH GL51; April 4, 2012
Commenter	**Page No.**	**Section No.**	**Current Text**	**Proposed Text/Comments/Questions**
AHI	Page 4	1.1 Objectives of the Draft Guidance	Application of this draft guidance is entirely optional and it is up to the applicant to decide whether or not to use statistical analysis to support the claimed retest period/shelf-life.	AHI Comment: AHI would like to ensure that this guidance remains optional when finalized.
AHI	Page 4	1.2 Background	The parent guidance states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25.	AHI Proposed Text: *The parent guidance states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25 or some other justifiable significance level.* AHI Comment: The significance level used does not have any justification other than "*to compensate for the expected low power of the design due to the relatively limited sample size in a typical formal stability study*," as described on page 14 under Section B.2.2.1.
AHI	Page 5	2.1 General Principles	The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or the veterinary medicinal product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.	AHI Question: Can the "*minimum of three batches"* be randomly selected or should they be sequential batches?
AHI	Page 6	2.1 General Principles	In general, certain quantitative chemical attributes (e.g., assay, degradation products, preservative content) for a drug substance or a veterinary medicinal product can be assumed to follow zero-order kinetics during long-term storage1. Data for these attributes are therefore amenable to the type of statistical analysis described in Appendix B, including linear regression and poolability testing. Although the kinetics of other quantitative attributes (e.g., pH, dissolution) is generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.	AHI Comment/Question: Please clarify, by providing specific examples, of when "*Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis*" within the context of this statement. Specifically, is the use of linear regression to extrapolate stability data generated for microbiological assays an acceptable practice?

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AHI	Page 6	2.1 General Principles	Data for these attributes are therefore amenable to the type of statistical analysis described in Appendix B, including linear regression and poolability testing.	AHI Comment: Please address the IFAH-Europe 2009 Position Paper, including where it was requested that the term "*amenable to the type of statistical analysis*" be clarified. Please reference the IFAH argumentation in the Position Paper for details.
AHI	Page 9	2.5 Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Medicinal Products Intended for Storage Below Room Temperature	Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Medicinal Products Intended for Storage Below Room Temperature	AHI Proposed Text: *Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Veterinary Medicinal Products Intended for Storage Below Room Temperature* AHI Comment: The term *Veterinary* should be added to remain in accordance with VICH terminology which is applied throughout the document.
AHI	Page 13	B.1 Data Analysis for a Single Batch	In general, the relationship between certain quantitative attributes and time is assumed to be linear.	AHI Proposed Text: *In general, the relationship between certain quantitative attributes and time is assumed to be linear. However, for some cases such as feeds in the CVM area, the relationship may not be linear but may be "piecewise" linear. If such cases arise, submit justification for using such procedures.*
AHI	Page 13	B.1 Data Analysis for a Single Batch	The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the upper acceptance criterion until later.	AHI Proposed Text: *The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the lower acceptance criterion until later.*
AHI	General Comment			AHI Comment: It would be useful to see examples of data treatment that CVM finds acceptable according to the references cited. Examples of data that CVM feels is unfit for statistical treatment would be useful to see as well.

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AHI	General Comment			AHI Comment: In regards to footnotes and references, it is difficult to differentiate between the two in the text. For example, the sentence on Page 5 states, "…*recommendations on the setting and justification of acceptance[1] criteria*…," where 1 refers to a footnote. The sentence on Page 6 states, "…*to follow zero-order kinetics during long-term storage[1]*…," where it seems that 1 refers to a reference since there is no footnote on this page. AHI would suggest that footnotes and references be written in a different format and/or hyperlinked to the exact footnote or reference.