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Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

May 11, 2001

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

Re: Docket No. 01D-0056- FDA Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines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

Dear Sir/Madam:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, is submitting written comments on the "Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines".

Wyeth-Ayerst is a major research-oriented pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, anti-infective agents, vaccines and biopharmaceuticals. American Home Products corporation is one of the world's largest research-based pharmaceutical and healthcare products companies, and is a leading developer, manufacturer and marketer of prescription drugs and over-the-counter medications.

The following table provides both general and specific comments on the various sections of the draft guidance document. Numbering of the specific comments section corresponds to the numbering used in the draft guidance document.

We appreciate the opportunity to comment on this document.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President, Worldwide Regulatory Affairs

RJB:cmj:84

01D-0056

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LTH-1019

Section	Line #'s	Issues	Comments
General Comment (1)		Throughout the guidance, "drugs" and "form 3500A" are mentioned, but not vaccines and or biologics and form VAERS.	We suggest that wherever "drugs" or "3500A" are mentioned that vaccines and/or biologicals and VAERS should be mentioned, as applicable. If a statement does not apply to vaccines and/or biologicals or VAERS, then that should be clearly stated.
General Comment (2)	271-278 308-324 377-390 609-709	Throughout the document there are instructions regarding follow-up of AEs.	We recommend all follow-up guidance be combined under one section.
1.A	43-45	21 CFR 600.80 and 600.81 cover human biological products with approved BLAs. Older biologic products may not have BLAs.	Please clarify if regulations cover all biologic products or only those with BLAs.
1.A.	47	…., you should discuss….	We recommend changing the word "should" to "may." The word "should" implies that anytime a company follows an alternative to the guideline that they need to contact the agency. In many cases the alternative procedure may be minor or administrative in nature and not warrant dialogue with the agency.
I. B.	61-64	Devices are not covered by this guidance, but are not mentioned in the list of items that the guidance does not apply to.	For the sake of clarity, please add, "devices" to the list of products not covered by the guidance.
III.	163	The document states, "Any person whose name…." Company or corporate names are on labels, not individuals.	We recommend replacing, with, "Any entity whose name…."
IV.	189-191	1. The definition of adverse experience includes the statement "whether or not considered product-related by the applicant".	1. The phrase "by the applicant" is new to this definition, and does not appear in the definition of adverse experience in Appendix A. Please clarify the intent of adding this phrase to the definition or delete the phrase "by the applicant" or add "… by the applicant and/or reporter."

IV. A.1	214-218	1. The document includes in vitro and animal postmarketing studies as sources of AEs for reporting. 2. Says only submit reports if applicant believes there is reasonable causality.	1. Adverse events are defined as events occurring in humans. In vitro and animal AEs should not be reported as 15-day alert reports. Therefore, the reference to in vitro and animal studies should be deleted. These would be more appropriately captured in the Annual Report and/or mentioned in the current section IV of the periodic report (studies involving safety issues). 2. We recommend changing to read, "if applicant or investigator believes there is reasonable causality." This is consistent with ICH E2A.
IV.A.3	242	"Life -threatening adverse experience" is mentioned as a serious criteria, but no where does it specify that the AE must be life threatening as it occurred to that patient.	Please add a paragraph that explains that the AE must be life-threatening as it occurs to the patient, not that the event could be life-threatening had it occurred in a more serious form or refer reader to the glossary.
IV.A.3	251-253	As described, same day hospitalizations (with release on the same day) are considered to be hospitalizations.	Hospitalization should imply overnight stay. As written, it is unclear if events treated in a short-procedure unit (ie day-surgery) should be considered hospitalizations. We suggest that less than overnight hospitalizations and day surgery be evaluated for seriousness based on the other available criteria. Example - day surgery for gall bladder removal (medically important), and day-surgery for removal of sebaceous cyst (non-serious).
IV.A.3	260-263	Incarceration is considered a disability.	Incarceration is not a medical event. It is generally the result of a legal action; however, clarification of exactly what is meant by incarceration would be helpful. Also, consider that a person could commit a homicide, allegedly due to taking a drug, be acquitted and thus not be incarcerated. Shouldn't this event be serious for the same reason as the incarcerated person? Rage reactions and similar events resulting in bodily harm or mental incapacity should be evaluated and if significant harm or mental incapacity is involved, the events should be considered medically important.

