

Alexander S. Mathews  
President and CEO

October 15, 2004

Division of Dockets Management  
U.S. Food and Drug Administration  
HFA-305  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

Re: Docket No. 2004D-0283 – Draft Guidance for Industry: Waivers of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles

The ANIMAL HEALTH INSTITUTE (“AHI”) submits these comments to the Docket number 2004D-0283 requesting input on the Agency’s draft Guidance for Industry #171: Waivers of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

AHI member companies are having difficulty reconciling GFI 171 with the Center requirements imposed on pioneer companies for bridging studies when new active ingredient sources are added to an existing NADA. It would appear that the requirements for the pioneer company, combined with the lowered requirements in GFI 171 for generics, penalizes the pioneer while giving an advantage to the generic industry.

AHI provides the following general and specific comments for your consideration prior to finalization of this guidance document.

Sincerely,



Alexander S. Mathews

Enclosure

2004D-0283

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### Comment Form

				Date October 15, 2004	Document GFI #171: Waivers of <i>In Vivo</i> Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles
Commenter	Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale	
AHI		General comment	Formatting of draft guidance documents.	The Animal Health Institute would like to suggest that CVM utilize line numbers when issuing draft Guidance for Industry documents. This aids the commenter in properly identifying the specific area of the document on which they want to provide comments	
AHI	I	General comment		We question the overall premise of using water solubility to predict absorption/efficacy/residues given that it is known that intake of other materials can affect these parameters (ex. Drinking milk while taking certain antibiotics).	
AHI	I	General comment		Although CDER may determine that solubility data is sufficient to determine bioequivalence of generic and pioneer products, they are dealing with one species and general "set of physiological conditions" This is not the case with CVM where multiple species/feedingstuffs/physiological conditions may impact the suitability of solubility data to predict absorption/efficacy/residues.	
AHI	I	General comment		Has CVM obtained "new science" that changes previous views that bioequivalence waivers are not appropriate for feed additives? If so, this new information should be included in the Background section of GFI 171.	
AHI	I	Sentence 2		<p>We question the basis for this expansion, especially in regard to Type A Medicated Articles. There does not appear to be any new science upon which CVM bases this decision. GFI # 35 clearly states that Type A medicated articles are not eligible. The new guidance appears to be based solely on chemical measures rather than biological ones. Request explanation.</p> <p>Solubility does not mean a drug is absorbed; likewise, insoluble does not mean non-absorption.</p>	
AHI	II	Paragraph 2, 5 <sup>th</sup> sentence		The referenced document refers to use of dissolution studies for solid oral dosage forms, and does not necessarily support the use of solubility only	

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AHI	II	Paragraph 2, 6 <sup>th</sup> sentence		The referenced document refers to use of a combination of solubility, permeability and dissolution studies, and does not necessarily support the use of solubility only	
AHI	III.A	Paragraph 2, 1 <sup>st</sup> sentence		"Will usually" does not mean always. With the described method, it will be impossible to determine if an approved generic is the exception (does have a formulation/ingredient that influences bioavailability) until after it is on the market.	
AHI	III.B	Sentences 3 and 4	CVM's language From a mechanistic perspective, if such a drug readily goes into solution across the range of physiological pH values, it will likely go rapidly into solution when exposed to the fluids in the GI tract Accordingly, such medicated feeds will behave as oral solutions shortly after administration.	While the argument may apply when dealing with drugs placed in water, the product formulation, feed matrix as well as gut contents (depending on species) impact the rate of solubilization which raises doubts as to whether this rationale applies. Additionally, particle size is known to play a role in the dissolution, solubility and absorption of drugs and that drug's ability to either act at the intended site or pass through the animal.	
AHI	III.B III.B.2	Last sentence  Last paragraph		Please clarify two points: 1) if the API of a Type A Medicated Article is not soluble (per Table 1), this guidance document does not apply; and 2) a biowaiver will be denied if a potential feed ingredient of a Type A Medicated Article is purported to cause adverse pharmacological effects.	
AHI	III.C	Paragraph 2	CVM language: If a waiver of the need to submit <i>in vivo</i> bioequivalence studies is granted, the sponsor may request a waiver for the need to submit tissue residue depletion data. If CVM waives the requirement to submit a tissue residue depletion study, it will assign the withdrawal time established for the pioneer product to the generic product.	The reference to pages 24 to 26 of GFI # 35 does not support this statement. The conclusion is a residue depletion study is needed in addition to the bioequivalence due to differences in tissue disposition kinetics that cannot be assessed by plasma disposition profiles when a blood level bioequivalence study is performed. Additionally, GFI #35 requires that residue depletion be conducted for each major food-producing species. Given our concerns about reliance solely on chemical measures to determine bioequivalence, waiver of the tissue residue depletion requirement is inappropriate.	
AHI	IV.A		Comment applies to this section and throughout the entire document.	Please explain how the generic manufacturer would have access to the manufacturing process used by the pioneer. Isn't this information confidential? Isn't it necessary to compare API(s) of the generic and pioneer products?	

