



**sanofi aventis**

Because health matters

April 11, 2005

Via fax and UPS

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

0360 5 APR 12 MD:15

**Re: Docket No. 2005D-0021**

*Draft Guidance for Industry on ICH Q8: Pharmaceutical Development*

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "*ICH Q8: Pharmaceutical Development*".

This guideline provides guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH topic M4).

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications in Appendix 1 for your consideration.

On behalf of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry XXXXX* and are much obliged for your consideration.

Sincerely,

Steve Caffé, M.D.  
Vice President, Head US Regulatory Affairs

2005D-0021

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Appendix 1:

**ICH Q8: Pharmaceutical Development  
Key Items for Consideration**

<u>Key Philosophical or Strategy Issues</u>
In general this Step 2 draft was well received and people agreed with the improvements made since the last V 3.1 draft of ICH Q8.
Overall, we agreed with the philosophy of the document aimed at providing guidance on definition and content of specific Module 3 CTD, 3.2.P.2 Pharmaceutical development section. However, it is understood that the guideline covers all types of pharmaceutical product/dosage forms and that each one of the sections described may not have to be completely covered, and that each type of pharmaceutical studies may not be applicable according to the specificity of the product and its intended use.
It is understood that 3.2.P.2 Pharmaceutical development section, by adequately presenting information and scientific knowledge of the medicinal product gained from pharmaceutical development studies, will provide scientific understanding to support the design space and establish specifications which are suitable for the manufacture of the product and future industrial quality management. However, clarification is definitely needed on “flexible regulatory approaches” that pharmaceutical development can create a basis for, with an adequately supported design space. In particular, examples of “risk based regulatory decisions” in the context of application review as well as pre-approval inspection would be necessary for better understanding and adherence to the concept worldwide.
Following the approach used in the EU Note for Guidance on development pharmaceuticals (CPMP/QWP/155/96), it would be of benefit to illustrate the development of specific common dosage forms with examples of pharmaceutical development studies that would support minimum requirements (as well as additional ones to enlarge design space).
Clarifications would be also needed on the scope of this guideline: original marketing applications and over the life cycle of the product (post- approval submissions) as well as the type of products covered (examples may be given).

<u>Item with Reference Line #</u>	<u>Relative Importance</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
Section 1.1 - Objective of the Guideline Line 11	1	Clarity	Suggest to start this sentence with “ <b>This section</b> <i>is first</i> ...” rather than “ <i>It is first</i> ...”.
Section 1.1 - Objective of the Guideline Lines 13-15  “The guideline also indicates areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for <u>flexible regulatory approaches</u> .”	2	Please, clarify what is meant by “flexible regulatory approaches”	
Section 1.1 - Objective of the Guideline Lines 15-17	1	It is stated that the pharmaceutical development section is intended for use by both reviewers and inspectors: <ul style="list-style-type: none"><li>• It should be precisely stated that the use by inspectors does not necessarily require that pharmaceutical development studies have to be performed under GMP conditions.</li><li>• Suggest additional explanation on “how and why reviewers and inspectors will be using this pharmaceutical development section”.</li></ul>	<ul style="list-style-type: none"><li>• Keep the sentence but add a statement e.g. “... <b>for use by both reviewers and inspectors to obtain an in-depth understanding about the product development complementing the GMP-relevant data and commitments reported in other parts of the dossier.</b>”</li><li>• Knowledge of the general expectations may also stimulate continued opportunities for pharmaceutical companies to better and more clearly identify measures to improve manufacturing processes/analytical testing during development and/or explain difficult process steps.</li></ul>
Section 1.3 - Scope Lines 31-38	2	<ul style="list-style-type: none"><li>• Please, define more specifically what type of product and registration dossier the guideline applies for (MAs for NCEs, line extensions, post approval variations, ...)</li><li>• Please, clarify what is meant by “<i>other types of products</i>”: Is that the same scope as for CTD Module 3 guidance in ICH topic M4?</li></ul>	Include examples of other types of products as in CTD introduction in ICH M4 (herbal products, cosmetics, ...)

