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Food and Drug Administration
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MERCK
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RE: Docket No. 99N-1852
Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act (FDAMA) of 1997

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.

We commend the FDA for issuing a draft guidance to ensure that reports on the status of postmarketing studies are submitted in accordance with the Final Rule published on October 30, 2000 (65 FR 64607). However, the final guidance should clarify the following points to be consistent with statutory requirements and existing regulations:

1. Scope of the final rule and how it is presented in the Guidance
2. Phase 4 studies and review of results
3. Logistics of writing and filing postmarketing status reports
4. Public access to information filed in postmarketing status reports
5. Application of the Guidance to Abbreviated NDAs

Each point is referenced to the page where it appears in the draft Guidance.

Since the draft guideline addresses the topic of the timing for FDA review of final study reports for post-marketing (Phase 4) studies, we are also taking the opportunity to comment on a closely related topic, the timing for review of Phase 4 protocols.

1.0 SCOPE

1.1 Page 3, II. Background, B. Summary of the Final Rule that Implements Section 506B, Item 1, Scope

Comment: The Scope of the Final Rule as reflected in this Guidance appears too late in the document. In addition, the order in which the elements that comprise the Scope is presented lacks clarity.

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Recommendation: The Scope should appear as II. immediately following I. Introduction, prior to the presentation of "Background" information. The presentation of information under "Scope" should be reordered to clarify what applications, products, and studies are affected by postmarketing status reports. A suggestion of how to order the information follows:

1. The rule applies only to approved applications....
2. The rule applies only to approved human drug products and licensed biological products that meet the definition of drug under the act.....
3. The rule applies only to postmarketing studies that FDA has required or that you have agreed with FDA, in writing, to conduct.....
4. The rule distinguishes different types and purposes of postmarketing studies.....
5. Report the other types of postmarketing studies .....

The information presented in current section II. Background should appear after Scope.

1.2 Page 3, II. Background, B. Summary of the Final Rule that Implements Section 506B, Item 1, Scope, Second Paragraph

The draft guidance states, "If a postmarketing study fits one of these four categories [clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology], we will include information about its status in the Agency's annual *Federal Register* report on postmarketing studies and in the Agency's special report to Congress."

Comment: The preamble to the list of the kinds of postmarketing studies that might be included should make it clear that these studies will ONLY be included in the Federal Register report and in the special report to Congress, IF they are studies that FDA has required or that sponsors have agreed with FDA, in writing, to conduct.

Recommendation: Modify the text of Paragraph 2 to read as follows.

> "If a postmarketing study fits one of these four categories **and is a study required by FDA or a study that a sponsor has agreed with FDA, in writing, to conduct,** we will include information about its status ....."

1.3 Page 4, II. Background, B. Summary of the Final Rule that Implements Section 506B, Item 1, Scope, Fourth Paragraph

The draft Guidance states, "Fourth, the rule applies only to approved applications. It does not apply to applications that have been withdrawn after approval."

Comment: The term "withdrawn" is commonly used to refer to indications and products that are withdrawn from the market as well as applications for which approval has been withdrawn.

Recommendation: The FDA should modify the text as follows,

> "Fourth, the rule applies ~~only~~ to approved applications, **regardless of whether the product is marketed or not**. ~~It does not apply to applications that have been withdrawn after approval.~~"

2.0 PHASE 4 STUDIES AND RESULTS

2.1 Page 2, II. Background, A. Reasons for Conducting and Types of Postmarketing Studies, Item 1

The draft Guidance states, "FDA might require you to conduct a postmarketing study as a condition of marketing approval."

Comment: There are established procedures that the FDA follows to withdraw approval of a product. The reasons for a withdrawal of an approval are limited to the discovery of previously unrecognized safety or efficacy issues. These are in fact properly presented within the draft guidance as subsections II.A.1.a nd II.A.1.b (Accelerated Approval Clinical Benefit Studies and Deferred Pediatric Studies, respectively). The phrase used, "as a condition of marketing approval", is misleading because it implies that the FDA can withdraw approval of a drug unless certain general "conditions" are met, without specifying that there are very specific conditions for withdrawal of an approval.

Recommendation: The sentence should be modified to read:

> "FDA might require the Sponsor to conduct a postmarketing study ~~as a condition of marketing approval~~ **in the case of the accelerated approval requirement for studies to verify clinical benefit or in the case of pediatric studies that are deferred because the product is otherwise ready for approval in the adult population.**"
> **a. ……..**
> **b. ……..**"

2.2 Page 3, II. Background, A. Reasons for Conducting and Types of Postmarketing Studies, Item 2

The draft Guidance states, "If you and FDA agree before approval of the drug that a postmarketing study should be performed, the study will likely be used to address some concern about the safety, benefit, or use of the drug that does not warrant delaying approval of the application."

