Merck & Co., Inc.
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10 May 2001

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

MERCK
Research Laboratories

Dear Sir or Madam:

[Docket No. 01D-0056] "FDA Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines" – 66 Federal Register 14391: March 12, 2001

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 and biological products on the market today.

As a leading human health care company responsible for providing health care professionals with full and complete prescribing information for its many marketed products, Merck is very interested in, and well-qualified to comment on the FDA Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines.

The text that follows is divided into: (1) Merck's general comments and recommendations regarding the Draft Guidance, (2) specific comments from Merck addressing line item changes proposed by FDA, (3) editorial comments, and (4) conclusions.

I. General Comments

A. Document Organization

To a naive reader or person unfamiliar with the existing FDA reporting requirements for marketed drugs, biologics, and vaccines, the Draft Guidance Document tends to present broad generalizations on a particular subject when, in fact, these generalizations are not correct for all categories of reporting requirements that are included under the broad statement.

For example, according to Section I (Lines 25-33), spontaneously reported adverse experiences that occur domestically must be reported for serious/unexpected, serious/expected, non-serious/unexpected, and non-serious/expected adverse experiences. However, this is only true after administration of an approved product. 21 CFR 310.305 requires manufacturers, packers, and distributors of prescription products marketed without approved applications to report only serious/unexpected adverse experiences.

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Another example appears in Section V(A) with respect to 15-day reports of serious/unexpected adverse experiences. Line 352 states that "individual case safety reports of serious, unexpected adverse experiences from all sources (domestic and foreign) must be reported to the FDA as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the applicant. Section VI(B) Special Reporting Situations – Post-marketing, Clinical Trial, or Surveillance studies modifies the generalized information presented in Lines 352-354 and appropriately discusses the specifics of 21 CFR 314.80(e)(1). Under 21 CFR 314.80(e)(1), an applicant is not required to make such reports of experiences occurring in a post-marketing study unless there is a reasonable possibility that the drug caused the adverse experience.

Recommendation: Rather than requiring a user of the Guidance to read the entire document to avoid misunderstandings due to over-generalizations, Merck recommends consolidation of all relevant reporting requirements for each report category within a single section of the Guidance, thus enabling the reader to go to one section of the Guidance and obtain all appropriate information.

B. **Proposed Rules Revision**

Section II(C) indicates that the Agency is planning to "propose additional amendments to its updated safety reporting regulations based on the ICH E2A guidance." Additionally, the FDA is planning to "re-propose amendments to its post-marketing periodic safety reporting requirements that were initially proposed in the Federal Register October 27, 1994 (59 FR 54046)" and "to issue a proposal requiring the electronic submission of post-marketing safety reports consistent with recommendations developed by ICH." Merck commends the Agency for basing proposed rules for post-marketing safety reporting on recommendations developed under ICH initiatives.

Since the Agency acknowledges that "this post-marketing safety reporting guidance for human drug and biological products will be revised to provide industry with assistance in fulfilling the new regulatory requirement," it is premature to update the existing guidances for post-marketing safety reporting at this time.

Recommendation: Merck recommends that the Agency defer the issuance of the post-marketing safety reporting guidance until publication of its new post-marketing regulations. Merck commends the Agency for development of a guidance concerning the electronic submission of post-marketing case safety reports consistent with recommendations developed under ICH E2B/M2 and recommends that the Agency consider development of a guidance concerning new post-marketing periodic safety reporting proposals based on recommendations developed under ICH E2C.

II. Specific Comments

I. Introduction

As described in the General Comments, the "Introduction" of the Draft Guidance contains overstatements of the regulatory reporting requirements. For example, Lines 494 and 495 refer to non-serious/expected adverse experiences not submitted to FDA but maintained on file by the applicant. Although this statement appears to be a contradiction to the reporting requirements outlined on Page 1, it is valid if the applicant seeks a waiver for post-marketing reporting as described in Section XI(A).

Consistency in terminology throughout the document should be maintained. For example, "spontaneous report" is defined in Appendix A, but the term used in the Guidance (Line 28 and Line 221) is "spontaneously reported adverse experience."

Merck recommends consolidation of all relevant reporting requirements for each report category into a single section. Merck commends the Agency for providing a Glossary of terms in Appendix A. To ensure specificity of meaning, Merck recommends that first use of a term in the Guidance should refer the reader to Appendix A for its definition.

A. What does this Guidance discuss? (Line 48)

Merck recommends that a specific reference to a particular Office or Division within CDER or CBER be provided to applicants who believe that the procedures described in the Guidance are inapplicable or that other procedures are appropriate.

B. What does this Guidance not discuss? (Line 65)

Merck recommends adding devices to this list.

III. What do I report? (Line 190)

Merck recommends adding vaccines to the definition of an adverse experience.

