Aventis Pharmaceuticals

May 9, 2001

Via fax and UPS

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

Re: Docket No. 01D-0056
Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines; 66 Fed Reg, P 14391-14392 (March 12, 2001)

Dear Sir/Madam:

Aventis Pharmaceuticals, Aventis Behring, and Aventis Pasteur together are pleased to provide the following comments on the above-referenced draft guidance for industry entitled "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines." The guidance would revise the agency's existing guidances on postmarketing safety reporting and assist applicants and other responsible parties in fulfilling FDA's postmarketing safety reporting requirements for marketed human drugs and biological products.

While Aventis Pharmaceuticals, Aventis Behring, and Aventis Pasteur (henceforth: Aventis, unless otherwise specified) strongly support FDA's efforts in providing the industry with guidance in fulfilling FDA's reporting requirements, we are directly affected by this guidance and offer the following comments for your consideration:

General Comment

The guidance appears to be very drug-focused and neglects specific mention of vaccines and/or biologics throughout. Aventis suggests that for greater clarity, wherever "drugs" are mentioned, vaccines and biologics be mentioned too, where applicable. If a particular passage does not apply to vaccines/biologics, then such exclusion should be clearly stated.

Similarly, there are numerous instances in the guidance where FDA Form 3500A is the only form mentioned, and many cases where the text clearly states "*must* use FDA Form 3500A," which is misleading. Wherever FDA Form 3500A is mentioned and the situation described pertains also to vaccines, the VAERS form should be referenced as well.

01D-0056

Specific Comments on the Guidance Proposal

Aventis comments appear as boxed text below the draft guidance reference.

Lines 75-77, p. 3

"...The use of mandatory language (e.g., must, have to, required*) will signify a regulatory requirement while the use of words such as* should *and* recommend *will indicate Agency policy."*

Please clarify how manufacturers, applicants, etc. should interpret and react to this statement. Is assessment of compliance to be extended to include not only the regulations but also Agency policy?

Lines 123-143, p. 4

Aventis supports and encourages the FDA's efforts to conform to ICH recommendations in developing PSUR requirements, and urges the Agency to adhere as closely as possible to the ICH recommendations, for maximum accord with the other ICH parties, and to avoid the generation of multiple types of PSURs.

Lines 163-165, p. 5

"Any person whose name appears on the label of a marketed drug as its packer or distributor (§310.305(c)(1)(i)) or manufacturer, packer, or distributor (§314.80(c)(1)(iii) has postmarketing safety reporting responsibilities."

Aventis proposes clarifying this by adding at the end additional text from *§314.80(c)(1)(iii)*: "To avoid any unnecessary duplication in the submission to FDA, obligations of a nonapplicant may be met by submission of all reports of serious adverse experiences to the applicant."

Lines 210-212, p. 6

"Scientific literature reports include published and unpublished scientific papers...."

Please provide examples of what might be considered "unpublished scientific papers."

Lines 237-239, p. 7

"The outcome of an adverse experience must be determined before a report can be identified as serious. *A serious report must have one or more of the following outcomes:"*

Aventis believes that use of the term "outcome" here is confusing, as it can imply a *final* or *permanent* result of the adverse experience. We suggest rewording the passage to read: *"The nature of an adverse experience must be determined before a report can be identified as* serious. *An adverse experience is considered serious if it is associated with one or more of the following:"*

Lines 246-249, p. 7

"Important medical event based upon appropriate medical judgment that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious."

For improved clarity, Aventis proposes rewording the phrase as follows: *"Important medical event that may, based upon appropriate medical judgment, jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other consequences listed above."*

Lines 260-263, p. 7

Incarceration is NOT a medical consequence, it is a legal one. It does not describe how the patient's health is affected, nor how the patient is "incapacitated" in a medical context. Will manufacturers now be expected to monitor legal literature in search of such circumstances? Please clarify, as this issue has many legal implications and complications.

Line 266, p. 7

Please be more specific about the term "convulsions" in this context, especially following vaccine administration, since this is a symptom and not a diagnosis.