Comment: The Guidance should avoid speculating as to the motives for postmarketing studies. It should clearly state that the ONLY reason FDA will seek an agreement with a sponsor to conduct a Phase 4 study is for a product the FDA has found to be safe and effective when FDA concludes that additional information may contribute to the safe and effective use of the product for the claimed indication.

Recommendation: Item 2 should be revised to read:

> "A postmarketing study might be conducted because the Sponsor and FDA agree, **consistent with applicable regulations, that** it should be performed. Such agreements can be reached either before or after FDA has granted marketing approval for the product. If the Sponsor and FDA agree before approval of the product that a postmarketing study should be performed, the study will ~~likely~~ be used to ~~address some concern about the safety, benefit, or use of the drug~~ **provide additional information about the drug's risks, benefits, and optimal use, the absence of which** ~~that~~ does not warrant delaying approval of the application. If the Sponsor and FDA determine after approval of a the drug that a postmarketing study should be performed, the study will ~~generally~~ be used to **address** ~~a safety concern~~ **an issue** that has been identified during the post-approval use of the drug."

2.3 Page 16, V. Timeframes for FDA's Review of Postmarketing Annual Status Reports and Study Final Reports, B. Study Final Reports

Section B states that the FDA will review study reports that are not submitted in a labeling supplement within one year of receipt.

Comment: FDA may ask a sponsor to conduct Phase 4 studies, for a product the FDA has found to be safe and effective, when the additional information may further define conditions of use of the product for the claimed indication. Phase 4 study reports may be submitted in labeling supplements that are reviewed under PDUFA timeframes or independent of such supplements. Regardless of how the results are submitted, the FDA should promptly evaluate the Phase 4 results.

Recommendation: The time in which results from Phase 4 commitments are reviewed when the results are not included in labeling supplements, should be within 10 months of receipt (as is the case for Clinical Supplements).

3.0 LOGISTICS

3.1 Page 8, Procedures Concerning Postmarketing Study Status Reports, B. Postmarketing Study Protocols: When and How to Submit Them, First Paragraph

The draft Guidance states, "Generally, protocols for required studies (e.g., accelerated approval clinical benefit studies) should be submitted prior to application approval, and protocols for other postmarketing studies should be submitted within three months after the date of the postmarketing study commitment."

Comment: This draft Guidance should not impose time-frames for protocol submission. Such time-frames are better negotiated between the sponsor and reviewing Division on a case-by-case basis. A general rule for the timing of protocol submissions is impractical because the time-frames depend on many factors, such as the objectives of the study, the

availability of study subjects (rarity or seasonal nature of the condition), and the importance of obtaining Agency concurrence on the protocol design.

Recommendation: Modify the first paragraph so that it reads,

> "The type of study and the agreements reached with the Agency before product approval will influence when the final protocol for a postmarketing study should be submitted. **Time frames should be negotiated between the sponsor and the reviewing Division on a case-by-case basis.** ~~Generally, protocols for required studies (e.g., accelerated approval clinical benefit studies) should be submitted prior to application approval, and protocols for other postmarketing studies should be submitted within three months after the date of the postmarketing study commitment.~~ Protocols for studies requiring an investigational...."

3.2 Page 12, III. Procedures Concerning Postmarketing Study Status Reports, E. How Should Study Final Reports be Submitted?, First Paragraph

The draft Guidance states, "When a postmarketing study has been completed, you should submit a final report as a separate submission to the NDA, ANDA, or BLA in an original and 2 copies with form FDA 356h and a cover letter attached."

Comment: The required number of copies is inconsistent with 21 CFR 314.81(b)(2) that requires two copies be submitted.

Recommendation: The guidance should be revised to read,

> "When a postmarketing study has been completed, **the Sponsor** ~~you~~ should submit a final report as a separate submission to the NDA, ANDA, or BLA in an original and **1 copy** with ....."

3.3 Page 12, III. Procedures Concerning Postmarketing Study Status Reports, E. How Should Study Final Reports be Submitted?, Second Paragraph

The draft Guidance states, "If a postmarketing commitment includes multiple studies, the study final report is the report that addresses the last outstanding study of that commitment."

Comment: The term, "study final report," as used in other sections of this Guidance (such as III.F. and V.B.) means the final report of an individual study, whereas in this section, it means the last report for a series of studies. If the "study final report" is the report that addresses the last outstanding study of a multi-study commitment, it is not clear what is expected from the sponsor with regard to handling the final reports of earlier completed studies.