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AHI	IV.A	Paragraph 1, 2 <sup>nd</sup> sentence, 1)		In the case of biomass products, what constitutes "sufficient evidence that the generic product contains the same active ingredient"?	
AHI	IV.A	Paragraph 1, 2 <sup>nd</sup> sentence, 2)		Please clarify "composition statements" in regards to mycelial or biomass products. Will "mycelial cake" be sufficient, or will a detailed description of the biomass components (before/after fermentation) be required?	
AHI	IV.A	Paragraph 1, 2 <sup>nd</sup> sentence, 3)		Please clarify if the manufacturing process description is for the Type A product, the API or both? If the Type A is produced using a biomass, will a detailed description of the fermentation processes (both generic and pioneer), including bacterial strains, substrates, conditions, etc. be required? If so, how closely must the generic and pioneer processes match to ensure that impurities/contaminants do not differ?	
AHI	IV.A IV.B IV.B IV B.2 Figure 1	Line 4 Line 2, 2 <sup>nd</sup> para. Line 3, 2 <sup>nd</sup> para. Line 2, last para. Text box on right	Suggest clarification of the word "same" as it relates to active ingredient.	Does "same" mean same active ingredient or does it mean same active ingredient manufactured at the same plant as the pioneer active ingredient?	
AHI	IV.B	Paragraph 2	For Type A medicated articles, a biowaiver may be granted <del>without</del> after a direct comparison to the pioneer product's formulation and manufacturing process if the generic product contains the same API(s) as the pioneer product, the API is soluble, and there are no ingredients in the generic product's formulation likely to cause adverse pharmacological effects. CVM recommends that the sponsor demonstrate solubility using <del>one</del> the following <del>two</del> methods.	CVM has not provided a rationale as to why they will not compare formulations or given a basis for negating previous guidance on fermentation products.  We feel the generic should do additional testing, i.e., particle size, show statistical equivalence at various pHs in different dissolution media such as simulated gastric fluid, purified water, simulated intestinal fluid, acetate buffer, and phosphate buffer, as water alone does not measure in vivo solubility conditions. A battery of tests should be conducted to demonstrate equivalence.	