Lines 268-269, p. 7

How should "important medical events" be indicated on a VAERS or CIOMS 1 form? Should it be included as part of the narrative text, and if so, how (as a header, an opening statement, etc.)?

Lines 284-286, p. 8

"An adverse experience would be considered unexpected *if it is not included in the product's current FDA-approved labeling and* expected *if it is included in this document."*

Aventis suggests rewording and adding clarification from the regulations: *"An adverse experience would be* expected *if it is included in the product's current FDA-approved labeling, and* unexpected *if it is not included or if it is symptomatically and pathophysiologically related to a labeled event but differs by greater severity or specificity."* Further adding the examples in the regulations (21 CFR 310.305(b), 21 CFR 314.80(a), 21 CFR 600.80(a)) would be helpful.

Lines 308-314, p. 8

"If any one of these basic elements remains unknown..., a report on the incident should not be submitted to the FDA... a report to the FDA that lacks any of the four basic elements,...will be returned...."

There are instances when a doctor calls after hours to report an adverse reaction in a patient (no identifiers), and no further information is obtainable. Please reconfirm that the FDA really does not want the applicant to submit such cases and, if submitted, will reject them.

Lines 316-324, p. 9

Verbal contact is not always the most efficient way to obtain follow-up information, and actively seeking verbal follow-up for ALL adverse experience reports is impractical for most manufacturers. For nonserious events this passage conflicts with lines 637-641, which state that additional follow-up is not necessary. Aventis proposes focusing on serious-unexpected events and/or serious events only, and in line 317, adding the word "documented" as follows: *"...should use documented, direct verbal contact..."*

Line 330, p. 9

"Patients should not be identified by name or address."

Aventis proposes amending this sentence to read: *"Patients should not be identified by name or address, except on VAERS forms."*

Lines 337-342, p. 9

If an adverse experience report contains vague or non-specific information (for example, "suffered irreparable damages"), should it be submitted in a PSUR or periodic report, coded as "Reaction Unevaluable" or "Injury NOS"?

Line 340-341, p. 9

"Thus, a report...should not be included until more specific information...can be determined."

Aventis proposes changing "included" to "reported to FDA."

Lines 373-375 & 392-395, p. 10

For foreign affiliates, is there any accounting for their local national holidays with regard to the 15-day time clock?

Lines 377-380, p. 10

"...all the information for an individual case safety report...(e.g., completion of all the applicable elements on FDA Form 3500A)."

Aventis proposes changing this to: *"...all the information needed to complete a VAERS or MedWatch form...(e.g., completion of all the applicable fields on the relevant form)."*

Lines 381-383, p. 10

"The applicant should ...include in the narrative section of FDA Form 3500A (i.e. item B5), a chronological description of these efforts..."

Providing in the narrative a "chronological description" of failed attempts to obtain follow-up information would be burdensome and unnecessary, and detract from the medical information being reported. It runs contrary to standard practice and prior guidance from the FDA, and conflicts with several passages in this guidance:

- Lines 308-314, which recommend that the applicant maintain records of its information-gathering efforts
- Lines 633-635, which request that the narrative be kept brief due to FDA database field size limitations
- Lines 671-672, which state: "...applicants should maintain records of their efforts to obtain additional information, particularly for serious adverse experiences. **FDA may request this documentation.**" (emphasis ours)

21 CFR 314.80(c)(ii) states: "...If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information." Documentation of follow-up attempts is appropriately maintained in the applicant's files, not in the adverse experience report. The report should focus on the medical information necessary to understand and interpret the adverse experience.

Lines 386-387, p. 10

"...all the applicable elements for an individual case safety report..."

See comment for lines 377-380.

Lines 389-390, p. 10

"...after obtaining the new information..."

Aventis proposes qualifying this with the word "relevant" as follows: *"...after obtaining new, relevant information."*

Lines 392-393, p. 10

Does the term "foreign affiliate" include international distributors?

