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

RE: [Docket No. 01D-0368] Draft Guidance for Industry on Submitting Marketing Applications According to the ICH/CTD Format; General Considerations; Availability

Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the most important pharmaceutical products on the market today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment, to ensure that important therapeutic breakthroughs reach patients without unnecessary or unusual delays.

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). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical and biological products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

In the course of bringing our 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 which is filed electronically and, less often, on paper in most countries in the world. For these reasons, we are very interested and well qualified to comment on this FDA Draft Guidance for Industry on Submitting Marketing Applications According to the ICH/CTD Format, hereafter referred to as *The Draft Guidance*.

General Statement

We commend 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 At this stage in the ICH cycle of *The Draft Guidance*, Merck has very few comments to offer, since *The Draft Guidance* regarding the format of the Common Technical Document (CTD) has been well thought-out and is relatively complete as written.

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We understand that *The Draft Guidance* is intended to replace existing regulatory requirements for format of applications for drug and biological products in the US. *The Draft Guidance* also indicates that a sponsor "...may submit a BLA for a specified biotechnological product,..."[1]. We recognize that the contents of a "biotechnological" application or definition of what constitutes a "biotechnological product" may be spelled out elsewhere. However, since some types of applications such as this are pre-specified in *The Draft Guidance*, we are not sure whether or not, by omission, applications for vaccines, some of which are neither biologicals nor biotechnological products, will use the CTD format.

Merck Recommendation: *All* products for human use, submitted to the Center for Drug Evaluation and Research (CDER) or to the Center for Biologics Evaluation and Research (CBER), should use the same CTD format addressed in *The Draft Guidance*.

Comments Specific to Certain Sections of *The Draft Guidance*

The remainder of Merck's comments, outlined below, will provide additional clarity for sponsors who put these applications together and should eliminate questions during that process. Our comments reference specific sections of *The Draft Guidance*.

III. CTD Format for Each Submission

A. Module 1 - Administrative and Prescribing Information

3. Administrative documents

a. administrative documents

- Environmental assessment or request for categorical exclusion (page 5)

Comment III A *3.* a: *The Draft Guidance* requires placement of an environmental assessment or a request for categorical exclusion in Module 1. This information is, now, routinely provided in the Chemical Manufacturing and Controls (CMC) documentation, where it is reviewed with other related information, which is required to be in Module 3 – Quality. Including this information in Module 1 would be a distinct change from current practice that is not fully explained in *The Draft Guidance*. If FDA intends to change the location of this information, then rationale for this change should be provided.

Merck Recommendation: The environmental assessment (or request for categorical exclusion) should be included with regional information within Module 3 – Quality, where it will be reviewed with other related information. If necessary, a reference to the location of this information in Module 3 may be noted in Module 1.

IV General Issues for Submissions

C. Number of Copies

3. Field copy (page 9)

Or

[1] *The Draft Guidance*, page 3 paragraph 1, line 2

G. Binding volumes Table 2: Binder Colors for NDA or BLA Review Copies (page 11)

Comment IV C and G: Field copies of the NDA are typically distinguished by using maroon colored binders. This information is missing both from the text (page 9) and from Table 2 (page 11). If this is no longer required, sponsors should be informed of this change in the text of Section IV C.

Merck Recommendation: Unless the requirement for maroon binders has been discontinued, information about the use of maroon binders for *field copies* of information should be included in Table 2: Binder Colors for NDA or BLA Review Copies.

J. Volume Identification

Comment J: FDA allows submission of information to be filed as it is collected, rather than as part of a finished and complete application, in cases where review of the application needs to be expedited (also known as "rolling" submissions). For example, for *Fast Track* applications, some subsections within a major section of non-clinical information may be filed ahead of the completion of the full section of non-clinical data and well before the NDA is completely assembled. In cases like this one, providing consecutive volume numbers across a complete section of non-clinical data through to the end of the completed NDA may not be possible at the time the non-clinical data are submitted. In these situations, module numbers and page numbers will be adequate to locate information. However, at the time the completed NDA is filed, the numbering of volumes recommended in *The Draft Guidance* may be accommodated.

Merck Recommendation: To accommodate those instances when "rolling" submissions of data are allowed for expedited reviews, flexibility in the requirement for consecutive volume numbering should be allowed.

L. Cross referencing documents

Comment L: As noted above, there will be instances when certain information filed as "rolling" submissions will not allow consecutive numbering of volumes at the time these submissions are filed. Similarly, cross-referencing of information is also done when all sections of the NDA are completed, assembled and numbered. Therefore, information may be found using the CTD module, tab identifier and page numbers applied as the volumes are created.

Merck Recommendation: In the case of "rolling" submissions, volume numbers and cross-referencing should not be required. The text should read:

> "You should reference documents by CTD module, tab identifier, and page number and, if possible, by volume."

Summary of Comments

The Draft Guidance should clarify certain issues in order to simplify implementation of the CTD and it should reflect an understanding of the sequencing of events during the assembly of a typical CTD. That is, addition of volume numbers occurs at the end of the process and, therefore, cross-referencing using volume numbers is impossible for sections of information filed early for expedited reviews. If the requirement for using colored binders for field copies of information has changed, sponsors should be notified of that change in current practice. Finally, all applications, filed to CDER and CBER, should be required to use the new CTD format, specified in this guidance.

We welcome the opportunity to comment on *The Draft Guidance for Industry* on Submitting Marketing Applications According to the ICH/CTD Format, and, if appropriate, we would be pleased to meet with you to discuss these issues.

Sincerely,

Marie LeDay for Bonnie Goldmann & Henrietta Ukwu

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