



TEVA PHARMACEUTICAL INDUSTRIES Ltd.

NAVA ROTEM - API DIVISION, TEVA GROUP

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To: Division of Dockets Management (HFA-305)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
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From: Nava Rotem Ph. D.  
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**Re: Docket No. 2005D-0021**

**Comments to Draft Guidance for Industry ICH Q8: Pharmaceutical Development**

**Dear Docket Management Branch,**

Teva Group has reviewed the Draft Guidance ICH Q8: Pharmaceutical Development.

We appreciate the opportunity to comment on this draft guidance and hope our comments will be taken into consideration upon finalizing it.

Our comments are listed in the table below.

Sincerely,

*Nava Rotem*

Nava Rotem

Global QA/RA Knowledge Management Director

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## Comments On ICH Q8: Pharmaceutical Development (Draft Guidance Version 4.3)- Step 2 Docket No. 2005D-0021

Line No(s).	Section No. / Item	Statement of Concern(s) with Explanation	Comments / Proposed Changes
	1. Introduction		
	1. I Objective of the Guideline		
11-12	1.1 Objective of the Guideline	"It is first produced for the original marketing ..."	The word "first" does not seem accurate. Pharmaceutical development is an on-going process.
15		"...flexible regulatory approaches."	Clarify with samples
16-17		"Development section is intended to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors."	It should be clearly stated that the development studies do not necessarily have to be performed under GMP conditions. Also, changes are expected during process development.
35	1.3 Scope	".. the principles in this guideline are important to consider during the clinical research stage of drug development."	It is suggested to consider that the FDA should have an opportunity to review the pharmaceutical development document in the clinical research stage of drug development. Such a section could be integrated into guidelines for IND for Phase II and III, detailing the extent data expected for each clinical phase. Please note: Pharmaceutical Development is a required section for an Investigational Medicinal Product Dossier for clinical trials in EU. See guideline CHMP/QWP/185401/2004.
36		"..other type of products"	Please clarify what type of products are being referred to and add examples.



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Line No(s).	Section No. / Item	Statement of Concern(s) with Explanation	Comments / Proposed Changes
			It is unclear whether this document is intended to relate to small molecules (synthetic drug products or chemical substances) only. Does it cover peptides and polypeptides, biotechnological/biological, radiopharmaceuticals, herbal products etc. ? It would be desirable that the guidance covers a wide range of product types.
37 - 38		“To determine the applicability of this guideline for a particular type of product, applicants should consult with the appropriate regulatory authorities.”	This statement is practically not feasible.
	2. Pharmaceutical Development	Please clarify: How does this section compare to the section Pharmaceutical Development in the Draft Guidance “ Guidance for Industry - Drug Product” - January 2003? Should Q8 replace or substitute the above section of the draft guideline? If yes, the above guideline should be changed accordingly. Please consider that this is a very confusing situation as the above guideline is partly more explicit –which is more helpful for the industry - than this proposed Q8 guideline, as can be seen in some of the comments below.	
43		“...in a reproducible manner”.	Need to define more clearly , to avoid misinterpretation of this important term.  Suggest to add - “...manner, so that potency, quality and predetermined specification and limits are accurately reproduced”.
68		“...the applicant can choose to conduct other pharmaceutical development”	Please clarify, other than described in the previous paragraph?
76		“ risk based regulatory decision (reviews and inspections)	Please, clarify by giving examples.



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Line No(s).	Section No. / Item	Statement of Concern(s) with Explanation	Comments / Proposed Changes
84-86		"..application of formal experimental designs or PAT. Appropriate use of risk management principles.."	It would be helpful to see how the authorities would like to see such an approach in the dossier.
	2.1 Components of the Drug Product		
99	2.11 Drug Substance	"Crystal engineering"	Should be explained in the glossary.
100		"..Examples of physicochemical and biological properties"	In section P.2.1.1 in the Draft Guideline for Drug product, January 2003 the Physicochemical Characteristics seem to be given in more detail e.g. If the drug substance is structurally modified from an active moiety (e.g., salt, endogenous protein, polymorphs, different solvates) and the modification affects a key physicochemical (e.g. solubility) and/or biological characteristic, this should be discussed. This discussion should cross-reference any relevant stability data in S.7.3.
115-117		"the compatibility of the drug substance..."	Please consider to add the lines 412-418 (if there is evidence of chemical or physical incompatibility, justification for using the component should be provided...) of the Drug product draft guidelines to proposed Q8.
129-130	2.12 Excipients	".. and to support the justification of the drug product specification (3.2.P.5.6)"	Please consider to continue the sentence: "and of the excipient specifications " (3.2.P.4.4)
		Please consider keeping the more explicit section of P.2.1.2 Excipients from the Drug Product Draft Guideline. There are subchapters for novel excipients; noncompendial and non novel excipients and excipients that can impart their own pharmacological activity.	



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Line No(s).	Section No. / Item	Statement of Concern(s) with Explanation	Comments / Proposed Changes
	2.2 Drug Product		
171	2.2.1 Drug product formulation development	“Any special design features of the drug product...”	Please consider to be more specific regarding: 1. Overfill Overfill should be discussed in this section more in details, as in the Draft Guideline from January 2003, lines 514 to 524. 2. Anticounterfeiting measure – can you please give some explanation and example (are there primary or secondary packaging components involved)?
		Advisable to add discussion about Placebo ▪ Comparators and other study drugs used during the development ▪	
239	2.3 Manufacturing process development	“ Significant differences between the manufacturing process used to produce the clinical ...”	Please add –”and commercial product”.
272	2.4 Container closure system	“... possible interaction between product and container ..”	It would be advisable to include the two paragraphs which were omitted from the Q8 proposed guideline and were part of the draft guidance from January 2003 in Q8 as they give helpful examples. If an NDA is submitted for a new plastic that will be used for blood component storage, adequate information on the plastic should be submitted. Etc. Lines 608 – 611. The results of suitability studies can form the basis for inclusion, or omission, of specific tests on the finished product, container closure system, or individual packaging components. For example, ... etc. Lines 613 to 619. Cross-reference to additional guideline could be useful.