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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. 94D-0325: International
Conference on Harmonizations; Q3A (R)
Draft Revised Guidance on Impurities in New
Drug Substances**

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 Q3A guidance which was developed for impurities in new drug substances. We, however, have these following comments for consideration.

GENERAL COMMENTS:

- 1) The definitions of 'organic impurities', 'inorganic impurities' and 'residual solvents' (as provided in 2 Classification of Impurities) should be included in the glossary.
- 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 other criteria for the tests described." We should suggest that term 'specification' be replaced with 'acceptance criteria' throughout the document.
- 3) Forced degradation of the API is not covered in this guidance. We feel that this should be a mentioned, since testing is performed to find possible degradates.

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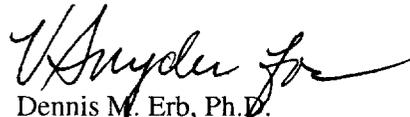
- 4) In the glossary, thresholds are defined as the limits above which (>) an impurity needs to be identified or qualified. It is clear therefore (for drug product where the maximum daily dose is $\leq 2\text{g/day}$ and the threshold is 0.1%) if analytical results for individual impurities are found 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) Under 6. Specifications for Impurities (2nd paragraph, 3rd sentence) read as follows: “Specific identified impurities.....”. That sentence should be revised to read “Specified identified impurities.....” for consistency with “specified unidentified impurities”.
- 2) Under 2, Classification of Impurities, it is suggested that Heavy Metal should simply be listed as “Metals or Residual Metals”.

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.
Senior Director
Regulatory Affairs

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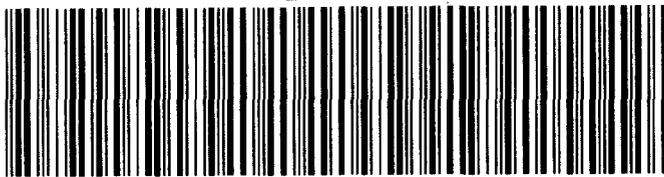
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