

Alexander S. Mathews  
President and CEO

2003D-0571-0008  
June 30, 2004

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

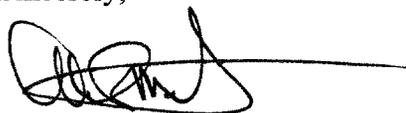
Re: Docket No. 2003D-0571 – Draft Guidance for Industry on Drug Substance;  
Chemistry, Manufacturing, and Controls Information

The ANIMAL HEALTH INSTITUTE (“AHI”) submits these comments to the Docket number 2003D-0571 requesting input on the Agency’s recommendations on the chemistry, manufacturing, and controls information for drug substances that should be submitted to support original new drug applications, abbreviated new drug applications, new animal drug applications, and abbreviated new animal drug applications.

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

Sincerely,



Alexander S. Mathews

Enclosure

2003D-0571

### Comment Form

				Date June 30, 2004	Document Draft GFI Drug Substance Chemistry, Manufacturing and Controls Information
Commenter	Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale	
AHI	II. Background, A. The Common Technical Document	Line 101 (footnote 5)	AHI seeks clarification of Footnote 5.	The footnote implies that the sponsor may choose which format to present the required CMC information for APIs (common/alternative vs. via a CTD). It is not clear that there is any advantage in submitting the required information in the CTD format. Therefore, it is unclear if CVM wants to harmonize the format of animal drug submissions for APIs.	
AHI	II.D.2.	Line 239- 240	Modify sentence to read "...for the information recommended in S.2.2 through <b>S.2.7.</b> "	Stability data of an API itself could be considered proprietary information. Cross-reference to stability data that are contained in the DMF as mentioned on line 272 should be allowed.	
AHI	II.D.2.	Line 281  Line 282	Add "Comparability protocols..... and application (R.2.S) <b>if appropriate.</b> ... (R.3.S.) <b>if applicable.</b> "	Comparability protocols are of added value only if there has been a change of significant importance. Usually it is not provided separately for submissions to CVM.	
AHI	III.General Information, C. General Properties	Line 340	Remove last five words of sentence, removing "and, as appropriate, drug product."	This is a bulk drug substance guidance, so it appears to be out of scope to discuss drug products here.	
AHI	IV.B.2.	Line 452- 453	AHI recommends the insertion of an example into this sentence to read "...biological names and quantities (e.g., <b>molar</b> ) specified"	During API manufacture the reactions occur on a molar basis. Precise quantities can be managed under Quality Systems.	
AHI	IV.B.2.	After Line 471	Include an additional bullet that states " <b>Identification of processes that involve seeding operation</b> "	Seeding is often used in the synthesis of active ingredient in order to obtain the expected polymorphic form and is key for defining the API Quality.	

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AHI	IV.B.2.	Line 482	AHI recommends inserting a phrase at the end of this bullet to read: "Holding times and storage conditions during manufacture, <b>if critical</b> "	If not critical, it should be managed under Quality Systems	
AHI	IV.B.2.	Line 491	AHI recommends replacing the word "facility" with " <b>building.</b> " Sentence would now read: "... are not used or manipulated in the same building."	The term "facility" could be too restrictive in this sentence. Substitution of "building" adds clarity to the sentence.	
AHI	IV.C.1	Line 687 to 695	Clarify the definition of the starting material for application purposes similar to that outlined in ICH Q7A Table 1 (which is the step that requires use of GMP).	To be consistent with ICH Q7A guideline in the approach to GMP.	
AHI	IV.C.1	Line 698	Modify the line to read "...molecular structure that <b>significantly</b> contributes to the structure of the drug substance."	Every component of a given synthesis that brings even a small part of the final structure of the API is not a Starting Material. Consistent with ICH Q7A guideline.	
AHI	IV.C.1	Line 713	Rephrase this bullet point to read: "Flow diagram of process from starting materials to API included for information purposes to justify the choice of starting material, if applicable"	Not applicable if proprietary information is contained in a Master File. The flow diagram of the synthesis of the starting material should be used only in the context of choosing the starting material and should not bind regulatory to report changes.	
AHI	IV.C.1	Line 715	Delete bullet	Bullet becomes redundant with the AHI modification to Line 713 recommended above.	
AHI	VI. Control of Drug Substance A. Specification	Lines 1086-1088	Add the phrase "When applicable," to the beginning of this sentence.	It may not be known at the time of the submission of the API information if additional processing/preparation of the API is necessary prior to drug product formulation. The CM&C technical section for the drug product will provide this information.	

