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

RE: Docket No. 03D-0465
Draft Guidance, Providing Regulatory Submissions in Electronic Format – General Considerations

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- necessitates an expenditure of more than $3 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 supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment to ensure that therapeutic advances reach patients without unnecessary or unusual delays.

In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists file many original INDs, NDAs and related submissions that are directly impacted by the *Draft Guidance on Providing Regulatory Submissions in Electronic Format – General Considerations*. Thus, we are very interested in and well qualified to comment on this Draft Guidance.

In general, we find the Draft Guidance appropriate as it applies to INDs and NDAs/BLAs. However, we suggest some minor points of clarification be addressed in the Guidance. On the other hand, the application of this Guidance to the submission of advertising and promotional materials via electronic means is problematic and we strongly encourage the Agency to consider developing a separate Guidance that is specific to the submission of advertising and promotional materials.

<u>Advertisements and Promotional Material</u>

The comments provided below were recently submitted to Docket No. 03D-0367, *Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format –*

Human Pharmaceutical Applications and Related Submissions. We now submit them to Docket No. 03D-0465 as they are widely applicable to the submission of advertising and promotional materials to DDMAC in electronic format and merit your attention.

This Draft Guidance focuses primarily on the submission of regulatory documents in support of product development (INDs) and marketing (NDAs, BLAs, and related submissions). However, the Draft Guidance states that, "the guidance is being revised to address electronic submissions coming into ***all*** centers of the Agency," which includes promotion and advertising submitted to DDMAC. While Merck supports the electronic submission of advertising and promotional materials, it is important to recognize the significant differences in the nature of advertising and promotional materials that are the subject of DDMAC submissions versus the types of documents that are typically submitted to FDA Reviewing Divisions.

Thus, Merck strongly recommends that advertising and promotion materials submitted to DDMAC be explicitly excluded from this Guidance. We encourage the Agency to draft a separate Guidance that is specific to advertising and promotional materials to guide the development of electronic submission formats that will be most useful in facilitating DDMAC review and retention of these fundamentally different materials.

For example, this Draft Guidance encompasses manuscript submissions. This is evident in the general guidelines, which refer to printing documents page-by-page, providing a table of contents, and the ability to copy sections of the document into other common software. It is also evident in the technical guidelines, such as the limited number of type fonts, restrictions on font size and page size, submission in PDF format, and naming conventions. However, unlike manuscripts submitted to the Reviewing Divisions, advertising and promotional materials submitted to DDMAC frequently include extensive use of high definition color graphics, a wide variety of font styles and sizes, and are created in a wide range of sizes and three dimensional configurations. The format of the digital files from which these types of materials are most often created and most conveniently transmitted are often not compatible with the electronic platforms that support document creation and transmission.

Therefore, if the FDA elects to issue a Guidance that encompasses product development, marketing, labeling, and advertising and promotional submissions, Merck recommends that the Guidance clearly separate document submissions that are independent of DDMAC, from materials submitted to DDMAC on Form 2253 and submissions requesting DDMAC advisory review and comment, with consideration to the different and varied design and content of the pieces and the respective technical limitations of each.

Specifically, Merck recommends that submissions with DDMAC Form 2253 include alternative formats to PDF for the following reasons: (1) advertising agencies generally

supply Quark files to their pharmaceutical clients. The requirement to submit PDF files for electronic submission would necessitate a careful translation from Quark files to PDF files in order to ensure clarity of images and complete conversion of text and graphics. Accepting submissions in various graphic formats would eliminate time and expense involved to create the PDF files; (2) dimensional items, such as cartons with flaps or interactive mechanisms, would be subject to interpretation as flat PDF files; and (3) items with considerable content, such as lengthy textbooks, may not transmit well as PDF files.

Thus, the Guidance should accommodate the submission of actual physical items in those instances where an electronic file does not adequately represent the item. For example, in cases when promotional writing is lengthy and not easily transmitted as a PDF file, a physical copy of the writing or manuscript should be acceptable for submission. Likewise, sponsors should be permitted to supply actual samples of multidimensional promotional materials.

Suggested Points of Clarification

K. Naming PDF Files
On Page 8, Line 311, this Guidance recommends against using punctuation, dashes, spaces, or other nonalphanumeric symbols in file names; underlines can be used. Whereas the eCTD guidance states that no special characters may be included in file or folder names, other than hyphens (-). We suggest that hyphens be included in this Guidance to align with the eCTD guidance.

Appendix A, CBER, Roadmap File
On Page 17, Lines 707 to 711, this Guidance states, *The contents of the original application and any subsequent amendments to that application should be briefly described in a roadmap.pdf table. The location of these files and folders on the submitted media should be indicated in the roadmap.pdf. Where portions of that application have been submitted only as paper documents, they should be included in the roadmap and table of contents and tagged as paper only.*

For most Merck biologics, the original application and all supplements have been filed as hardcopy (paper). We have many products that are several years old, some predating the STN system for application and supplement numbering and others predating the PLA/ELA system. The Guidance can be interpreted as requiring a list of the original application and all supplements - a list that would not add much value since it is apparent that previous years of correspondence would naturally be paper. Therefore, we suggest that the Guidance be amended to provide for a simple entry in the roadmap that would indicate that the original application, supplements, and correspondence up to a given date were provided as paper copies, without listing each individual item.

Supplements Involving Multiple Products
Many of our license supplements involve multiple products. Currently our practice is to submit to CBER four copies of a given hard copy supplement along with individual Forms 356h for each product that is affected. CBER then assigns multiple STNs to the supplement.

However, the Guidance appears to require that we provide an individual updated roadmap for each product affected. Because the roadmap links an individual existing product file to all supplements including the new supplement, it would appear that we would have to provide separate electronic supplements for each product affected. For instance, a change in the site of formulation and filling may affect many biological products. Does this mean that we will have to send multiple CD-ROMs to CBER (or multiple electronic mailings), each containing a roadmap file for one of the affected products, along with the files for the supplement? This does not appear to be the most efficient way to handle the affected applications. Therefore, we suggest that the Guidance address how future multi-product supplements will be handled electronically.

We welcome the opportunity to comment on this Draft Guidance and to meet with you to discuss these issues.

Sincerely,

Lauren M. Hetrick

for David Blois, Ph.D.
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