Global Regulatory Policy

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Food and Drug Administration
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MERCK
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Docket No. 03D-0367
Draft Guidance, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Applications and Related Submissions

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend 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trials, Merck scientists file many original INDs, NDAs and related submissions that are directly impacted by the *Draft Guidance on Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Applications and Related Submissions*. Thus, we are very interested in and well qualified to comment on this Draft Guidance. In general, we find the Guidance appropriate. Therefore, we limit our comments specifically to the submission of INDs and advertisements, followed by a few general comments referenced by the line number corresponding to the statement in the Guidance.

INDs

The Guidance does not provide sufficient detail regarding the IND submission component and file placements. The *Comprehensive Table of Content Headings and Hierarchy* appears slanted toward marketing applications (NDA/BLA). For example, component and file placements cannot be determined for the submission of a Protocol Amendment-New Investigator that includes CVs and Forms 1572 for each investigator. We suggest that the Agency specifically address IND submissions.

Advertisements and Promotional Material

The Draft Guidance focuses primarily on the submission of regulatory documents in support of product development (INDs) and marketing (NDAs and related submissions), although as drafted the Guidance includes Promotion and Advertising submissions to DDMAC within its scope. While Merck supports the electronic submission of advertising and promotional materials as useful, it is important to note 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.

Specifically, materials submitted to DDMAC frequently include extensive use of high definition color graphics 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 mostly conveniently transmitted are often not compatible with the electronic platforms that support document creation and transmission. Merck strongly recommends that advertising and promotion submissions to DDMAC be explicitly excluded from this Guidance and that a separate Guidance be issued for advertising and promotional materials to provide electronic submission formats that will be most useful in facilitating DDMAC review and retention of these fundamentally different materials.

Previous comments notwithstanding, if the FDA elects to release a Guidance document that encompasses product development, marketing, and labeling as well as advertising and promotion submissions, 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.

The Guidance should accommodate the submission of either electronic or physical representations of items, depending on which provides the best model. 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 (refer to Lines 427-433). Likewise, sponsors should be permitted to supply actual samples of multidimensional promotional materials.

General Comments by Line Number

Line 2: Although a minor point, Footnote 1 on the bottom of Page 1, should read, *This guidance has been developed by the Center for Drug* ***Evaluation*** *and Research (CDER)...*

Lines 197-198: The Guidance states, *If you provide a document in electronic format, paper copies of the document, including **desk copies**, are not needed.* We note that prior guidance on electronic submissions used the term, ***review copies***.

- Are these two terms synonymous to the Agency such that no supplemental paper copies are to be submitted?
- If no paper copies are to be submitted, has the Agency considered how it will provide submissions to Advisory Committee members and consultants?

Lines 450-476: This section, *Marketing annual reports*, acknowledges the regulations governing annual reporting obligations for sponsors of NDAs; it should also include the relevant citations for biologics.

Line 669: *Case report forms*, states, *You should provide each individual subject's complete CRF as a single PDF file.* This statement could be interpreted to mean that sponsors are required to submit CRFs for <u>all</u> patients who participated in each clinical study; this conflicts with the July 1988 Guidance, *Format and Content of The Clinical and Statistical Sections of an Application*, which requires that CRFs be submitted <u>only</u> for patients in FDA Item 12 categories (i.e., Deaths and Discontinuations Due to Serious AEs). Has the CRF requirement been expanded to include all patients in each clinical study versus only those patients as defined in the 1988 guidance?

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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