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

RE: [Docket No. 00N-1545]
Proposed Rule: Applications for FDA Approval to Market a New Drug: Proposed Revision of Postmarketing Reporting Requirements

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 $2 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.

Maintaining a varied portfolio of approved products over the course of many years has provided Merck scientists and regulatory professionals with broad experience with the principles and requirements for postmarketing reporting that are affected by this proposed rule. Indeed, Merck recognizes the importance of sole source products to certain patient populations lacking alternative treatments and has worked closely in the past with the Food and Drug Administration (FDA) to assure that patient needs are met when decisions to cease manufacture of such products were being considered. For these reasons, Merck is both interested and well qualified to comment on this proposed revision of postmarketing reporting requirements.

The proposed revision is intended to implement the provisions of section 131 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) by requiring an applicant who is the sole manufacturer of products that are life supporting, life sustaining or intended for use in the prevention of a debilitating disease or condition to notify FDA at least 6 months before discontinuing manufacture of the drug product.

Comments

1. ***Recommendation:*** The definition of "life supporting or life sustaining" that appears only in the preamble of the Proposed Rule should be incorporated into the final rule

2. Of the three criteria for prior notification of discontinuance described in FDAMA section 131 [life supporting, life sustaining, or "intended for use in the prevention of a debilitating disease or condition"] the last criterion, without further definition is very broad. Without clarification, virtually all sole source products may be judged to be subject to prior notification of discontinuation under this criterion. FDA's decision to interpret "debilitating disease or condition" to mean "serious disease or condition" fails to resolve the ambiguity.

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FDA's prior discussion of the meaning of "serious disease or condition," to which the preamble refers, lack precision. In that discussion, FDA has stated that "determination of seriousness of a disease or condition is a matter of judgment but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." While these concepts may be meaningful for products intended to *treat* a disease or condition, they are difficult to apply with respect to products strictly *"intended to prevent"* disease.

Likewise, the scope of the term "prevention" in the context of the proposed rule is unclear. If a product is indicated to *treat* one condition (such as hypertension or diabetes), and if control of that condition is generally believed to prevent or delay potential sequelae of such condition left untreated (such as the emergence of cardiovascular events or kidney disease), is that product "intended for the prevention" of disease under the terms of the proposed regulation and section 131? The ambiguity of the proposed rule with respect to these terms makes it impossible for applicants to clearly identify products subject to prior notice of discontinuation of manufacturing.

Recommendation: The meaning of the term "intended for use in the prevention of a debilitating disease or condition" should be clearly defined to apply to products that are specifically indicated in approved labeling for prevention or prophylaxis of a disease or condition that is, or has the potential in its fullest manifestation to be, chronically debilitating.

3. Further definition of the term "discontinuance" should be provided. While it is unlikely that the rule is intended to apply to temporary cessation of manufacturing resulting, for example, from technical production difficulties, the term is ambiguous without further clarification

In addition, because most drug products are not manufactured continuously but are produced periodically to generate inventory necessary to assure uninterrupted supply, a decision to "discontinue" a product may occur long after the actual manufacture of the previously produced lot. Because the discontinuance notification period is defined in terms of cessation of manufacturing, it is not clear when an applicant should notify the agency when a decision to discontinue a product is made after the last production run but before inventories have been depleted or expired.

Recommendation: The rule should stipulate that the prior notification requirements under 21 CFR 314.81 and 314.91 apply to situations in which a manufacturer is ceasing production with the intent of withdrawing the product from the market. Unexpected and unpredictable technical problems that arise in the manufacture of products that require the temporary cessation of product production are beyond the scope and the intent of the pre-notification requirement. In addition, the timing for notifying FDA of a decision to discontinue a product upon depletion of existing inventories should be addressed.

4. Proposed 21 CFR 314.81(b)(3)(iii)(a) requires "an applicant who is the sole manufacturer of an approved drug product" to notify FDA 6 months prior to discontinuing manufacture of the specified drug products. There is, to our knowledge, no reliable, publicly available source that provides information on *manufacturers* of drug products. While the "Orange Book" lists all applicants with approved NDAs and ANDAs for each listed drug, it is not possible to determine whether the listed approved products are, in fact, being manufactured.

Recommendation: For the purpose of this regulation, "sole manufacturer of a drug" should be defined as an applicant listed in the "Orange Book" who is the holder of the only listed approved application under section 505(b) or section 505(j).

5. Proposed 21 CFR 314.81(b)(3)(iii)(b) states:

> "For drugs regulated by the Center for Drug Evaluation and Research (CDER), the notification required by paragraph (b)(3)(iii)(a) of this section must be sent to the director of the division responsible for the application as identified to the applicant under 314.440(a)(1). The applicant must send one copy of the notification to the Drug Shortage Coordinator, at the address of the director of CDER, and one copy of the notification to the Drug Listing Branch. For drugs regulated by the Center for Biologics Evaluation and Research (CBER), the notification required by paragraph (b)(3)(iii)(a) of this section must be sent to the Director of CBER."

a) All drugs approved under section 505 of the FD&C Act, whether regulated by CDER or CBER are subject to the drug listing requirements of section 510 of the FD&C Act. Therefore, it is not clear why notification of the Drug Listing Branch is not required for drugs regulated by CBER.

b) FDA should clarify whether notification of the Drug Listing Branch under the paragraph cited above will result in the de-listing of the product upon the expiration of the discontinuance notification period or whether additional correspondence with Drug Listing Branch will be required.

These points are particularly important because annual product fees are assessed under the Prescription Drug User Fee Act for products that are both approved *and listed* under section 510 of the Food, Drug, and Cosmetic Act.

Conclusion:

In this proposed rule, FDA has set forth regulations intended to implement section 131 of FDAMA (Notification of Discontinuance of a Life-saving Product). Further definition of certain terms used in this section is necessary to resolve ambiguity. Specifically, the terms "sole manufacturer" and "prevention of a debilitating disease or condition" should be defined and included in the final rule. The definition of "life supporting and life sustaining," which appeared only in the preamble to the proposed rule, should be incorporated into the final rule. In addition, clarification of the scope of the term "discontinuance" with regard to temporary

cessation of manufacturing due to unanticipated technical problems as well as the effect of the required notification of Drug Listing Branch for CDER regulated drugs but not those regulated by CBER should be considered.

We welcome the opportunity to comment on this Proposed Rule and, if appropriate, to meet with you to discuss these issues.

Sincerely,

Dennis M. Eck for

Bonnie J. Goldmann, MD
Vice President
Regulatory Affairs

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