Line 395, p. 10

Aventis proposes adding to the end of this sentence the following: "...to allow report submission within the required time frame for 15-day alert reports."

Lines 399-404, p. 10-11

A summary of relevant available information is included in the narrative of all reports. An additional summary listing the available documents would not provide FDA with any additional information that would be helpful in evaluating the case. Furthermore, it would present added burden and conflict with the "minimum narrative" specifications in lines 633-635 and with the Paperwork Reduction Act. Removing patient identifiers from such documentation, due to Privacy Act issues, would be additionally burdensome.

Lines 405-407, p. 11

In the case of foreign adverse experiences, supporting medical documentation will be in the native foreign language. Please clarify the Agency's expectations with regard to foreign-language medical documentation, keeping in mind that expedient translations of medical documents are very cost- and resource-intensive.

Lines 415-418, p. 11

Does this apply also to vaccines and biological products?

Lines 433-453, p. 11-12

If a company's waiver to submit PSURs is accepted, will the quarterly reporting period be waived as well? Can applicants proceed to the international standard of 6-month periodicity for PSUR production, rather than a quarterly production schedule?

Lines 455-526, p. 12-13

Automated systems and electronic templates have been set up by manufacturers to comply with the current format of the US periodic report. Changes to this format would require computer system and electronic template changes, which are resource-, cost- and validation-intensive. Since most manufacturers will be converting to PSUR format in the near future, Aventis proposes that the current periodic report format be retained as an acceptable alternative.

Lines 486-495, p. 13

"A summary tabulation by body system (...)"

Aventis proposes adding "or MedDRA SOC" as follows: *"A summary tabulation by body system (...) or MedDRA SOC..."* In addition, for consistency with ICH formats, Aventis proposes that if a PSUR is submitted as a US periodic report, then this listing be presented as a separate addendum (appendix) for the US.

Line 494-495, p. 13

Aventis proposes adding to the end of the line: *"(not applicable to vaccine-related experiences, all of which are reported)."*

Lines 497-498, p. 13

Does the product interaction section apply also to vaccines?

Lines 505-525, p. 13

Aventis proposes that these two paragraphs be reorganized to present the information more clearly, perhaps with a bulleted listing of the desired elements for the narrative discussion.

Line 538, p. 14

Should the "list of studies initiated" include <u>all</u> studies, or just mandated Phase IV studies per the new Draft Guidance for Reporting Postmarket Studies?

Line 559, p. 14

See comment for lines 497-498.

Lines 579-581, p. 15

Please specify the meaning of "lack of effect" for vaccine products: Is it a lack of pharmacological effect (absence of titers)? The occurrence of the disease the vaccine was designed to protect against?

Lines 583-587, p. 15

It appears FDA is now requesting documentation also for serious, expected cases, which departs significantly from the March 1992 guidelines, which addressed only 15-day cases in this context. Including "relevant medical documents" with periodic reports is too difficult to do by computerized means, and conflicts with the Paperwork Reduction Act and patient privacy issues.

Lines 613-614, p. 15

"...A followup report provides information..."

Aventis proposes changing *"provides information"* to *"provides new, relevant information."*

Lines 618-619, p. 16

"...receipt of new information..."

Aventis proposes changing *"new information"* to *"new, relevant information."*

Lines 619-620, p. 16

"...Followup information to adverse experiences submitted initially in a periodic report can be submitted in the next periodic report."

Aventis proposes changing *"can be"* to *"should be."*

Line 625, p. 16

Please provide examples of what is considered "relevant information."

Lines 626-630, p. 16

"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 repeated 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)."

Aventis strongly disagrees with this proposed return to the practice of highlighting, which was the method prior to the introduction of computers and prior to the MedWatch form. Many adverse-experience computer systems have not been set up to asterisk, highlight, or underline changes made from initial reports to follow-up reports. The MedWatch form would need extensive revision, as would some of our practices:

- Follow-up reports would need to show data items that changed.
- Follow-up reports would need a revised, rather than an addended, narrative.
- Foreign reports would require the NDA number next to the drug name.

