3M Pharmaceuticals

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May 10, 2001

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

Re: Docket No. 01D-0056
Comments on the Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Dear Sir or Madam:

On behalf of 3M Pharmaceuticals, I am writing to register comments to Docket Number 01D-0056 on the *Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*, dated March, 2001. This availability of this document was published in the Federal Register on March 12, 2001 as a Notice. The comments begin on the next page.

Should you have any questions regarding the comments, please don't hesitate to call me at (651) 736-1590.

Sincerely,

Amy E. Fowler

Amy E. Fowler
Senior Regulatory Associate

C13

01D-0056

3M Pharmaceuticals' Comments to FDA's Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Line numbers from the guidance are identified and followed by the text in italics, except when the referenced section is very lengthy.

- **Lines 237-239 compared to lines 271-273**

  The outcome of an adverse experience must be determined before a report can be identified as serious.

  Applicants should seek the outcome for a suspected serious adverse experience reported to them.

  The first statement points out that seriousness cannot be determined before an outcome is known. The second statement admonishes an applicant to actively seek the outcome of a "....*serious* adverse experience....". The second statement presumes the outcome is known. Please modify one of the statements to make them compatible.

- **Lines 433-453: Timing of Postmarketing Periodic Reports**

  The FDA is still out of step with the timing recommended by the ICH guidelines which specify that periodic reports for a newly approved application are due every 6 months for the first 2 years of marketing, annually for the next 3 years and every 5 years thereafter.

- **Lines 455-607**

  We are disappointed to see FDA diverge from ICH requirements on the content of postmarketing periodic reports. Several examples are listed here:

  -- cross-reference with another NDA, etc. (lines 499-503)

  -- narrative assessing clinical significance by body system (lines 509-513)

-- summary of important foreign regulatory actions (lines 528-544)

-- narrative discussion of any increased reporting frequency of serious, expected, adverse experiences (lines 506-509)

The last example listed above is particularly disappointing, since it had already been dropped some time ago.

We would prefer FDA more closely adopt the ICH format for Periodic Safety Update Reports (ICH E2C), including the waiver approach discussed in lines 1299-1376.

- **Lines 624-631**

A followup report should provide a complete picture of the current understanding of the adverse experience. Relevant information from the initial report should be combined with the followup information to present an accurate and comprehensive description of the adverse experience as it is understood at the time of the followup. Information from the initial report later found to be inaccurate should not be repreated in the followup report. All new information including correction of previously submitted inaccurate information that is included in a followup report should be highlighted (e.g., with an asterisk, underlined).

Instead of including information from the initial report in the followup report, it would be more appropriate to list the different reports received and to indicate the dates of reporting (such as initial dated*, followup 1 dated *, followup 2 dated *) and avoid combining information from the initial and followup reports.

It is not easy to highlight the previously submitted inaccurate information with an asterisk or underline, as recommended. It would be preferable to write an updated report containing followup information and to indicate the corrections at the beginning of the narrative description of the case.

We feel that information from the initial report later found to be inaccurate should not be repeated in a followup report. There is also a strong argument for just adding new paragraphs at the end of the text that give the date obtained and the new information. This serves to show due diligence and removes all concerns about which information is new.

Another local view for dealing with followup information is to merge everything directly into the existing text without any concern about when it was obtained. We feel the purpose of a pharmacovigilance report is to tell a comprehensive but succinct story about the AEs without being encumbered by due diligence documentation and other bureaucratic compliance issues.

- **Lines 652-659**

  If the initial report was submitted as a 15-day report, the followup report should be submitted as a 15-day followup report even if the followup information shows that the adverse experience was expected or not serious. All subsequent followup reports for adverse experiences that are expected or not serious should be submitted in periodic reports. A 15-day followup report should be submitted if the adverse experience is found to be serious and unexpected, even if the original report was not submitted as a 15-day report.