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AHI	VI. A	Line 1126	Add " or retest" to this bullet point so that it would read: "Release and shelf-life or retest criteria when both are used"	This would make this guidance document consistent with ICH Q7A approach.	
AHI	VI. Control of Drug Substance, C. Validation of Analytical Procedures	Line 1226	Replace "...all analytical procedures..." by "...all <b>non-compendial</b> analytical procedures..."	Generally, laboratories validate only non-compendial methods as per the validation ICH Q2B guidelines. However, compendial methods are qualified in laboratory as per internal procedures prior to use.	
AHI	VI. Control of Drug Substance, C. Validation of Analytical Procedures	Box after line 1236	Add the VICH impurity guidance document to the list in the box (CVM Guidance for Industry #92: Impurities in New Veterinary Drug Substances VICH GL10).	Omission.	
AHI	VI. Control of Drug Substance, D. Batch Analyses	Lines 1240-1241	Delete the word "relevant" from line 1240 and replace the word "all" with the word "relevant" in line 1241.	The words "relevant" (line 1240) and "all" (line 1241) appear to be in conflict in this sentence.	
AHI	VI. Control of Drug Substance, E. Justification, Acceptance Criteria	Line 1369	Add "/NADA" after NDA in this sentence.	Omission.	
AHI	VII. Reference Standards or Materials	Line 1398	Clarify what is meant by "fully characterized." The referenced draft guidance states that a reference standard should not be characterized by comparison to a previously designated standard. AHI suggests the addition of the following sentence to the current guidance: <b>A reference standard should not be characterized solely by comparison to a previously designated non-compendial standard.</b>	The guidances do not clearly differentiate between compendial and non-compendial primary standards.	
AHI	VIII. Container Closure System	Line 1411	AHI suggests the addition of the following sentence after "specification": A masterfile can be referenced for proprietary information.	The exact composition of primary packaging materials can be considered proprietary and may be available as a DMF.	

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AHI	IX. Stability	Line 1431	Change "shelf-life acceptance criteria" to "shelf-life or retest acceptance criteria."	Consistent with ICH Q7A approach	
AHI	IX. Stability	Line 1449	The term "primary batches" is not clear. Change the term "primary batches" to be consistent in approach to ICH and VICH guidelines.	The primary batches could be the pilot-scale batches in commercial containers that support label storage and retest or shelf-life acceptance criteria as in ICH Q1A guideline and VICH GL3 for stability of drug substance and drug products.	
AHI	Attachment 1	General comment	Throughout Attachment 1 change "market" to "use."	This section does not provide criteria for a starting material. The significance of separating starting materials by the market volume is questionable. The document should focus on establishing standards for starting materials. As long as the quality of the designated starting materials is controlled to well-defined specifications, changes to the synthesis of the designated starting materials may not be justified.	
AHI	Attachment 1	Line 1683- 1685	Drug substances are not necessarily inappropriate candidates for designation as starting materials. AHI recommends that the sentence be reworded to read: <b>Not all substances used to synthesize another drug substance are appropriate candidates for designation as a starting material. For example, a drug substance used to synthesize a salt or ester form of that drug substance is not suitable for designation as a starting material.</b>	Acetyl salicylic acid (parent) can be used as a starting material to create a new chemical moiety with no structural or pharmacological relationship to the parent. An existing drug substance may have well-defined specifications, be well studied and be very pure.	
AHI	Attachment 1. I A.	Line 1742- 1751	Add a sentence under Propinquity to state, It is applicable only if there is a possibility that impurity in the starting material or the starting material itself is carried over as an impurity into the drug substance.	API quality is not controlled because of the number of reaction steps between starting material and the final API. The quality is controlled via specifications, based on knowledge of process/purification efficiency/behaviour of starting material impurities.	

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AHI	Attachment 1 I D	Line 1801	Add a sentence to state: <b>Complexity of structure as a criteria for selecting starting materials should be applicable if they are not well-established chemical entities.</b>	If a chemical entity has been well known and established, it should not matter, if it is complex. Complex molecules with several chiral centres, enantiomers on one of those centers usually have differing physical properties and therefore give separate peaks on HPLC. On the other hand, stereoisomers of simple molecules (e.g. lactic acid) require a much more sophisticated chiral column to distinguish between the two forms. The reasoning is really not correct since more "advanced techniques" than IR or UV are available to reduce the risks (better risk assessment in line with FDA requirements). These "advanced techniques" are now really common techniques.
AHI	Attachment 1 II.B	Line 1831-1841	The flow diagram is provided for informational purposes to justify the choice of the API starting material during the development process.	API quality is not controlled because of the number of reaction steps between starting material and the final API. The quality is controlled via specifications, based on knowledge of process/purification efficiency/behaviour of starting material impurities.
AHI	Attachment 1 II.C	Line 1863-1867	This sentence is applicable only if there is a possibility that an impurity in the starting material or the starting material itself is carried over as an impurity into the drug substance.	Once again, the reasoning is not correct. Same comments as Line 1742-1751
AHI	Attachment 1 II.D	Line 1884-1885	Delete "who are able.....markets"	There is no scientific value to this statement.
AHI	Attachment 1 II.D	Line 1886-1893	Change the third bullet to: <b>Confirm that the material was not manufactured exclusively for use in your synthesis.</b>	Simplification.
AHI	Attachment 1 II.D	Line 1961	Add a sentence to state "Complexity of structure as a criteria for selecting starting materials should be applicable if they are not well-established chemical entities.	If a chemical entity has been well known and established, it should not matter, if it is complex. Complex molecules with several chiral centres, enantiomers on one of those centers usually have differing physical properties and therefore give separate peaks on HPLC. On the other hand, stereoisomers of simple molecules (e.g. lactic acid) require a much more sophisticated chiral column to distinguish between the two forms. The reasoning is really not correct since more "advanced techniques" than IR or UV are available to reduce the risks (better risk assessment in line with FDA requirements). These "advanced techniques" are now really common techniques.