This guidance is the same as the March 1992 guidance, and does not reflect current industry practice since the transition to MedWatch. Rewriting narrative to eliminate incorrect information and integrate new information corrupts the initial report narrative, which violates good practices. The preferred method to add

new information is to add text, not modify it. Highlighting is a manual, labor-intensive process prone to human error, and current computerized reporting systems are not equipped to handle the task.

Lines 633-635, p. 16

"The narrative section of the followup report should be concise...because the FDA's adverse event reporting database (AERS) is limited for this section of the form."

This limitation contradicts the requests for additional summary information in lines 377-383 and 402-407. The limitation is an FDA/CBER/AERS/VAERS technical issue, and one that should not constrain manufacturers from accurately and completely reporting adverse experiences.

Please specify the maximum number of characters for this field. What is the Agency's suggested solution when an individual report is complicated (e.g., cancer, AIDS patients, multiplicity of therapies)? Does this limitation exist for VAERS forms too?

Lines 638-639, p. 16

"...all the applicable elements for an individual case safety report..."

See comment for lines 377-380.

Lines 652-667, p. 16

Aventis proposes reiterating at the end of this paragraph that in all cases, the 15-day clock begins the day the new follow-up information is received at the first company unit, domestic or foreign.

Lines 701-702, p. 17

"Box 27 – Mark followup, *and indicate whether this is the 1st, 2nd, 3rd,... followup report."*

Many manufacturers' computerized adverse-experience systems print the follow-up number in parentheses following the manufacturer's report number in box 24 of the VAERS form, e.g., U2001-00XXX(0) = initial report; U2001-00XXX(1) = 1st follow-up. Box 27 does not have a field in which to enter a follow-up number. This proposed change would entail computer system modification and validation costs.

Lines 736-770, p. 18-19

Frequently, abstracts are available expeditiously to manufacturers and are submitted as an initial version of an alert report. Obtaining full-text literature citations can take long periods of time and delay alert submissions beyond the 15-day time period. Aventis proposes that this section be amended to allow a manufacturer to initially submit a literature abstract, and then follow-up with a full-text article when it is received by the manufacturer.

An additional concern is foreign-language literature reports, as translations can cause delays in expedient reporting. Is an English abstract sufficient in such cases?

Please additionally clarify how to handle abstracts from scientific meeting presentations, poster presentations, and works in progress.

Lines 762-765, p. 19

"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."

Why should manufacturers submit alert reports for products that they neither manufacture nor have licensed in the USA? For example, if one has a product that is topical for acne, etc., but receives a literature article in which the product is used intravenously in cancer, AND one knows the other manufacturer, then one shouldn't have to report it, if the other manufacturer is notified. Aventis objects to submitting literature

reports to the active moiety to our NDA/BLA if we are able to identify and notify another manufacturer of the suspect product.

Lines 767-770, p. 19

Aventis proposes adding to the end of this paragraph the same text as in section C, Foreign Reports, i.e. *"Foreign literature reports of serious, unexpected adverse experiences must be submitted as 15-day reports. Other foreign literature reports, including serious and expected, non-serious and unexpected, and non-serious and expected adverse experiences are not required to be submitted."*

Line 785, p. 19

See comment to lines 217-218.

Line 787, p. 20

"...occurring with marketed drug or biological products during IND trials..."

Aventis proposes adding the qualifier "licensed" as follows: *"...marketed drug or licensed biological products...."*

Line 803, p. 20

"Foreign reports of serious, unexpected adverse experiences must be submitted...."

Aventis proposes adding the qualifier "individual" and the clarifying phrase "associated with US products distributed outside the US" so that the sentence reads: *"Individual foreign reports of serious, unexpected adverse experiences associated with US products distributed outside the US must be submitted...."*

Lines 810-813, p. 20

Having the foreign trade name, generic name, and NDA number for the product would necessitate a change in MedWatch programming and is redundant, as the NDA number is already under G5.

