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September 14, 2000



Dockets Management Branch (HFA-0305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**RE: Docket No. 96D-0009: International  
Conference on Harmonizations; Q3B (R)  
Draft Revised Guidance on Impurities in New  
Drug Products**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck support regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck supports and adheres to the ICH Q3B guidance which was developed for impurities in new drug products. We, however, have these following comments for consideration.

**GENERAL COMMENTS:**

- 1) The guidance seems inappropriately titled since it is stressed in 1.3 (Scope) that the guidance applies to degradates as a result of change or interaction with other substances, but NOT to impurities from excipients or active drug substance, for example. A more appropriate title would be "Degradation Products in New Drug Products." The same comment applies to various section headings throughout the document. For example, 2.2 Rationale for the Reporting and Control of Impurities would be more appropriately labeled as "Rationale for the Reporting and Control of Degradation Products."
- 2) Use of the term 'specification' throughout the document conflicts with the definition of the word as defined in *ICH 6QA Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*. In the 6QA guidance, a specification is clearly defined as "quality standards (i.e., tests, analytical procedures and acceptance criteria)...to confirm the quality of drug substances, drug products..." An acceptance criteria on the other hand is the "numerical limits, ranges or

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other criteria for the tests described.” We should suggest that term ‘specification’ be replaced with ‘acceptance criteria’ throughout the document.

- 3) Accelerated stability for the drug product is not covered in this guidance. It is felt that since these accelerated stability studies are performed to find possible degradates, should this be mentioned in the guidance.
- 4) In the glossary, thresholds are defined as the limits above which ( $\geq$ ) an impurity needs to be identified or qualified. It is clear therefore (for drug product where the maximum daily dose is  $> 2\text{g/day}$  and the threshold is 0.1%) if analytical results for individual impurities are found to be between 0.05 and 0.14%, the results may be rounded to 0.1% and the individual impurity need not be identified or qualified. This clarification should be included within the text of the document to give clear, explicit guidance.

**SPECIFIC COMMENTS:**

1. The last sentence of 1.3 Scope of the Guidance proposes that: “Impurities present in the new drug substance need not be monitored or specified in the drug products unless they are also degradation products.” This may suggest that tracking of process impurities is not needed. Revision to the statement should be made to clarify that this is not the intention. Suggested revision to the statement may be: Impurities present in the new drug substance are not covered within the scope of this guideline and need not be monitored in drug products unless they are also degradation products.
2. Attachment I – Tables for Identification and Qualification thresholds. A threshold level of 1%, which is less stringent than the ICH threshold of 1.0% is listed. It is suggested that the threshold level be revised to 1.0%

We appreciate the opportunity to provide comments which, from our perspective, will clarify some of the outstanding issues. We trust that these comments will be considered in further development of the proposed rule.

Sincerely,



Dennis M. Erb, Ph.D.  
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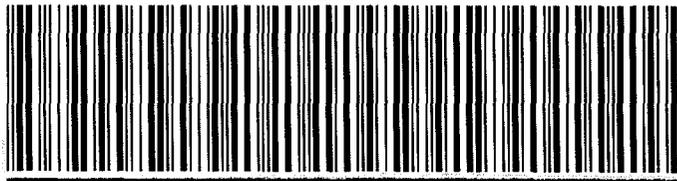
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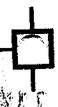
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