February 27, 2003

0690 '03 FEB 28 A9:05

GlaxoSmithKline

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

Tel 919 483 2100
www.gsk.com

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

Re: Docket Number 02D-0509
International Conference on Harmonisation; Draft Guidance on the M4 Common Technical Document-Quality: Questions and Answers/Location Issues

Dear Sir or Madam:

Enclosed please find the comments from GlaxoSmithKline, both general and specific, for the International Conference on Harmonisation; Draft Guidance on the M4 Common Technical Document – Quality: Questions and Answers/Location Issues. These comments are presented for consideration by the FDA. The specific comments are presented in order by the section of the guidance.

General Comments

Our major concern is that this document is overly prescriptive in a number of respects, and does not allow enough flexibility in formatting the "core" CTD-Q data requirements. However, if the implementation of the final guidance fulfills its major aim of reducing screening deficiencies, then it will serve a useful purpose. If this were not a likely outcome, then we question the value of developing this guidance to Step 4/5.

The guidance does not address one of the major formatting issues associated with the ICH CTD guidance, namely the presentation of information on pharmacopoeial excipients in P.4. Control of Excipients. We believe more consideration should be given to this aspect.

The guidance provided does begin to impact on content of the CTD dossier in certain sections. This needs to be carefully managed, so as not to lead to an escalation of data requirements. This is particularly true where there may only be a regional requirement, and this could translate into becoming an ICH requirement. The inclusion of statements like "if necessary" or "as appropriate" are welcomed as these will seek to minimize this problem. Every effort should be made to retain such statements.

02D-0509 C6

Finally, the batch analysis sections (S 4.4. and P 5.4.) should include the release data on batches manufactured according to the proposed commercial method, which will be used to justify the acceptance criteria. All other batch data should be provided in the Regional Information Section.

Specific Comments

2.1 Definition of a Quality Document

Definition of "Quality documents" presented leads to a large number of small documents.

Module 2

Two options for providing documents for Module 2(QOS) are presented.
The first option is much preferred i.e. provide 3 larger documents on Drug Substance, Drug Product and Appendices in a total of 40 pages.

The second option would result in approx. 20 separate document/40 pages being submitted.
We believe this is unwieldy and should be discouraged as an option.

Module 3

The breakdown of individual documents for Module 3 is sensible, as this will facilitate maintenance activities.

Further allowance for granularity should be made however where there is more than one container closure system, i.e. bottle, bottle closure and blister pack, such that there is an option for each pack configuration to be included in one or multiple documents.

This option for granularity should also be extended in the stability section whereby the stability data could be presented and discussed in one or multiple documents for each pack configuration. These options would facilitate maintenance of applications through the lifecycle.

2.3 Table of Contents Formatting

Module 3

The first sentence of third paragraph reads "Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided."

This only allows the inclusion of an attachment or appendix in an existing section. This does not allow the inclusion for example of batch details of drug substance used in clinical trials and/or safety studies as a separate appendix. We believe this is too inflexible, and would recommend that there needs to be some flexibility in formatting around current section headings where this would facilitate review.

Excipients

The first sentence states "If appropriate where a novel or non-compendial non-novel excipient is proposed, the guidance asks for an Appendix (3.2.A.3) that repeats the format of the drug substance section."

This statement is too prescriptive in nature and will lead to significant problems for pharmaceutical companies, unless a number of changes are introduced.

Firstly, there needs to be a clear, unambiguous definition (agreed by regulatory agencies of EU, US and Japan) of what constitutes a "novel" excipient, included in this section. We believe that the definition of a novel excipient, provided in the Notice to Applicants Volume 2B is reasonable and should be included here. This states that a novel excipient is "an excipient used for the first time in a drug product or by a new route of administration."

Secondly, there may be instances where a non-compendial non-novel excipient is so widely used either as an excipient in a pharmaceutical product or as a food additive, that it should not be treated as a new active substance.

We believe this section requires re-drafting to take into account these major points.