A. Types of Adverse Experiences (Line 214)

Post-marketing study reports from in vitro or animal investigations are generally submitted in narrative format if they qualify as 15-day reports. Merck recommends that in vitro or animal findings would be most appropriately captured in the Annual IND Report or in the Annual NDA Periodic Report Section for studies involving safety issues.

Serious Adverse Experiences (Line 242)

Merck recommends providing the entire definition of life-threatening as it appears in the regulation in the Appendix A Glossary in order to ensure clarity for a term that is frequently misunderstood.

Persons Incarcerated (Lines 260-263)

This paragraph is confusing since the focus seems to be on the outcome [incarceration (penal or medical)] rather than on the adverse experience or behavior which led to the outcome. Merck recommends removing this paragraph.

Health Care Professional (Line 275)

Merck recommends that a definition be included in the Appendix A Glossary which is compatible with international standards under ICH.

B. **Data Elements to Include in a Post-marketing Individual Case Safety Report**

- **Identifiable Patient** (Line 302)

  Merck recommends that specific examples be provided and that the Agency clarify its expectations for patient-specific identifiers (e.g., age, sex, date of birth, initials).

- **An Adverse Experience or Fatal Outcome** suspected to be due to the suspect drug or biological product (Line 305).

  The concept of "implied causality" with reference to a spontaneous report is not introduced until Line 332. To achieve clarity between Lines 305 and 332, Merck recommends that Line 305 be rewritten to convey the concept of temporal association and implied causality.

- **Active Follow-up** (Lines 316-325)

  The Guidance states that an applicant should use direct verbal contact with the initial reporter of an adverse experience. As outlined in the CIOMS V document (to be published shortly), telephone follow-up should be used for serious/unexpected adverse experiences and not for all serious reports.

Merck agrees with the Agency that telephone follow-up should be used for serious, unexpected reports but believes that the applicant should decide the best approach for obtaining follow-up information for other report types depending on the nature of the adverse experience, the current labeling, and the benefit to risk profile of the product involved. Merck also supports collaborative initiatives with the Agency to obtain, for specific spontaneous reports, critical data elements necessary to address product specific safety issues.

V. **Types of Reports**

A. **15-Day Reports of Serious, Unexpected Adverse Experiences**

- Merck recommends that reference to Section VI(B) of the Special Reporting Situations be included here so that expectations for post-marketing study reports are understood.

1. **Determination of 15-Day Reporting Period**

- **15th calendar day** (Line 373)

  Merck commends the Agency for providing a practical approach towards implementing ICH E2A in the United States (US) when Day 15 falls on a US weekend or US Federal holiday.

- **Record of Follow-up Activity** (Lines 380-383)

  Given the Agency's commitment to the ICH E2B/M2 initiatives and the need for applicants to produce universally acceptable documents, Merck recommends that the documentation of follow-up activities should be provided at the time of an inspection or upon request, but should not be incorporated into the narrative section of Form 3500A. Since the narrative section of a spontaneous report is often incorporated into other regulatory documents, inclusion of administrative data would be problematic and provide no additional value to the report itself.

- **Supporting Documentation** (Lines 399-407)

  Merck does not understand the rationale for the Agency requesting that a list of relevant documents maintained in the applicant's product safety file for a spontaneous report be included as part of the narrative summary on Form 3500A.

Since the ICH E2B has data fields addressing the existence of these types of documents, Merck recommends that the Agency remove the requirements for including a list in the narrative summary.

B. **Periodic Reports**

1. **Timing of Post-marketing Periodic Reports** (Line 443)

The Guidance does not define the "reporting quarter." Merck recommends that the Guidance specify that periodic reports are due "within 30 calendar days of the last day of the reporting quarter based on the NDA/PLA anniversary date of approval."

2. **Contents of a Post-marketing Periodic Report** (Lines 486-495)

The proposal to rearrange the sections of the Post-marketing Periodic Report will be resource intensive to reprogram and revalidate safety databases. Additionally, the requirement to paginate each page of the periodic report (Line 450) will require significant technical resources to combine word processing text with computer output.

Since the Agency is supportive of the ICH initiatives, specifically ICH E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, Merck recommends that the Agency provide guidance on its expectations concerning the recommendations developed under ICH E2C.

- **Index Listing** (Line 556)

  Merck recommends coordination of ICH E2B/M2 for transmission of periodic reports, thereby eliminating the need for pagination of Forms 3500A or VAERS form.

- **Attachments** (Lines 583-587)

  As discussed earlier, Merck does not understand the rationale for the Agency's request that a list of relevant documents be included in the narrative summary of a spontaneous report.