Recommendation: The last paragraph of Item E. should be revised as follows,

> "If a postmarketing commitment includes multiple studies, ~~the study final report is the report that addresses the last outstanding study of that commitment. T~~**the** cover letter should identify the submission dates of all previously concluded and submitted study reports."

3.4 Page 16, IV. Content and Format of a Postmarketing Study Commitment Status Report, Explanation of the Status of the Study, Item 2

Item 2 explains the schedules to be included in the status report.

Comment: This section is inconsistent with the schedule information described in 314.81(b)(2)(vii)(a)(7), in which an applicant is required to submit the original schedule, the revised schedule, and the last submitted revised schedule (if there was a prior revision).

Recommendation: Item 2 should be revised to read,

> **"Original schedule and revised schedule (if the study schedule has changed since the last annual report). If you are unable to meet the original schedule or revised schedule, you should provide a third schedule and explain why it was revised."**

3.5 Page 21, Appendix B, Sample Postmarketing Status Summary [To be displayed on FDA Website]

Comment: Page 4, Section II(B)(2)(a), second bullet, says that any schedule for completion [of Phase 4 commitments] will NOT be included in FDA's annual report published in the Federal Register, its special report to Congress, or on its website. However, Attachment B, a sample web posting, includes dates for patient evaluation and projected completion.

Recommendation: The examples in Attachment B should be revised to comply with the text of Section II(B)(2)(a). No dates should be included in Attachment B.

4.0 PUBLIC USE OF INFORMATION

4.1 Page 1, I. Introduction, Paragraph 3

The draft Guidance states, "Section 506B also requires FDA to keep the public and medical community informed about the postmarketing obligations and activities of applicants."

Comment: This statement overstates the statutory requirements in two ways:
1. Section 506(B)(b) ONLY states that the information provided shall be considered public to the extent necessary to identify the sponsor and the status of a study (including failure to carry out the study). The statute does not require that FDA specifically keep the "medical community" informed except to the extent that members of the medical

community have access to public information. Further, there is no requirement to inform the medical community via established means, such as Dear Doctor letters and print advertisements.

2. The statute ONLY applies to information necessary to identify the sponsor and the status of a study (including failure to carry out the study) for studies that an applicant made a commitment to FDA to conduct. It does NOT extend to all "postmarketing obligations and activities of applicants" as stated in the Guidance.

Recommendation: The text of the Introduction, Paragraph 3, should be modified to be consistent with the statute as follows:

> ~~"Section 506B also requires FDA to keep the public and medical community informed about the postmarketing obligations and activities of applicants. More specifically,~~ Under section 506B(c), FDA must develop and publish annually in the Federal Register a report on the status of postmarketing studies that applicants have agreed to conduct and for which status reports have been submitted (21 U.S.C. 356b(c)). For these purposes, section 506B(b) indicates that any information necessary to identify the sponsor of a study and establish the status of a study and the reasons, if any, for any failure to carry out the study, shall be considered to be public information (21 U.S.C. 356b(b))."

4.2 Page 5, II. Background, B. Summary of the Final Rule that Implements Section 506B, Item 2, Specific Provisions, a. Human Drug Products, Third Paragraph

At the top of Page 5, the draft Guidance states that the contents of status reports will be included in the *Federal Register* and in FDA's special report to Congress. In addition, FDA will post this information on FDA's website. Page 17, IV. Information About Postmarketing Studies That Will Be Available to The Public, describes how the information published in the FR differs from that posted on the Agency website.

Comment: From the brief statement on Page 5, it is not clear if FDA intends that some status reports that are published in the *FR* and the report to Congress will not appear on the website while others will appear in all three locations and, if so, how it will distinguish between the two options. This requires clarification.

Recommendation: The second bullet on page 4, describing how FDA intends to disseminate information to the public, should be deleted in deference to the complete discussion of the topic on page 17.

4.3 Page 14, V. Content and Format of a Postmarketing Study Commitment Status Report, Original Schedule for Conducting, Completing, and Reporting the Postmarketing Study Commitment

The draft Guidance lists the common time-frames or milestones in determining study progress that are to be included in the 314.81(b)(2)(vii) report. However, on page 4 (bottom), the Guidance states, "The contents of status reports submitted under 21 CFR

314.81(b)(2)(vii) *with the exception of any schedule for completion submitted under 314.81(b)(2)(vii)(a)(7)* [italics added] will be included in FDA's annual report published in the *Federal Register*...."

Comment: It would be helpful to reiterate in this section that schedules for completion will NOT be included in any public dissemination of information.