2.5 Multiple Containers and Multiple Strengths

During the lifecycle of the product changes to pack are only likely to occur to one pack configuration at a time, therefore to facilitate maintenance of the CTD-Q we believe that further allowance for granularity should be made where there is more than one container closure system, i.e. bottle, bottle closure and blister pack, such that there is an option for each pack configuration to be included in one or multiple documents, rather than as suggested combining the details of the pack configurations into subsections on 3.2 P.7.

This granularity should also be extended to the stability section whereby the stability data could be presented and discussed in one or multiple documents for each pack configuration.

2.6 Bioanalytical Methods

We consider that the guidance provided on Bioanalytical Methods is particularly useful.

3. Multiple Links between Different Sections

Whilst this section provides useful guidance on multiple links between different sections, it is not exhaustive and would benefit from expanding upon.

For instance, there are no links presented for Justification of Specification, a key document in the overall CTD-Q submission.

We believe that it would be much more appropriate to present the Quality Information on Investigational Formulations as a single appendix, rather than dispersed throughout the various sections as outlined under Section. 3.3. Consideration to this alternative approach should be given.

4. Location Issues in Drug Substance

S 2.5 Process Validation and /or evaluation

Does rework need to be mentioned in this section?

S 2.6 Manufacturing Process Development

Under Issues/Questions it is unclear whether "product comparability" refers to NCEs as well as biotech products. Clarification on this point is needed.

S 3.1 Elucidation of Structure

We believe that it would only be relevant to provide physico-chemical characteristics in the Elucidation of Structure document, where this contributes to the confirmation of structure.

S 3.2 Impurities

1. This indicates that "structural characterization data and a summary of the method of preparation of impurities" should be included in section S.3.2.

We believe that this should not be the general case, but only where relevant. Therefore we would advise that the words "when appropriate" should be inserted after "Such information should be included in 3.2.S.3.2."

S 4.1 Specifications

1. In the answer to question 1 it refers to a "specification sheet". The term "sheet" in this context would seem inappropriate.

S 4.2 Analytical Procedures

2. We agree with the response to question 2. This is a positive statement.

S 4.4 Batch Analyses

1. The batch analysis section should include the release data on representative batches manufactured according to the proposed commercial method, which will be used to justify the acceptance criteria. All other batch data should be provided in the Regional Information Section.

S 4.5 Justification of Specification

2. We welcome the response to question 2, which states that "A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of the specification."

S 5 Reference Standards or Materials

1. We welcome the inclusion of the statement "if information is required..." under response to question 1.

S 7.3 Stability Data

4. We fully support the statement included as a response to question 4.

5. Location Issues in Drug Product

P 2 Pharmaceutical Development

P 2.2.1 Formulation Development

1. and *2.* The responses to questions 1 and 2 are welcomed.

P 4 Control of Excipients

In our opinion the section headings provided in the ICH CTD-Q guidance are inappropriate for the provision of data for pharmacopoeial excipients. For instance, we do not believe it would be necessary to complete sections P4.3 and P4.4 for well established pharmacopoeial excipients.

We believe there is an opportunity to resolve these major formatting issues for pharmacopoeial excipients with appropriate Q&A's included here.

P 5.4 Batch Analyses

1. The batch analysis section should include the release data on representative batches manufactured according to the proposed commercial method, which will be used to justify the acceptance criteria. All other batch data should be provided in the Regional Information Section.

P 6 Reference Standards or Materials

We do not believe that the FDA have been routinely requesting reference standards or materials for this purpose, so this could be seen as an escalation of data requirements (i.e. a content issue.) if applied across all 3 ICH regions. However, the inclusion of the words "If information is required..." could prevent this being an issue.

P 8.1 Stability Summary and Conclusion

1. The response to question as currently worded is open to interpretation and would benefit from re-wording to improve clarity, for example is it the intent that the shelf-life specification is cross-referenced or reproduced in P8.1.

P 8.3 Stability Data

5. We welcome the inclusion of the words "if included" in the response to question 5, as this maintains an element of flexibility.

Regional Information Section

The batches listed would support all studies in the specific region. The tables would be in the order of drug substance batches followed by drug product batches.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America
Global CMC Regulatory Affairs