  Since the ICH E2B has data fields addressing the existence of these types of documents, Merck recommends that the Agency remove the requirements for including a list in the narrative summary.

- **Content of Follow-up Reports** (Lines 628-632)

  Highlighting new or corrected information embedded in the initial narrative is very difficult to do in a computer system. To show WORD-like revision marks in narratives would be difficult technically and would also require guidance for electronically marking the changes in the ICH E2B message.

- **Lines 640-642**

  Merck requests that this sentence be expanded to clarify that additional follow-up is not necessary for both non-serious expected and non-serious unexpected reports.

- **Line 669**

  The draft Guidance states that follow-up reports not be submitted if "additional relevant information" is not obtained. Current regulations state that follow-up reports should be submitted when "new information is received." Merck requests clarification on the distinction between the language in the regulations ("any information") versus the language in the Guidance ("relevant"). Merck recommends the term "relevant" be defined in Appendix A Glossary.

VI. Special Reporting Situations

A. Scientific Literature Reports (Line 743)

The Guidance states that "it is not sufficient to submit only abstracts of articles." In some cases, authors only generate an abstract and do not write a formal publication.

Merck recommends that a sentence be added to clarify that abstracts are acceptable in the event that a more complete report was not published.

- **Line 762**

  The Agency's proposal to require a Company to submit serious, unexpected literature reports for products that have the same active moiety as a product marketed in the US even if the excipient, dosage form, strength, route of administration, or indication vary will lead to duplicate reporting since NDA's may be held by different companies.

Furthermore, a given active moiety is often marketed outside of the US by firms other than those licensed in the US.

Merck recommends that the Guidance clarify that each company with a US license for an active moiety be responsible for reporting those adverse experiences associated with administration of that compound only if it was manufactured by themselves or a licensee. If a specific manufacturer's brand can be identified from a literature report, then only that manufacturer should be required to submit a report.

B. **Post-marketing, Clinical Trial or Surveillance Studies** (Line 776)

The Guidance indicates that studies which do not involve "monitoring" adverse experiences should be handled as spontaneous reports. The Guidance further states that reports from company-sponsored patient support programs and disease management programs should be handled as study reports and not as spontaneous reports.

Merck questions whether the intent of the term "monitoring" refers to usual Good Clinical Practices (e.g., investigator visits, review of site source data) and suggests that clarification be included in the definition of a study found in Appendix A Glossary.

C. **Foreign Reports** (Lines 807-813)

The Guidance indicates that for foreign reports submitted on a product that is not identical to a product marketed in the United States, the Form 3500A (Item C1) "should contain the foreign tradename, the generic name, and the NDA number of the product with the same active moiety that is marketed in the United States."

Merck questions why the foreign tradename needs to appear in Item C1 since this procedure adds multiple complexity to computer systems if one is to maintain reliable, drug validation files. Also, the NDA number is displayed in Item G5 of Form 3500A. Repeating the NDA number in Item C1 is redundant.

F. **Lack of Effect Reports** (Lines 839-840)

Although routinely requested, lot number is not always provided for drug products. The Guidance should be revised to reflect this: "The lot number, *if available*, of the suspect product should be included in Item C6 of FDA Form 3500A."

G. **Information on the Internet** (Lines 848-855)

Merck recommends the Agency clarify their expectations concerning adverse experience reports from the Internet. Guidance on what constitutes an "identifiable reporter or patient" is necessary.

K. **Multiple Suspect Products** (Lines 917-918)

The Guidance suggests that for a reportable adverse experience involving two or more suspect products, and two or more applicants, both applicants have an obligation to contact the original reporter and separately provide follow-up information to the Agency.

Merck recommends that the Agency encourage an organized approach to obtain follow-up from a single reporter. Multiple company contacts may encourage a lack of cooperation by the original reporter.

L. **Suspect Drugs with Multiple NDA's or ANDA's by the Same Applicant** (Lines 927-928)

The Guidance states that "... if a drug substance has more than one applicant and it cannot be determined which of the approved applications is involved, the report should be submitted to the application for the drug product that was approved first and that has the same general route of administration as the suspect drug substance. This could usually be the application with the lowest number."

While the first approved application would usually have the lowest number, when route of administration is taken into account, one cannot say it would usually be the lowest number. Therefore, the last sentence should be deleted.

R. **Reporting Ambiguities** (Lines 976-981)

Merck recommends that this entire paragraph be moved to Section IV, Subsection B. The Guidance provided by the Agency in Subsection R would most appropriately fit into the general discussion of Section IV, "What Do I Report?".

VIII. **Reporting Formats** (Lines 1018-1023)

Merck questions the value added in using the NA, NI, UNK abbreviations, which at best are subjective, when specific information is not available.