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AHI	IV.B	Solubility discussion		The discussion of "solubility" measurement does not include a discussion of " <b>rate</b> of dissolution" to reflect a reasonable time within which the compound will have dissolved or it will have passed beyond the area of absorption, and thus be unavailable for pharmacological benefit.
AHI	IV.B.1	Paragraph 1, 1 <sup>st</sup> sentence		Please comment on the scientific background of how the levels "very soluble", freely soluble" and "soluble" were chosen by CVM to consider an API sufficiently soluble
AHI	IV.B.1	Paragraph 1, 2 <sup>nd</sup> sentence	"In using this table, the product should be tested in a pH range of 1.2 (0.1N HCl) to <b>9.0</b> "	In many animal species, pH of the lower gut, site of absorption of many drugs, may be as high as 9. Testing at a pH maximum of 7.5 does not ensure solubility/absorption under all physiological conditions.
AHI	IV.B.1	Table 1		Although mentioned elsewhere in the GFI, this section and its table do not indicate that the "solvent" must be aqueous and could be misinterpreted to include any solvent.
AHI	IV.B.2	Paragraph 1, 1 <sup>st</sup> sentence	"In this approach, the aqueous solubility (across a pH range of 1.2 to <b>9.0</b> ) . "	In many animal species, pH of the lower gut, site of absorption of many drugs, may be as high as 9. Testing at a pH maximum of 7.5 does not ensure solubility/absorption under all physiological conditions.
AHI	IV.B.2	Paragraph 1, last sentence before table	CVM language: When using this approach, we recommend using the species-specific animal weight and fluid volume estimates summarized in Table 2.	Animal weight and fluid volume used should be appropriate to the label claim ( <i>i.e.</i> , calves, growing swine, etc.).
AHI	IV.B.2	Table 2	Swine, 200 kg	We question the appropriateness of using this size animal as the basis for estimating solubility. This class of animals is not the usual intended group for drug administration.
AHI	IV B.2	Table 2		Gastric volume estimation for cattle appears to be very high (factor of 10) for weight shown.

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AHI	IV.B.2	Table 2		This table should include an additional column "Estimated feed intake" in order to standardize this parameter as it is a key component of the required calculations for dosing and should not vary between waiver requests
AHI	IV.B.2	Paragraph 1, 5 <sup>th</sup> sentence  Paragraph 2, 2 <sup>nd</sup> sentence	If the Type A medicated article is to be used in the manufacture of medicated feeds across several animal species, the most conservative condition (largest dose to fluid volume ration) should provide the basis for determining whether the drug is "soluble"  Therefore, we recommend that the solubility assessment within a given target animal species be based upon only one solute/solvent ratio.	We recommend that testing be done under the conditions to be encountered for each labelled species and class to assure equivalence, not just using the most conservative condition.
AHI	IV.B.2	Paragraph 2, 1 <sup>st</sup> sentence		"CVM <b>assumes</b> the amount of medicated feed consumed per day and the "gastric volume" will vary proportionally with animal age " Please include the information that supports this assumption as we question its validity.
AHI	IV.B.2	Paragraph 4, 1 <sup>st</sup> sentence	"The pH-solubility profile of the test drug substance should be determined at 37 ± 1 °C in aqueous media with pHs of approximately 1.2, 4.6, 7.5 and <b>9.0</b> ."	In many animal species, pH of the lower gut, site of absorption of many drugs, may be as high as 9. Testing at a pH maximum of 7.5 does not ensure solubility/absorption under all physiological conditions.
AHI	IV.B.2	Paragraph 5, 1 <sup>st</sup> sentence, 1)		In the case of biomass products, what constitutes "sufficient evidence that the generic product contains the same active ingredient"?
AHI	IV.B.2	Paragraph 5, 1 <sup>st</sup> sentence, 2)		Please clarify "composition statements" in regards to mycelial or biomass products. Will "mycelial cake" be sufficient, or will a detailed description of the biomass components (before/after fermentation) be required?
AHI	IV.B.2	Figure 1		In the case of APIs in mycelial cakes, Does "ingredients" mean "biomass", the ingredients that are used to create the biomass, or the resulting components of the fermentation/biomass?

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AHI	IV.B.2	Figure 1		Does the manufacturing process mean the Type A manufacturing, fermentation/production of the API, or both? How detailed must the description be in order to determine that the processes for the generic and pioneer are "the same"? For APIs made by fermentation, must the bacterial strains, substrates, conditions, etc be identical?