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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20857

**RE: Docket No. 00N-1652  
Requirements for Submission of Labeling for Human Prescription Drugs  
and Biologics in Electronic Format**

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 nearly \$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 and biological products on the market today.

As a leading pharmaceutical manufacturer, Merck submits labeling to the Food and Drug Administration (FDA) in paper and electronic forms. In recent years, Merck has relied on the electronic submissions processes at FDA for the majority of its filings, particularly labeling submissions. Therefore, Merck is very interested in, and well-qualified to comment on the FDA-proposed rule, *Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format*, hereafter referred to as the Proposed Rule.

Merck supports the FDA's overall goal of reviewing and approving regulatory applications in a paperless business environment. We specifically endorse the proposal to require applicants to submit package inserts electronically to facilitate processing, reviewing, and archiving by the FDA. The submission of electronic labeling will benefit both sponsors and regulators.

We suggest that FDA clarify logistics and harmonize processes between CDER and CBER to facilitate the processing, reviewing, and archiving by FDA, as described in Items 1 through 5 below. In order to facilitate the review and negotiation of labeling text between the FDA and sponsors, we suggest that the Agency consider a process whereby sponsors and FDA utilize electronic means (for example, MS WORD) to exchange revisions in proposed labeling, as described in Item 6.

00N-1652

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1. In CDER, official electronic submissions of original NDAs and supplements are submitted to the Central Document Room, whereas official paper submissions are directed to the reviewing Divisions. Official paper submissions of NDA Annual Reports are submitted to the reviewing Divisions with no involvement of the Central Document Room. If the labeling section of the Annual Report is required to be submitted electronically, but the remainder of the report is paper, to what location should the report be sent?

Merck Recommendation: The FDA should clarify the location(s) where electronic labeling versus paper labeling should be submitted, and should clarify if the submission address varies depending on the type of submission (e.g. original marketing application, supplement, Annual Report) and by Center. Paper and electronic labeling submissions should be made to the same location, regardless of the type of submission (NDA, supplement, and Annual Report). However, if there are legitimate reasons to submit electronic and paper labeling to different sites or to vary the sites by application type, the reasons and locations should be made public. Ideally, Annual Reports should be submitted as electronic documents to the Central Document Room for archival purposes, along with a cover letter identifying the personnel in the reviewing Division that should be contacted for FDA review; this process is consistent with that used for original applications and supplements.

2. The Office of Generic Drugs (OGD) has limited experience working with electronic submissions. While OGD may gain valuable experience in processing submissions under the recently issued Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – ANDAs* (June 2002), it remains to be seen how many electronic applications will be submitted by the generic industry prior to the requirement to submit labeling electronically.

Merck Recommendation: Therefore, it may be worthwhile for OGD to pilot a program with industry through which they accept and process electronic labeling in advance of the requirement to do so.

3. It would benefit sponsors if FDA could identify the software referred to on page 22369 (second column) of the May 3, 2002, Proposed Rule, where FDA states, "...we can use our current software to compare the text of the file received with other PDF files and view, search, annotate, and print the file," so that sponsors have the option of purchasing similar software. The comparison of files is important if an electronic approach to labeling is to result in significantly decreased resource utilization both by the FDA and sponsors.

Merck Recommendation: The FDA should identify the software the Agency proposes to use when working with sponsor's labeling and state whether the software is commercially available or proprietary.

4. Sponsors of biological products are required to complete and sign FDA Form 2567 to submit each labeling component (e.g. package insert) to CBER. CDER does not require this particular form to accompany labeling.

Merck Recommendation: In the spirit of harmonization, this additional CBER requirement should be eliminated.

5. CDER requires a comprehensive Annual Report, including labeling, per 21 CFR 314.81(b)(2), whereas CBER does not require a comprehensive Annual Report. For biologics, each element of the Annual Report (e.g. labeling, CMC, and postmarketing status) is filed separately as described in the applicable sections of 21 CFR 601.

Merck Recommendation: CBER and CDER should harmonize the requirements for all elements of Annual Reports to facilitate electronic filing.

6. Sponsors submit package inserts in PDF format and MS WORD per FDA Guidance, *“Providing Regulatory Submissions in Electronic Format – NDAs.”* The submission of labeling text in MS WORD has proven useful in cases where the reviewing Division modifies the sponsor’s labeling using the sponsor’s document and clearly indicates FDA’s proposed modifications using revision marks, as can be done with the *“Tools, Track Changes”* function in MS WORD.

Merck Recommendation: We recommend that FDA take advantage of the electronic submission of labeling to develop final labeling text. We suggest that the Agency consider a process whereby sponsors and FDA exchange revisions in proposed product labeling via electronic means (for example, MS WORD) using clear markings so that changes can be easily identified. This will conserve resources as electronic labeling may be easily compared to prior versions and the changes highlighted.

In conclusion, Merck supports the FDA proposal to require applicants to submit package inserts electronically to facilitate processing, reviewing, and archiving by the FDA. We recommend that the Agency address the logistical and harmonization issues noted above and welcome the opportunity to discuss our comments before the Final Rule issues.

Sincerely,



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