A. **FDA Form 3500A** (Lines 1038-1039)

For completeness of the Guidance, Merck recommends that a distinction between the voluntary and mandatory reporting forms (Form 3500 versus Form 3500A) be made.

XI. **Requests for Waivers to Post-marketing Safety Reporting Requirements**

A. **Submission of FDA Form 3500A for Non-serious, Expected Adverse Experiences** (Lines 1310-1322)

Merck recommends that the Agency reference the Guidance issued August 27, 1997 "Post-marketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report in the Discussion.

B. **Submission of PSUR Format for the Periodic Report** (Lines 1332-1334)

The Guidance in this section should be restated to make it clear that applicants can seek a waiver to submit post-marketing periodic reports in the ICH E2C format rather than the format described in current regulations. For clarity, the second bullet under this section (Lines 1347-1351) should be rewritten to state that "although not required under ICH E2C, copies of FDA Form 3500A or VAERS forms that are required by the regulations must be included."

C. **Submission Data and Frequency for PSUR Reports** (Lines 1375-1377)

Merck requests clarification concerning the waiver request for a PSUR frequency other than required in current regulations (i.e., does the Agency support six monthly reporting for the first two years, post-approval, annually for the next three years, and thereafter?).

Appendix A Glossary (Line 1503)

The definition of a study should reference the Agency's expectations for "monitoring" as discussed previously.

III. Editorial Comments

For purposes of clarification Merck recommends consideration of the following changes:

Lines 146-180: Condense discussions to three bullets representing drugs covered under 21 CFR 310.305, drugs covered under 21 CFR 314.80 and 21 CFR 314.98, and biologics/vaccines covered under 21 CFR 600.80.

Line 151: Expedited safety reports should be clarified as 15-day reports.

Lines 172-174: Defaulting to the term "Applicant" to refer to all parties with reporting responsibilities is not conducive to clarity. "Applicants" have different responsibilities defined in the regulations than packers, distributors, or other non-applicants." If general terms are needed, the Guidance could adopt the precedent set in regulations and reduce the number of terms to "Applicants" and "Non-Applicants."

Lines 201-250: This section purports to describe "types" of adverse experiences but fails to adhere to any logical grouping by type. There are five disparate categories presented:

1. Serious and unexpected
2. Spontaneously reported
3. Definition of serious
4. Definition of expected vs. unexpected
5. Definition of a spontaneous report

For purposes of reporting, adverse experiences are basically divided into two groups, serious and non-serious. Since this Guidance is intended to clarify reporting requirements, perhaps discussion of these two groups should be considered. Merck recommends that the definitions of the different categories be moved to the Glossary.

Lines 251-252: Change "A patient admitted to a hospital for one or more days as a result of an adverse experience even if released on the same day, would qualify ..." to "A patient admitted to a hospital as a result of an adverse experience even if released on the same day, would qualify ...".

Lines 290-295: Line 290 states that spontaneous reports are "unsolicited communications from individuals". The second sentence (lines 290-295) states that "spontaneous reports should not include adverse experiences identified from information solicited by applicants such as individual cases...". Unless the intent of lines 290-295 is to provide guidance to individuals submitting unsolicited communications, the second sentence should be rewritten to convey that "submissions of spontaneous reports should not contain information solicited by applicants."

Lines 373-375: The implication is that the applicant should not submit the 15-day report sooner than the first working day after the weekend or US Federal holiday. The wording should be rewritten for clarity "... the 15-day report should be submitted on or before the first working day after the weekend or US Federal holiday."

Line 424: The title at Subsection B "Periodic Reports" differs from the term in the regulations for drugs "Periodic Adverse Drug Experience Reports" [21 CFR 314.80(c)(2)] and for biologics "Periodic Adverse Experience Reports" [21 CFR 600.80(c)(2)]. The correct official term should be used at least once, particularly in the heading of a section. An abbreviated term may be used after first defining it. If multiple synonyms will be used in the document, all versions should follow the first use of the official term.

Lines 1018-1023: The third paragraph should be moved up to appear before lines 1013-1016.

Line 1319: Change "Applicants who obtain a waiver for the requirement" to "Applicants who obtain a waiver to the requirement."

IV. Conclusions

In conclusion, Merck commends the Agency for basing changes for post-marketing safety reporting on recommendations developed under ICH initiatives. In light of the Agency's acknowledgment that this post-marketing safety reporting Guidance will need to be revised pending publication of impending regulatory requirements (i.e., "The Safety Tome"), Merck recommends that the Agency avoid redundancy and update the Guidance following publication of new post-marketing regulations. Merck recommends that the Agency consider development of a guidance concerning new post-marketing periodic safety reporting proposals based on recommendations developed under ICH E2C.

We appreciate the opportunity to provide comment on the "FDA Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines."

Sincerely,

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