Lines 834-840, p. 21

See comments for lines 579-587.

Line 860, p. 20

"...should be included under item A2 of FDA Form 3500A.."

Aventis proposes adding to the end of the sentence: *"or items 3 and 4 of the VAERS form."*

Line 862, p. 20

Aventis proposes adding to the end of the paragraph: *"If known, the birth weight and number of siblings should be reported under items 22 and 23 of the VAERS form, for children 5 years of age and younger."*

Lines 932-933, p. 23

"If two or more companies that co-market a specific drug product have an approved NDA for the product, one of the companies should be identified as having primary responsibility for reporting..."

Aventis proposes adding "by written agreement" as follows: *"...should be identified by written agreement as having primary responsibility."*

Lines 969-972, p. 24

Aventis proposes adding at the end of this paragraph a reminder to applicants that adverse experiences may also be considered product complaints, and should be properly reviewed as such. The proposed passage should cite 21 CFR 211.198.

Line 973, p. 24

Aventis proposes adding another section after **Q. Product Defects**, that would be titled "Errors and Accidents of Professional Practice," with parallel wording to that of section Q, to clarify that:
"If an error or accident of professional practice results in an adverse experience, the adverse experience should be reported as any other spontaneously reported adverse experience occurring in the United States (e.g., 15-day report for a serious, unexpected adverse experience or periodic report for a nonserious, unexpected adverse experience)."

Lines 974-981, p. 24

Aventis proposes placing this section earlier in the guidance, at line 200 in "IV. WHAT DO I REPORT?"

Lines 1181-1186, p. 29

Aventis proposes adding a clarification that the CIOMS 1 form can be used also for foreign vaccine report submissions.

Line 1324, p. 32 and Line 1351, p. 33

Aventis proposes clarifying that the waiver for reporting non-serious, expected adverse events does not apply to vaccine products.

Lines 1353-1358, p. 33

1. What is the basis for expectedness when an applicant opts to use the PSUR format: the US labeling or the "core" labeling? Are the listings identical with ICH E2C?
2. Please clarify how consumer reports should be handled when follow-up information has been supplied by a healthcare professional, since the status of such reports would then change.

Line 1356, p. 33

See comment to lines 486-495.

Line 1361, p. 33

"...to the approved U.S. labeling for the dosage forms covered..."

Aventis proposes changing the phrase to *"...current U.S. labeling,..."* The term "approved U.S. labeling" is ambiguous, as FDA does not ordinarily "approve" labels for drugs. (One can send a change to be effective immediately.)

Lines 1415-1521, p.35-37 (Appendix A: Glossary)

Aventis proposes moving this section to Line 145, as a section entitled "Definitions."

Aventis also proposes the following changes to the Glossary content:

Deleting definition for:

- "Causality Assessment," as this term does not appear in the guidance

Adding definitions for:

- "Follow-up Report"
- "Individual Case Safety Report"

Clarifying definition for:

- "Disability," to provide examples "substantial disruption" as applicable to vaccine adverse experiences

Line 1523, p. 38 (Appendix B: Report Checklist)

Aventis proposes adding a similar checklist for VAERS forms and vaccine reporting, and for the CIOMS 1 form, too, either as part of Appendix B or as separate appendices.

Additional Specific Comments from Aventis Pasteur:

Lines 167-170, p. 5

Please clarify the circumstance when another company may be listed on the product label as the manufacturer of refined ingredient. Does a company fall into this category when the ingredient manufacturer is listed on the product label (insert)?

Does the supplier of a refined ingredient have the responsibility of fulfilling US AE reporting requirements? Are suppliers of refined ingredients covered in this passage as "any other participant involved in the divided manufacture" of a biologic?

Lines 217-218, p. 6

Please clarify how manufacturers should determine "reasonable possibility" for vaccine adverse experience reporting.

Line 244, p. 7

Please provide examples of what might be considered a "significant or persistent disability/incapacity," e.g., adverse experience persists for >X days, X=7, 14, 21?