  In a situation where a serious case was previously reported as a non-serious case, what date of receipt by the manufacturer has to be reported on the MedWatch or the CIOMS-I forms? A calculation for the timeframe between the date of the initial receipt of the report (regardless of the criteria of seriousness) and the submission to regulatory authorities might determine a timeframe of reporting above the 15 requested calendar days.

- **Lines 660-667**

  If a new adverse experience occurs that is associated with the initial adverse experience, a followup report should be submitted. However, if the new adverse experience is not associated with the initial adverse experience (e.g., occurs after a subsequent administration of the product), an initial report with a new manufacturer report number should be submitted for the new adverse experience. In these cases, the applicant should consider the clinical relevance of the adverse experiences to each other when determining whether an initial report or followup report should be submitted.

  In the case of a subsequent administration of the product for the same patient, a different report from the initial report should be submitted. Each report should have its respective and different manufacturer report number. We suggest cross-referencing the cases in order to keep the overall safety information for the same patient.

- **Lines 738-745**

  Serious, unexpected adverse experiences reported in the scientific literature (or in an unpublished scientific paper) that are known to the applicant must be submitted as 15-day reports on an FDA Form 3500A or comparable format. Applicants can use literature search services (e.g., Weekly Reactions) to identify adverse experiences in the scientific literature. A copy of the article or manuscript must be attached to the completed FDA Form 3500A; it is not sufficient to submit only abstracts of articles. All reports from the scientific literature and unpublished scientific papers should be marked Literature in item G3 of FDA Form 3500A.

  If the abstract is the only information that has been identified, do we have to report as followup information that no article or manuscript has been identified?

Submitting an abstract of an article should be sufficient because there are times when that is all that is available.

- **Lines 762-765**

  Reports of serious, unexpected adverse experiences described in the scientific literature should be submitted for products that have the same active moiety as a product marketed in the United States. This is true even if the excipient, dosage forms, strengths, routes of administration, and indications vary.

  If all (non-applicant sponsored) reports concerning the same active moiety from the scientific literature have to be reported, this will generate duplication. In order to limit such duplication of reports, it would be preferable to specify that the provision only applies to (non-applicant sponsored) publications occurring within the applicant's territories.

- **Lines 767-770**

  When a serious, unexpected adverse experience is based on a foreign language article or manuscript, the applicant should translate the publication into English promptly. The original article or unpublished scientific paper and translation should be attached to the submitted FDA Form 3500A.

  This is a difficult, if not impossible, section to comply with. Rarely is a translation available within the 15-day time frame for a serious, unexpected report. Often a foreign language literature article has an abstract written in English which is where the case report was recognized but a previous guidance says an abstract is not adequate. Why is a paper copy of the article needed when so much of our effort is aimed towards a paperless report?

We also need a clarification of "promptly". Do we have to submit the original non-translated article with the mention "awaited translation" or would it be possible to take into consideration the date of the receipt of the translation?

- **Lines 807-812**

Reports of foreign serious, unexpected adverse experiences should be submitted for products that have the same active moiety as a product marketed in the United States. This is true even if the excipient, dosage forms, strengths, routes of administration, and indications vary. When a foreign report is submitted on a product that is not identical to a product marketed in the United States, item C1 of FDA Form 3500A should contain the foreign trade name, the generic name, and the NDA number for the product with the same active moiety that is marketed in the United States.

It might be confusing to match a NDA number for a product with a product with the same active moiety especially in case of combination.

We find the requirement to include the US NDA number on a MedWatch form for a case report involving a foreign product difficult. It goes against all logical drug dictionaries, which are the usual basis for obtaining the information printed on our report forms. For example, a drug dictionary will contain all the products our company sells throughout the world but the relationship in the dictionary will be between the local license numbers and product names in their respective countries. It is a bit presumptuous to match all foreign product names to an NDA number. The NDA number can be included in the cover memo and it further supports electing to submit foreign case reports on a CIOMS form.

- **Lines 864-870**

For reports of a congenital anomaly, the age and sex of the infant should be included. Followup reports for the infant should be considered followup to the initial report; followup for the mother should be submitted as a new initial individual case safety

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