ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

Samata Veluvolu
Manager, Regulatory Affairs

June 23, 2011

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

Re: Docket No. FDA–2011–N–0259; Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments to Docket No. FDA–2011–N–0259; Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563**.** 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 the domestic market for veterinary pharmaceuticals, as well as serving a significant segment of the world market. As such, we have a tremendous interest in revising existing regulations that may be outdated or unnecessary.

The attached table lists several existing regulations and AHI comments on why they should be changed or revoked.

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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Date:	**Document:**	
June 6, 2011	Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563	
Commenter	**Name of Regulation/CFR Citation**	**Comments**
AHI	21 CFR Part 514.8 Supplements and other changes to an approved application. Section 514.8 (b)(4)(ii)(B) reads: (b) Manufacturing changes to an approved application (4) Changes and updated stability data to be described and submitted in an annual report (minor changes). (ii) These changes include but are not limited to: (B) The deletion or reduction of an ingredient intended to affect only the color of the drug product; while Section 514.8 (b)(2)(ii)(A) reads: (b) Manufacturing changes to an approved application (2) Changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major changes). (ii) These changes include, but are not limited to: (A) Except those described in paragraphs (b)(3) and (b)(4) of this section, changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application;	**Brief Description of Problem:** A change to delete or reduce an ingredient such as color would change the specification as it relates to the color, and therefore, by default means a prior approval supplement while not having an adverse effect on the identity, strength, quality, purity, or potency of the drug. The requirement to provide a PAS to change a specification impacting color only is an undue burden on both industry and FDA. **Proposed Solution:** Therefore, provision should be provided to allow a change in specification as a result of a color change impacting only the appearance/description section when analytical data and technical information is provided to demonstrate no adverse effect on the identity, strength, quality, purity, or potency with no effect on the safety or effectiveness of the drug.

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AHI	21 CFR Part 514.8 Supplements and other changes to an approved application. Section 514.8 (b)(2)(v) reads: (b) Manufacturing changes to an approved application (2) Changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major changes). (v) Comparability Protocols. An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of the drug produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect. A comparability protocol supplement must be labeled "Prior Approval Supplement--Comparability Protocol."	**Brief Description of Problem:** Any such protocols can only be submitted as Prior Approval Supplements which limits the scope and benefit to industry. **Proposed Solution:** Provision should be provided to allow for some Comparability Protocols to be submitted using the CBE-30 reporting process. Such Comparability Protocols would apply to those changes that are considered to have moderate or minor potential to adversely affect the identity, strength, quality, purity, or potency of the drug.

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AHI	21 CFR Part 514.8 Supplements and other changes to an approved application. Section 514.8 (b)(2)(iii)(J) and (b)(4)(iii)(J) read: (b) Manufacturing changes to an approved application (2) Changes requiring submission and approval of a supplement prior to distribution of the drug made using the change (major changes). (iii) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug made using a change under paragraph (b)(2) of this section. The supplement must be labeled "Prior Approval Supplement." Except for submissions under paragraph (b)(2)(v) of this section, the following information must be contained in the supplement: (J) Any other information as directed by FDA. (b) Manufacturing changes to an approved application (4)Changes and updated stability data to be described and submitted in an annual report (minor changes). (iii) For changes under this category, the applicant is required to submit in the annual report: (J) Any other information as directed by FDA.	**Proposed Solution:** (J) Should be clarified as follows: “Any other information as directed by FDA applicable to the change defined in the supplement or documentation provided to that supplement”.

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AHI	21 CFR Part 514.3 Definitions. *Serious adverse drug experience* is an adverse event that is fatal, or life-threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement.	**Brief Description of Problem:** FDA should align data analysis and reporting practices globally. **Proposed Solution:** Suggest revision of definition to include only cases where the event is life-threatening, results in death, abortion, stillbirth, or congenital anomaly, where hospitalization is required, results in a medically significant disability, or is persistent for an extended period of time requiring continuous medical attention.
AHI	21 CFR Part 514.3 Definitions. (2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).	**Brief Description of Problem:** FDA should align data analysis and reporting practices globally. **Proposed Solution:** Suggest revision of the definition to be more in line with the VICH definition which indicates if a perceived lack of efficacy occurs after non-labeled use or for a non-labeled indication, the case is not considered “lack of efficacy”.
AHI	21 CFR Part 514.80 Records and reports concerning experience with approved new animal drugs.	**Proposed Solution:** Clarification of regulations to insure compliance for electronic submission of Form FDA 1932. (AHI has provided CVM with a detailed list of questions regarding this regulation.) Clarification of requirements regarding reports of adverse events received by the MAH involving products that are the same/similar to approved NADAs (foreign products).

