

GlaxoWellcome

17 11 4 '00 SEP 20 10:24



September 15, 2000

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

**RE: ICH; Draft Revised Guidance on Impurities in New Drug Substances and
Draft Revised Guidance on Impurities in New Drug Products**

Enclosed please find comments from Glaxo Wellcome on:

- The International Conference on Harmonisation; Draft Revised Guidance on Impurities in New Drug Substances and
- The International Conference on Harmonisation; Draft Revised Guidance on Impurities in New Drug Products.

Thank you very much for your attention and the opportunity to provide comments on these draft guidance documents. If there is a need to contact Glaxo Wellcome regarding these comments, I can be reached by telephone at (919) 483-5754 or by fax at (919) 483-5381.

Kindest Regards,

A handwritten signature in cursive script that reads "Carmella S. Moody".

Carmella S. Moody, Ph.D.
Assistant Director
US CMC Submissions
Worldwide Regulatory Affairs.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

96D-0009

C 9

**International Conference on Harmonization;
Draft Revised Guidance on Impurities in New Drug
Substances**

Glaxo Wellcome Comments

Date: September 13, 2000
By: Carmella Moody

**International Conference on Harmonisation; Draft Revised Guidance on Impurities
in New Drug Substances**

Comments from Glaxo Wellcome

General Comments:

To avoid confusion, it would be helpful if qualifying terms such as “not more than” and symbols such as $>$ and \leq were used consistently throughout the document, e.g. in the final paragraph of Section 3.1, the term “levels of not more than” is used for the symbol \leq and “less than or equal to” is also used for the same symbol. Additionally, there is an error in Paragraph 1 of Section 5 where the symbol $>$ has been used incorrectly. The statement is, “Levels of impurities that are not more than ($>$) the reporting threshold given in Attachment 1 need not be reported”.

Further clarification on the principles of rounding would be appreciated.

Section 5:

- It is suggested that the title of the section would be clearer if it was changed to “Reporting Impurity Content of *Development* Batches as the batches being referred to are “all new drug substance used for clinical, safety, and stability testing, as well as batches representative of the proposed commercial process”.

Glaxo Wellcome would like confirmation that the following interpretations are correct:

- ◆ when reporting drug substance impurities to $\geq 0.1\%$, one decimal place reporting is appropriate;
- ◆ when reporting drug substance impurities to $< 0.1\%$, two decimal places reporting is appropriate.
- Clarification should be provided to indicate that information provided in Section 5 applies to reporting for Regulatory Submissions and not for routine reporting. This comment is not required if the heading is amended as requested.

Glossary:

- Consistency between the qualifying terms in the glossary and the body of the text should be achieved.
- The rounding definition example “a result greater than or equal to (\geq) 0.05 and less than ($<$) 0.15 is rounded to 0.1” is inconsistent with the information in Attachment 1. The specific concern is that if a value of 0.05% does not need not to be reported, when the value is rounded to 0.1%, as suggested as appropriate in the rounding definition, the impurity would then require reporting.

Attachment 1:

- Glaxo Wellcome would appreciate understanding the scientific rationale for the 0.03% Reporting Threshold for drug substances with a maximum daily dose of >2g/day and for the rationale as to why two Reporting Thresholds are necessary. For most methods, a 0.03% Reporting Threshold is below the limit of quantitation and would require justification of a higher Reporting Threshold. Additionally, during early development, the dose to be administered to patients is unknown. To make sure that there is no need to go back and retest batches if the dosing is > 2 g/day, all methods will need to be developed to the 0.03% Reporting Threshold until the final dose is determined to be ≤ 2 grams/day. In addition, the 0.03% Reporting Threshold may pose technical difficulties for a number of compounds.
- It would be beneficial if rounding examples relevant to the Qualification/Identification Threshold and the Reporting Threshold could be provided as a footnote to the table in Attachment 1.

Attachment 2:

- Due to differences in printing, the lines in the Decision Tree for Safety Studies are not clear and easily followed. It is suggested that arrows be added to the lines to clarify the Decision Tree flow.