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February 28, 2003

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

RE: Docket No. 02-0509] International Conference on Harmonisation; Draft Guidance on M4 Common Technical Document -- Quality: Questions and Answers

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's research has produced many of the most important pharmaceutical products on the market today.

Merck has participated with health authorities and industry scientists from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). Merck continues to support the objectives of ICH: to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical and biological products caused by incompatible regulatory schemes.

In the course of bringing Merck's product candidates through developmental testing and clinical trials to the market, Merck has filed numerous original and supplemental New Drug Applications (NDAs) and Biological License Applications (BLAs). Merck typically prepares a single Worldwide Marketing Application (WMA) which is filed electronically and, less often, filed on paper, in most countries in the world, simultaneously. Therefore, we are very interested in the *Draft Guidance on M4 Common Technical Document -- Quality: Questions and Answers,* hereafter referred to as the *Draft Guidance*, and we are well qualified to comment on it.

General Statement
Merck commends the U.S. FDA and all ICH participants for their pursuit of harmonized and streamlined documentation requirements for marketing applications for products for human use, over the last 10 years. At this stage in the ICH cycle of *this Draft Guidance*, Merck has a few comments to offer, below that may require clarifying language in certain sections of the document.

2. General Issues
2.1 Definition of a Quality Document
The terms 'document' and 'file' are not clearly defined.

Merck Recommendation-2.1 Definitions: It would be helpful to define a document as a single component of a hard copy submission and a file as a single .pdf in the case of an electronic submission.

Module 3

For all sections of the *Draft Guidance*, the sponsor should have the flexibility to submit, in each section, one or multiple documents, instead of a single separate document, as recommended. As long as the sponsor follows the Module 3 CTD-Quality structure and will follow the same presentation throughout the life of the product, this should not be an issue.

Merck Recommendation 1 - Module 3: Each section of the *Draft Guidance* should provide sponsors with the opportunity to submit more than one document, provided that a sponsor follows the same pattern for presentation throughout the life of the product.

The *Draft Guidance* seems to offer little flexibility for a sponsor, i.e., by strictly defining CTD Document as one document and providing inflexible instructions for that document's pagination and heading. There are sections and situations where more flexibility should be permitted to accommodate a sponsor's identification scheme and or pagination "superimposed" upon the headers/numbers of the collated documents, specifically in the case of highly modular submissions.

Merck Recommendation 2 - Module 3: It would be beneficial to allow a sponsor to determine the appropriate level of granularity and presentation as long as the submission complies with the "high-level" requirements as described in the *Draft Guidance*. The eCTD, which seems to have driven some of the specifications for granularity, pagination, volume identification, etc., should be addressed separately.

2.2 Document Pagination and Segregation

The requirement to include a unique header to identify subject matter for each document should not be necessary. Document headers should identify higher levels (e.g., 3.2.S Drug Substance or 3.2.P Drug Product), which would be consistent across all 3.2.S and 3.2.P documents. The document headings would adequately identify the subject matter for each document. Similar requirements for tabs are recommended.

A sponsor should have the flexibility to create additional section and subsection levels, when necessary, so that an individual subsection number identifies each individual quality document (as defined under 2.1).

Regarding pagination, we agree that each individual quality document should have its own page numbering. However, in addition, the sponsor should be allowed to number Module 3 globally (i.e., throughout all sections), since Module 3 can also be considered to be a global report, containing many smaller individual documents.

Merck Recommendations – 2.2 Document Pagination and Segregation: The *Draft Guidance* should allow sponsors to clearly identify high level headers and to use subsections, whenever necessary, provided there is a global scheme used throughout the submission. In addition, a global numbering system, commonly used by sponsors now, should be retained here, without interference with the numbering scheme for individual documents as noted in this *Draft Guidance.*

2.3 Table of Contents Formatting
Module 3
There appears to be a typo in this section.

According to the *Draft Guidance*, sponsors may not add "high level" sections beyond what is specified. For example, in sections 3.2.P and 3.2.S, sponsors would not be allowed to add 3.2.S.1 through 3.2.S.7 or 3.2.P.1 through 3.2.P.8. Given the complexity and volume of some submissions, this seems overly restrictive and will prohibit sponsors from providing important information in a logical related fashion.

Merck Recommendations: The last sentence in paragraph 2 - "*2.3* Document Pagination and Segregation" should be corrected to read: "*2.2* Document Pagination and Segregation" [emphasis added].

The Draft Guidance should allow sponsors the flexibility to expand sections to include related materials in logical proximity to appropriate pre-specified section.

3. Multiple links between different sections
3.3 New location of Quality Information on Investigational Formulations
It appears that quality information on investigational formulations is dispersed throughout various sections of the submission, as outlined in this section of the *Draft Guidance*.

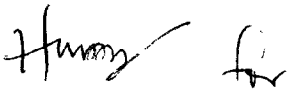
Merck Recommendation: It would seem more appropriate to present the Quality Information on Investigational Formulations as a single appendix or reference.

4. Location Issues in Drug Substance
P.8.1 Stability Summary and Conclusion
Guidance regarding the location of statistical analysis of stability data is lacking.

Merck Recommendation: Mention and/or cross-references to Stability Data section might be made in the Summary section and all details and discussion of details might then fit in the Stability Data section.

We welcome the opportunity to provide feedback on the *ICH Draft Guidance on M4 Common Technical Document -- Quality: Questions and Answers.*

Sincerely,



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