<b>Item with Reference Line #</b>	<b>Relative Importance</b>	<b>Key Concerns with Explanation of Position</b>	<b>Proposed change</b>
<p><b>Section 2 - Pharmaceutical Development</b></p> <p>Lines 68 to 79</p>	1	<p>A stronger position should be taken to reflect that there may be an increased probability of getting regulatory flexibility/relief from Agencies, when appropriate pharmaceutical development studies have been conducted to increase scientific knowledge of product performance and properly define the design space.</p>	<p>Suggested rewording of lines 70-74 as follows:  <i>"Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of manufacturing processes and in process controls, and establishes the design space. Along with application of quality risk management principles, this should increase the potential for procuring greater regulatory flexibility/relief with Authorities, to facilitate, for example:</i></p> <ul style="list-style-type: none"> <li>•</li> <li>•</li> <li>•</li> </ul>
<p><b>Section 2 - Pharmaceutical Development</b></p> <p>Lines 76-79</p> <p>Line 76</p> <ul style="list-style-type: none"> <li>• <i>"risk based regulatory decisions (reviews and inspections)"</i></li> </ul>	2	<p>Examples of Regulatory Flexibility: It is suggested that this topic be developed into a specific section.</p> <p>Please, clarify by giving examples of risk based regulatory decisions in case of reviews and inspections.</p>	
<p><b>Section 2 - Pharmaceutical Development</b></p> <p>Lines 77-78</p> <ul style="list-style-type: none"> <li>• <i>"manufacturing process improvements, within the approved design space described in the dossier without any further regulatory review"</i></li> </ul>	1	<p>Please, clarify that as long as the data were presented and discussed as part of the Pharmaceutical Development section, post-approval changes within the tested range should be allowed without submission of regulatory dossiers prior to implementation.</p>	

<u>Item with Reference Line #</u>	<u>Relative Importance</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
<b>Section 2 - Pharmaceutical Development</b> Line 85	1	Looking at the definition of PAT, there is a risk to be misleading and not clarify what is wanted.	Replace “ <i>or PAT*</i> ” with “ <b>or additional investigational in-process controls and scientific data to support results.</b> ”
Section 2.1.1 - Drug Substance Line 99 “(e.g. <i>crystal engineering</i> )”  Lines 103-104 “Some of these properties can change with time and may be supplier dependent”	1	Please, clarify what “ <i>crystal engineering</i> ” includes  It is suggested that this sentence be explained or elaborated to avoid any misunderstanding.	Reword accordingly (e.g. physical quality?)
Section 2.1.1 - Drug Substance  Lines 115-117	1	Discussion of compatibility of DS with excipients.	It is suggested that the minimum expectations for compatibility studies be listed.
<b>2.2 Drug Product</b>	2	Definition of <b>intermediate products</b> , their manufacture, control, stability... should be addressed at some point in Pharmaceutical Development. A paragraph should be added, as no specific section is available in Module 3 CTD format.	
Section 2.2.1 - Formulation Development  Lines 151-153	1	Justification of excipient ranges: Text seems too vague.	Please specify exactly what kind of studies and data are needed to justify excipient ranges.

<u>Item with Reference Line #</u>	<u>Relative Importance</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
<p>Section 2.2.2 - Overages Lines 177 and 180-182</p>	1	<p>The first sentence of the paragraph appears too restrictive and could be more explanatory. EU guidance approach describing different types of overages as examples would be welcome (differentiation between manufacturing overages and stability overages).</p>	<ul style="list-style-type: none"> <li>• Delete first sentence in section and move a modified version to line 184 before last sentence in section. Use wording similar to: <b>“In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product’s shelf-life, or to extend the expiration dating period, is not appropriate.”</b></li> <li>• Delete last sentence of this section, but include a fragment of it in sentence before: <i>“Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified and shown in the representative batch formula. Information should be provided on...”</i></li> </ul>
<p><b>Section 2.3 – Manufacturing Process Development</b> Lines 258-260</p>	1	<p>It should be clarified whether or not post-approval changes covered in the range(s) tested during process optimisation, robustness and/or validation studies would allow greater flexibility for less stringent filing mechanisms.</p>	
<p><b>Section 2.4 - Container Closure System</b> Lines 271-274 <i>“A possible interaction between product and container(s) or label should be considered. This applies also to admixture or dilution of products prior to administration e.g. product added to large volume infusion containers.”</i></p>	1	<p>This statement is vague; more guidance would be expected here: please, give example of pharmaceutical presentations/specific cases where interaction with label should be discussed.</p>	

<b>Item with Reference Line #</b>	<b>Relative Importance</b>	<b>Key Concerns with Explanation of Position</b>	<b>Proposed change</b>
<b>Section 2.4 - Container Closure System</b>  Lines 281-283	2	Please clarify the expectations in the case where the dosing device is classified as a medical device, and not as a medicinal product	
<b>Section 2.4 - Container Closure System</b>  Lines 281-283	1	Add Dry Powder Inhaler or Metered Dose Inhaler as examples.	
<b>Section 2.5 - Microbiological Attributes</b>  Lines 302-305	1	Demonstration of antimicrobial preservative effectiveness: Specify microbial challenge testing under testing conditions, which simulate patient use.	Suggest to add a sentence at the end of the paragraph: <i>"Microbial Challenge testing under testing conditions which, as far as possible, simulate patient use should be performed during development and documented in this section"</i>
<b>Section 3 - Glossary</b>	1	Additional terms should be defined in glossary, e.g. attribute, critical, overfill, overage, process robustness, Quality by Design.	

Relative Importance:

1 = we agree with the concept but it needs discussion to clarify

2 = we do not agree with the concept as currently stated, it must be modified