Aventis Pharmaceuticals

June 27, 2001

Via fax and UPS

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

Re: Docket No. 01D-0185
Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Postmarketing Expedited Safety Reports; 66 Fed Reg 22585-22586 (May 4, 2001)

Dear Sir/Madam:

Aventis Pharmaceuticals and Aventis Behring together are pleased to provide the following comments on the above-referenced draft guidance for industry entitled "*Providing Regulatory Submissions in Electronic Format – Postmarketing Expedited Safety Reports.*" The guidance discusses issues related to the electronic submission of postmarketing expedited safety reports for drug products marketed for human use with new drug applications (NDAs) and abbreviated new drug applications (ANDAs); prescription drug products marketed for human use without an approved NDA or ANDA; and therapeutic biological products marketed for human use with biologic license applications (BLAs), excluding vaccines.

Aventis Pharmaceuticals and Aventis Behring (henceforth: Aventis) support FDA's efforts in providing the industry with guidance in fulfilling FDA's reporting requirements. As manufacturers of human drugs and biologics, we are directly affected by this guidance and offer the following comments for your consideration. *Our comments appear as boxed text below the draft guidance reference.*

01D-0185

C J

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Lines 116-118, p. 3

"When sending a report to the FDA on physical media, applicants should identify the media as described in the current regulations (i.e., '15-day Alert report,' or '15-day Alert report-followup')."

Does this mean that initial reports and follow-up reports should be put on separate disks, or may multiple reports of different types (initial and follow-up) be put on one disk? Please clarify.

Lines 122-129, p. 4

"Once a submission reaches the EDI gateway and is successfully recognized and decrypted, an EDI gateway acknowledgement will be returned to the sender. The date of this acknowledgement will serve as the official receipt date of the submission.

After receipt of the submission, we will load the ICSRs in the AERS database. For submissions sent via the EDI gateway, an automated standard generalized markup language (SGML) acknowledgment message, which gives the status of each report in the transmission, will be returned to you via the gateway."

Will the receipt date change if an ICSR sent via the gateway is acknowledged as received, but cannot be loaded into AERS? Aventis believes it should not change, i.e. the receipt date should remain the date of first receipt. To do otherwise would be equivalent to rejecting a paper submission because of a typo.

Lines 131-136, p. 4

"For submissions sent on physical media, the Agency will determine the receipt date as it does with submissions sent to the FDA on paper (i.e., receipt date is the date it arrives at the Agency). The Agency will only contact you if there are problems with the format of the report or if the report does not load properly into the AERS database. We will contact you by phone or email, describe the problem, and request a resubmission of the report in the proper format. This resubmission should take place as soon as possible."

- Does this mean that for acceptable physical media (no problems in loading), no acknowledgement from the Agency will be received?
- Again, if cases require resubmission because of problems in loading data into AERS, will the receipt date change? Aventis believes the receipt date should remain the date of first receipt. (See previous comment.)

Lines 156-163, p. 4-5

"Section B.2. of E2B is designated for reaction/event terms. For these fields, the FDA prefers that applicants use the medical Dictionary for Regulatory Activities (MedDRA).[9] For the E2B field, B.2.i.1, you should insert the lowest level term (LLT) in MedDRA that most closely corresponds to the term reported by the primary source. For the E2B field, B.2.i.2, you should insert the preferred term (PT) in MedDRA that corresponds to the LLT used in B.2.i.1.[10] If you do not have access to MedDRA, you should populate the E2B field, B.2.i.2, with a reaction term (e.g., a COSTART term, a WHOART term) and leave the E2B field, B.2.i.1, blank."

"[9] Companies can license MedDRA from an international maintenance and support services organization (MSSO)...."

"[10] If you are using subsequent versions of E2B (e.g., E2BM), you should follow the explicit guidance for populating the B.2 fields as described in the document."

- When is FDA planning to move to DTD 2.1, which provides an additional field (B.2.i.0) for the "as reported" term we are currently required to provide to FDA and other agencies? While maintaining DTD 2.0, there is no field for this term. Also, DTD 2.0 indicates B.2.i.1 should have the "Reaction/event as reported by primary source," and not the LLT. For improved clarity, Aventis suggests providing separate instructions for each version.
- As there is more than one E2B field, Aventis recommends deleting the commas setting off the specific field names, per rules of punctuation for restrictive appositives, so that there will not appear to be two

names, B.2.i.1 and B.2.i.2, for a single E2B field. Specifically:
– *"For the E2B field, B.2.i.1, you should...."* should be changed to *"For the E2B field B.2.i.1, you should ..."*
– *"For the E2B field, B.2.i.2, you should...."* should be changed to *"For the E2B field B.2.i.2, you should ..."*
– *"...leave the E2B field, B.2.i.1, blank"* should be changed to *"...leave the E2B field B.2.i.1 blank."*

Lines 173-192, p. 5-6
"•E2B field A.1.10.1 should be filled in by the FDA (or other regulatory authority) if:
1. it receives a direct report from a health care professional or consumer ***AND***
2. the report is subsequently sent to one or more other entities.
•E2B field A.1.10.2 should be filled in by a company if:
1. it is the first company to receive a direct report from a health care professional or consumer ***OR***
2. It is the first company to receive an ICSR from the FDA (or other regulatory authority) ***AND***
3. the report is subsequently sent to one or more new entities.
•E2B field A.1.11.2 should be filled in by a company if:
1. it receives an ICSR from another company ***AND***
2. the report is subsequently sent to one or more new entities.
The A.1.11.2 field should be used by all companies that receive an ICSR from another company (i.e., this field may contain multiple identification numbers)."

- Does *"receive an ICSR"* refer only to electronic cases received from other companies or agencies, or should field A.1.11.2 be filled in also if paper is received?
- During the period of time that companies receive paper reports (not E2b) directly from the FDA, as in Scenario 1 (p. 6), should Company A insert the FDA identification number into field A.1.10.1, or leave it blank?
- In Scenario 2 (p. 6), if Company B receives a paper report (not E2b) from Company A, should Company B enter Company A's identification number into field A.1.10.2, or leave it blank?

Lines 250-256, p. 8
"We are able to archive ICSR attachments in pdf format. You should provide an individual pdf file for each attachment to an ICSR. If there is more than one piece of information in an ICSR attachment, include each piece of information in the same pdf file and provide a pdf bookmark to each piece of information. For example, if there is a hospital discharge summary and an autopsy report for a single ICSR, you should include both in a single pdf file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report."

The example given (placing a hospital discharge summary and an autopsy report in a single bookmarked pdf file) appears to contradict the instruction in lines 250-251, *"You should provide an individual pdf file for each attachment to an ICSR."* Please clarify.

Thank you for your consideration.

Sincerely,

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

On behalf of: James Boyd

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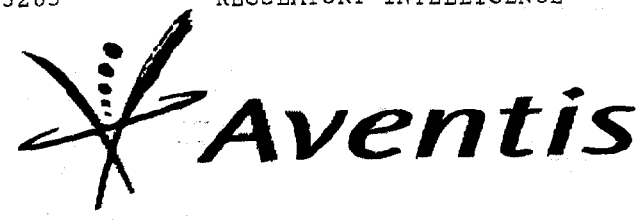

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FAX

Date: June 27, 2001

Number of pages including cover sheet: 5

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REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Re: Docket No. 01D-0185

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To Whom It May Concern:

Aventis Pharmaceuticals and Aventis Behring are pleased to provide comments on the above mentioned Draft Guidance.

We will also be sending a copy by UPS.

Regards,

Patti Stasiulaitis