IV.A. 3	265- 267	1. This paragraph implies the examples mentioned are the only events that would be medically important. 2. All blood dyscrasias are listed as medically important. 3. Drug dependency/abuse listed as medically important.	1. We recommend adding, "events such as" to line 265 - "important medical events would include events such as allergic....." 2. Not all blood dyscrasias are medically important. A report of a platelet count of 100,000 and the patient is asymptomatic or a mild anemia is not medically important. Please add, "Important medical events would include.....significant blood dyscrasias, ..." 3. These terms may be used incorrectly by consumers (ie without diagnosis from the physician). These events should be evaluated on a case by case basis for other serious criteria and for medical importance, and thus should not be used as an example
IV.A	271-278	1. "Outcome" is not defined. 2. 273 - "... applicant should continue to actively seek information....." 3. Not addressed in the guidance is the situation when a consumer refuses to provide the physician's name and address or asks company not to contact the physician.	1. Please clarify if outcome refers to outcome of the AE(s) or the status of the patient. 2. Recommend that this statement should not be left open-ended as sometimes despite considerable effort, a healthcare professional will not provide information. We suggest replacing with, "... applicant should exercise due diligence in actively seeking information...." 3. Please address this situation. We suggest exempting company from further follow-up in this situation.
IV.B	305-306	The draft does not mention who suspects the AE. It should make clear that the event is suspected by the reporter.	Recommend that this be changed to read, "An adverse experience or fatal outcome suspected by the reporter to be due to the suspect drug or biological product."
IV.B	316-324	Verbal contact to get follow-up for all serious cases. (Note: Later in the document it is clear that this verbal follow-up is for serious only cases, but it is not clear in this section. We suggest clarifying this point within this section also by adding the word serious.)	We recommend limiting verbal contact to US serious, unexpected cases when reported to the company by a healthcare professional. Please clarify if follow-up (F/U) is needed only when the 4 elements are not known, only when the outcome is unknown (is this until recovery?), or until all elements are known. We suggest ending F/U on 15-day cases when data for defined key fields of the 3500A are obtained. The data set of basic elements for serious expected vs non-expected cases presented by Dr. Murray Lumpkin at the conference on ICH V might be useful for identifying key fields. Verbal contact should not be required for serious, expected events. Healthcare professionals (HCPs) should only contact

			HCPs for F/U information. The guidance should specify that consumers are only contacted by mail.
IV.B	326-331	No guidance is provided for what identifies an identifiable reporter	Please provide this guidance. Is a person who calls or writes a company, but refuses to provide their name an identifiable reporter?
IV.B	335	Says, "if applicant concludes there is a reasonable possibility that the product caused the adverse experience…"	Recommend changing to read, " if applicant or investigator concludes…."
IV.A	377-379	378 - follow-up should start immediately upon receipt of report.	We suggest other wording, as often it is prudent to wait a short period of time to obtain follow-up, as in the case where an important diagnostic laboratory finding is expected within a week, or an event is reported while the patient is still hospitalized. Healthcare professionals will be more willing to provide follow-up if their time is used wisely.
V.A.1	380-383	The narrative section of the 3500A should include a chronological description of follow-up efforts if there is a delay obtaining such information.	These records are on file, but should not be part of the narrative. The guidance directs us to be concise as the AERS database has limited space for this section (633-635); therefore, this section should be limited to pertinent clinical details. It would seem to be in the best interest of the public health if this narrative space is used for a description of relevant medical-safety information rather than for administrative purposes.
V.A.1	393-395	Foreign affiliates	Please clarify that foreign affiliates do not include business partners.
V.A.2	401-404	Include in narrative a list of other relevant documents in their files (ie. medical records, lab data, EKGs, etc).	As above, this is not in keeping with being concise in the narrative. Also, no other agency has requested that this type of information be listed in the narrative; nor, is this consistent with ICH E2B guidance.
V.B.2	538	Narrative discussion of action taken section says list studies initiated.	We recommend clarifying that this is for studies initiated for safety concerns. This is consistent with the regulations.
V.B.2	583-587	Include relevant hospital documents as attachments to the 3500A for serious, expected adverse event reports.	The electronic submission pilot for Periodic reports does not support submission of attachments to 3500A reports. The guidance should be consistent with the pilot program, as it supports the eventual electronic submission of periodic reports for all companies.

V. C.1	628-631	1. Information from the initial report found to be inaccurate should not be repeated. 2. All new information including correction of inaccurate information should be highlighted in some way.	1. Please clarify what should be done with information not confirmed on follow-up (example physician does not confirm some events reported by consumer). We strongly recommend that this information be retained, but the narrative should clearly indicate events not confirmed by the physician. 2. Highlighting of new information while useful to the reader of the report is a significant technical challenge to automated computer systems. Programming to do highlighting of new or changed information can slow systems down so much as to be unusable. Please delete this sentence.
V.C.1	633-635	The AERS system has limited space for the narrative.	It would be useful to know if the number of characters allowed in the AERS system for the narrative is the same as in ICH E2B. If different than E2B, it would be useful to state the numbers of characters available.
V.C.3	701-702	For VAERS form mark follow-up and indicate whether follow-up is the 1st, 2nd, , etc.	The VAERS-1 form has no provision for indicating 1, 2, 3, etc. (ie no line or space after the check box), nor does the draft VAERS-2 form. We suggest adding provision for this information on the VAERS-2 form.
VI.A	743	"It is not sufficient to submit only abstracts of articles."	This needs clarification. For example, if the company becomes aware of an abstract that has the 4 elements, can the abstract be submitted and then a follow-up with the complete article in the event that a complete article can not be obtained in time to meet 15-day reporting requirements? If the author only publishes an abstract (ie as in poster presentation), please clarify if the abstract should be submitted as a literature report.
VI.B	785	"....reasonable possibility that the drug or .... caused the adverse experience."	We recommend adding, "....reasonable possibility <u>per the applicant or investigator</u> that the drug caused the adverse experience."
VI.B	795-796	...serious, unexpected adverse.....	We recommend changing to read "...serious, <u>reasonably related and</u> unexpected adverse..."
VI.C	810-813	When a foreign report is submitted on a product that is not identical to a product	Box C1 is not large enough to include all this information. The NDA number of the US product appears in box G5; repeating it in box C1 is