Lines 304-305, p. 8

Please clarify the term "suspect product" as it relates to vaccines, especially when more than one vaccine is administered on a given day or simultaneously.

Lines 332-337, p. 9

The phrases "suspect ...biological product," "implied causality," and "reasonable possibility that the product caused the adverse experience" have legal (liability) implications for manufacturers and need to be clarified. In the case of multiple vaccine administrations, for example, these concepts become ambiguous and potentially litigious, as the VAERS form does not have the same type of disclaimer as appears at the

bottom of FDA Form 3500A, i.e. "Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event."

Lines 747-753, p. 19

Please clarify how to identify individual patients in scientific literature, particularly with respect to vaccines.

Lines 762-765, p. 19

"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."

Please clarify with regard to the individual components of a multi-vaccine single-dose presentation (e.g., DTaP, HIB, and IPV administered concomitantly). Does FDA expect component reporting for combination vaccine products from vaccine applicants? What is the status of a foreign vaccine adverse-experience report for a product that contains an antigen component used or similar to an antigen in a US-license product?

Lines 807-813, p. 20

How does this section ("active moiety") relate to single-component vaccines and combination vaccines of domestic and foreign manufacture? What about non-vaccine biologics that may have more than one component, such as diagnostic products?

Does FDA really want to be informed of adverse experiences that occur outside the USA, with a foreign-made vaccine component (for example, tetanus toxoid made in Poland, used as an ingredient in a vaccine distributed in Bulgaria)? Are vaccine manufacturers expected to monitor for such instances?

Lines 891-894, p. 22

This passage suggests that a manufacturer should submit alert reports for products for which it does not hold a current US license and the manufacturer of the product is unknown. Please clarify with regard to biologics and vaccines.

Lines 896-918, p. 22-23

Please clarify the meaning of "suspect product" in the context of vaccine administrations of multiple products from different manufacturers.

Lines 911-918, p. 22-23

Please clarify with regard to vaccine adverse-experience reports. Often the reporter does not supply data on what the "suspect vaccine product" is when multiple vaccines are administered. Typically, manufacturers are not given the "suspect product" by the initial reporter and must then report their products(s) as the "suspect product" (implied causality of the complaint). Aventis is concerned about accepting responsibility by the act of spontaneous reporting, when an adverse experience could be attributable to another applicant's product, since the VAERS form does not have the same type of disclaimer as FDA Form 3500A.

Aventis suggests that when the initial reporter does not indicate a "suspect product," then the manufacturer receiving the report should list its licensed product(s) first on the VAERS form, box 13, lines a, b, etc.

Line 1299, p. 32

Aventis Pasteur proposes the following additional section with regard to waiver requests:

Manufactures of licensed vaccines and biologics may apply for a waiver from the periodic submission of MedWatch and VAERS forms on a quarterly or annual basis. Instead, manufacturers may apply to FDA to submit serious-expected (labeled) and non-serious spontaneous reports on a monthly basis, with reports due no later that the 15th of the following month, e.g., Period Jan 1 -31, due by Feb 15. Alert reporting would remain as legislated. Periodic reporting would consist of summary report texts and tables without adverse experience forms for the period. Under the present submission system, adverse-experience data for serious-labeled and non-serious cases will be entered into the FDA passive surveillance systems up to one year after the date the event was reported. Passive surveillance is meant to flag events that are important to the protection of the public health. This is not accomplished if the majority of adverse experience reports are entered into the surveillance systems in an untimely fashion. Annual submission of large numbers of VAERS forms presents workload imbalances to both applicants and the VAERS systems. By receiving the VAERS or MedWatch forms on a more frequent basis, the VAERS and AERS databases will be kept up to date, thereby facilitating government-sponsored surveillance efforts.

On behalf of Aventis Pharmaceuticals, Aventis Pasteur, and Aventis Behring, I thank you for your consideration of our comments.

Sincerely,

James Boyd

James Boyd, Ph.D., MBA
N.A. Regulatory Center Head
Global Drug Regulatory Affairs

On behalf of:

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