Recommendation: The text should be modified as follows,

> "If more than one study .....However, in conducting a study, certain milestones are common and important to determine study progress. ~~These include:~~ **The FDA will NOT publically disseminate any schedule for completion submitted under 314.81(b)(2). However, sponsors are expected to include the following information in status reports filed with the Agency:**"

4.4 Page 16, VI. Information About Postmarketing Studies That Will be Available to the Public, First Paragraph

The draft Guidance states, "Section 506B provides FDA with statutory authority to disclose data and information, including certain information that may be considered to constitute confidential commercial information."

Comment: Subsection b of the statute deals with the extent to which the information submitted in the annual reports is public. However, the language does not provide FDA authority to disclose "data," rather only to identify the applicant and establish the status of the study, and reasons for failure to carry out the study.

Recommendation: FDA should remove this sentence or clarify, by example, when it is necessary to disclose data from a postmarketing study in order to identify the sponsor and establish the status of a study, and reasons for failure to carry out the study.

> "~~Section 506B provides FDA with statutory authority to disclose data and information, including certain information that may be considered to constitute confidential commercial information.~~ However, FDA will not make public any trade secrets,[2] or any information the disclosure of which might cause an unwarranted invasion of personal privacy.[3]"

5.0 APPLICATION OF THE GUIDANCE TO ANDA

Pages 4-5, II. Background, B. Summary of the Final Rule that Implements Section 506B, Item 2, Specific Provisions, a. Human Drug Products

The text and schematic refer to ANDAs.

Comment: Reporting under new section 314.81(b)(2)(vii) is limited to studies on clinical efficacy, clinical safety, pharmacology, or non-clinical toxicology. It is not clear how these studies apply to ANDAs. An ANDA applicant must demonstrate that labeling is

the same as that of a reference listed drug and must show that its product is bioequivalent. Applications that require evidence from these kinds of studies are generally not eligible for submission under 505(j).

Recommendation: Clarify the conditions under which an ANDA holder would be required to evaluate clinical efficacy, safety, pharmacology, or toxicology or delete reference to ANDAs.

6.0 EDITORIAL SUGGESTIONS

- A description of the person or entity (e.g. FDA, sponsor) should be substituted for personal pronouns (e.g. 'you' and 'we') throughout the document.
- The Guidance could be improved through defining and consistently using the terms, 'applicant,' 'sponsor,' and 'holder.'
- On Page 6, b. Licensed Biological Products, the fourth bullet would be strengthened by replacing the text clarifying the handling of pediatric studies,

> "~~Section 601.28 has been amended to require that the status of postmarketing pediatric studies that fall within the scope of 21 CFR 601.70 be reported to FDA under 21 CFR 601.70 than under 21 CFR 601.28.~~ **Pediatric studies that are NOT part of postmarketing commitments should be reported under 601.28 and are not made public. Pediatric studies that fulfill postmarketing commitments should be reported under 21 CFR 601.70.**"

- On Page 8, III. Procedures Concerning Postmarketing Study Status Reports, A. Definitions of Terms Used in Reporting Postmarketing Studies, the definition of 'postmarketing study requirement' would be strengthened by rewording to state,

> "is a requirement by FDA, **consistent with applicable regulations,** that you conduct a study, e.g., accelerated approval clinical benefit studies."

SUMMARY

It is important that the scope of the rule be presented early in the final Guidance and that the Guidance speaks clearly to the issues of: (1) timely review of Phase 4 study results, (2) how to file postmarketing status reports and what to include in the reports, (3) what and how information will be publically disseminated, and (4) application of the Guidance to ANDAs.

In addition, Merck would like to take this opportunity to comment on an issue related to Phase 4 studies. The design and review of Phase 4 study protocols are critical factors to successfully satisfying a Phase 4 commitment. The objective of a Phase 4 commitment by a sponsor is to conduct one or more studies to provide information necessary to address potential safety and efficacy issues. To this end, sponsors may work closely with the FDA to design studies that will meet stated objectives. If studies are properly designed and executed, the data produced should satisfy the commitment.

Therefore, the Agency should provide sponsors an opportunity to request the timely review of protocols submitted to address Phase 4 commitments (e.g. as 45-day special protocol requests). The Agency's timely concurrence on the design to meet medical, scientific, and regulatory goals is of utmost importance. FDA should work with applicants to assure that resources are directed towards a plan that both the applicant and the Agency agree has the greatest chance of success. In addition, a sponsor's proposed schedule for Phase 4 study completion should be revised when FDA review of a protocol is delayed. A revised schedule for completion should substitute for the original schedule in status reports.

We welcome the opportunity to meet with you to discuss these issues.

Sincerely,

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