		marketed in the United States, the foreign trade name, generic name and NDA number of the US product with the same active moiety should be included in box C1 of the FDA 3500A form.	redundant. Current practice when this situation occurs is to list the foreign trade name, formulation, and generic name in the narrative (box B5), and the generic name and formulation in box C1.
VI.F	839-840	The lot number should be provided.	Please add "if available" as in many cases the lot number will be unknown.
VI.F	842-844	Lack of drug effect (LDE) for unapproved indications should not be reported to the FDA, but rather mentioned in the narrative.	Since industry does not consider emergency contraceptive a labeled indication and the FDA does, a special note of this situation should be made. For example, we recommend inserting text advising to report LDE for emergency contraception in the draft document. This will avoid confusion and legal liability issues.
VI. G	848-855	For Internet reports -report if knowledge of four basic elements.	Please provide guidance regarding what constitutes an identifiable reporter for adverse events encountered via Internet sites. Please clarify if a chat room "nickname" without a corresponding e-mail address would constitute identification of a valid patient or reporter. We strongly believe reports from chat rooms should not be reportable as there is no way to conduct confidential follow-up or ensure that there is an identifiable patient.
VI.J	885-886	Reports in which the suspect drug is that of another applicant should be promptly forwarded to that applicant.	Please clarify whether this guidance applies to all reports, serious and non-serious, as the regulations address forwarding only serious adverse experiences to the applicant. Please clarify the timeframe for forwarding reports to the applicant, as the regulations specify 5 calendar days, and the draft guidance just says "promptly".
VI. K	898-904	There is no mention of what to do when one suspect product is a drug and the other is a non-vaccine biological.	Please clarify if this guidance also applies when a drug product and a licensed non-vaccine biological product or device are equally suspect. Reports for these products are sent to different addresses. Please clarify if the Agency will handle the internal processing aspects of these situations, or if the guidance to submit only one FDA 3500A form does not apply in these situations.

VI.K	906-909	A separate form should be submitted for a non-vaccine biological and a vaccine when both are suspect.	We recommend that there also be separate forms for a drug and vaccine report or a drug and device report and a non-vaccine biological and device report. Please clarify.
VIII	1018-1023	When information is not available use NA (not applicable) or NI (no information now, but may be available later) or UNK (unknown).	We believe this is highly impractical – it is difficult to distinguish between NI and UNK. Additionally, if all follow-up attempts have been exhausted , would a follow-up report to change all NI's to UNK's be required? In most computer systems UNK, NA or NI would be a default and re-programming would be needed to manually enter these values. The benefit of these fields does not seem proportional to the work of reprogramming, validation and manual entry.
Glossary	1435-1436	"divided manufacturing"	Please define this term.
Glossary	1471-1472	Initial reporter is the original reporter	Definition of the term as used in the 3500A, Box E is not correct. For example, if the original reporter is a consumer and a physician gives follow-up either before the initial report is sent or on follow-up the physician's name and address is put in Box E. Also, if minimal information is received from Dr. A and then complete information is received from Doctor B, Dr. B would then be the initial reporter. More guidance consistent with actual practice regarding what reporter to put in Box E is needed.
Glossary	1474 - 1477	Consider event life-threatening if the reporter states it as such.	Please clarify whether company medical judgment can be applied when a consumer initial reporter mentions an adverse experience was life-threatening, and the facts do not support this classification (example - Consumer says "your drug almost killed me. I had an awful headache." Consumer also indicates he sought no medical treatment.) Also please clarify if an initial classification of life-threatening may be changed upon receipt of additional information from a health care professional indicating that the event was not life-threatening.
Glossary	1498-1501	Spontaneous reports do not include cases identified from information solicited by	Following "It does not include cases identified from information solicited by the applicant such as individual cases or findings derived

		the applicant such as individual cases or findings derived from a study.	from a study", please add a patient assistance program, or a registry.

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