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AHI	21 CFR Part 514.80 Records and reports concerning experience with approved new animal drugs. Section 514.80(b)(4) reads: (b) Reporting requirements (4) Periodic drug experience report. This report must be accompanied by a completed Form FDA 2301 "Transmittal of Periodic Reports and Promotional Materials for New Animal Drugs." It must be submitted every 6 months for the first 2 years following approval of an NADA or ANADA and yearly thereafter. Reports required by this section must contain data and information for the full reporting period. The 6-month periodic drug experience reports must be submitted within 30 days following the end of the 6-month reporting period. The yearly periodic drug experience reports must be submitted within 60 days of the anniversary date of the approval of the NADA or ANADA. Any previously submitted information contained in the report must be identified as such. For yearly (annual) periodic drug experience reports, the applicant may petition FDA to change the date of submission or frequency of reporting, and after approval of such petition, file such reports on the new filing date or at the new reporting frequency. Also, FDA may require a report at different times or more frequently. The periodic drug experience report must contain the following:	**Brief Description of Problem:** Due to advances in technology, this requirement should be repealed as it relates to previously submitted adverse event reports. This requirement is an added burden without added value. **Proposed Solution:** The agency will have electronic records of all cases reported to MAH, and thus this information is already available.

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AHI	(v) Summary report of increased frequency of adverse drug experience. The applicant must periodically review the incidence of reports of adverse drug experiences to determine if there has been an increased frequency of serious (expected and unexpected) adverse drug events. The applicant must evaluate the increased frequency of serious (expected or unexpected) adverse drug events at least as often as reporting of periodic drug experience reports. The applicant must report the increased frequency of serious (expected and unexpected) adverse drug events in the periodic drug experience report. Summaries of reports of increased frequency of adverse drug events must be submitted in narrative form. The summaries must state the time period on which the increased frequency is based, time period comparisons in determining increased frequency, references to any previously submitted Form FDA 1932, the method of analysis, and the interpretation of the results. The summaries must be submitted in a separate section within the periodic drug experience report.	**Brief Description of Problem:** Due to advances in technology, this requirement should be repealed. **Proposed Solution:** The agency will have electronic records of all cases reported to MAH, and can assess the frequency of serious reports internally as part of their mission to ensure safety and efficacy of veterinary drugs.

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AHI	21 CFR Part 514.4 Substantial evidence. Section 514.4(a) reads: (a) *Definition of substantial evidence.* Substantial evidence means evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect.	**Brief Description of Problem:** There is a lack of flexibility in the application of substantial evidence for new animal drugs which creates a barrier to innovation. **Proposed Solution:** Other alternatives to determine substantial evidence that should be adopted include: • Indexing – Apply MUMS provisions for conditional approval and indexing to all species by an amendment to the Act. In this way companies could market products sooner while continuing to collect efficacy data to satisfy substantial evidence. Indexing, if applied to all species, would allow for legally marketing limited-use and niche products at reduced regulatory costs to compete with illegally compounded drugs now competing with ethical products. • Use biomarkers or other in vitro/in vivo indicators of effectiveness. • Use of simulation (mathematical) models in lieu of animals or to decrease animal number. • After safety is established and particularly for line extensions, reduction in number required, based on statistical power analyses; <100 cases should be allowed in clinical field trials if justified statistically. See next page.

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AHI		21 CFR Part 514.4 Substantial evidence. (continued) • Use of subjective and objective measurements of endpoints as determined by pilot trials; for example force plate or clinical ratings should be allowed for evaluating NSAIDs. • Use of surrogate endpoints and post approval commitments to decrease animal number. • Allow for use of data generated outside the US as substantial not just supportive. • Development of biomarkers as surrogate endpoints.