AstraZeneca

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MAY 07 2001

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

Dear Sir or Madam:

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Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Reference is made to the March 12, 2001 *Federal Register* Notice announcing the availability of Draft Guidance for Industry entitled, ***Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines***. AstraZeneca Pharmaceuticals LP has reviewed this guidance document and our comments are attached.

Thank you for your consideration.

Sincerely,

Omaira B for MGM

Margaret G. Melville
Regulatory Affairs Director
(302) 886-2118
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MGM/OM/djr
Attachment

01D-0056

C2

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Comments for: Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Docket Number: 01D-0056

Federal Register: March 12, 2001, Volume 66, Number 48,
Notice, Pages 14391 - 14392

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comment
I	Page 2	43 - 44	Please clarify whether this guideline covers vaccines licensed prior to the BLA initiative or covers all currently licensed vaccines.
I	Page 2	59 - 64	We would advocate adding devices to the list of products the guidance does not cover.
II	Page 4	123 - 143	Since the guidance states that the Agency is in the process of developing proposed rules to further amend its safety reporting requirements for human drug and biological products, it seems redundant to update this guidance now, and then have to update it again when the new regulations are released.
III	Page 5	163	Since company or corporate names are on labels, not individuals, we suggest revising the statement "Any person whose name…."., with "Any entity whose name…."
IV	Page 5	190	For completeness, in addition to mentioning drugs and biological products, we suggest adding vaccines to the definition of adverse experience.
IV	Page 6	214	We suggest adding clarification that reports from *in vitro* and animal studies should be submitted in narrative format, not on FDA Form 3500A, VAERS, or CIOMs forms.
IV	Page 6	217	For post-marketing studies, we suggest changing the wording to "if applicant or investigator believes there is a reasonable causality."

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comment
IV	Page 7	242	"Life -threatening adverse experience" is mentioned as a serious criteria, but it does not specify that it 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.
IV	Page 7	260	It would seem to be unnecessary to include "incarceration because of actions allegedly caused by a drug" within the serious outcome criteria of *significant or persistent disability/incapacity,* since the type of events indicated by the examples provided would be considered serious according to the "important medical event" criteria, which would seem to be a more appropriate and less confusing classification of outcome. Additionally, incarceration is not a medical outcome; it is behavior modification. This type of event would be considered serious according to "important medical event" criteria. We would recommend removing this paragraph.
IV	Page 7	265	The current wording in this guidance implies that the examples of allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsion are the only events that would be medically important. Re-wording this sentence to include "important medical events would include events such as allergic..." would indicate other events could be medically important. Also, while the examples of important medical events presented in this guidance were taken from the current regulations, it would be helpful if some of the given examples were further specified in this document. For example, not all blood dyscrasias meet the criteria for important medical events; a platelet count of 100,000 and a patient with no symptoms is not necessarily medically important. We would recommend expanding the example to a specific type of blood dyscrasia, such as agranulocytosis or aplastic anemia, which definitely would have to be considered as important medical events. Additionally, we would ask that the terms drug dependence and drug abuse be further defined, since these terms may be used incorrectly by consumers.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
IV	Page 7	268	Instead of checking the "Other Box" in B2, why not modify the FDA Form 3500A form to accurately reflect all of the changes made in the April 1998 final rule?
IV	Page 7	271 – 278	If applicants seek to gather additional information from health care professionals concerning a serious adverse event reported by a consumer, there is the potential that patient/physician confidentiality could be jeopardized, especially if the consumer has refused authorization for such contact. There are consumers who refuse to provide any information concerning their health care provider. Is there a limit to efforts expended to gain additional information? It is also unclear in the document what "outcome" the agency is requesting. Please clarify if it pertains to the outcome of the AE or to the status of the patient.
IV	Page 8	292	We request clarification as to how companies need to report phase IV AE's and solicited AE reports on marketed products: should they be reported to the IND, the NDA or both?
IV	Page 8	303	We request clarification how to handle indirect AE reports from second-hand reporters (who have heard about an AE-report from other colleagues, during grand rounds, etc.). Should there be a distinction in the handling of reports from first-hand and second-hand reporters?
IV	Page 8	308	We receive many telephone calls from reporters who refuse to provide any of the information that meets the criteria of "valid reporter" as described in this guidance. Should we still consider these cases to be valid?

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
IV	Page 9	316	It should be explicitly stated here that this relates to the follow-up process of AE reports.
IV	Page 9	316	The recommendation for follow-up by telephone on all adverse experiences by health-care professionals would seem to contradict the Agency's guidance in a later section of this document to limit follow-up on non-serious events. CIOMs V recommends that this level of follow-up be reserved for serious unexpected AE's. In reality, telephone contact during business hours is logistically difficult, since busy physicians are often seeing patients, and many consumers are not at home. The advantage of a letter is that this allows the reporter to provide information at a time convenient for them.
IV	Page 8 & 9	316 - 325	We feel that it is not necessary to limit collection of adverse event information to health care professionals. It is more important that the individuals performing these activities are properly trained and provided with the appropriate tools (e.g., targeted follow-up questions for specific adverse events of interest, etc.) to carry out the activity.
IV	Page 9	332	Does the concept of "implied causality" for spontaneous reports apply when the reporting healthcare professional clearly indicates the AE is **not** due to the drug, but due to another cause? Please clarify.
IV	Page 9	332 - 342	Guidance is provided regarding three of the four essential elements for a valid report (identifiable patients, adverse experience and outcome). Please add guidance regarding what constitutes an identifiable **reporter**.
V	Page 10	373	We request additional clarification that a report whose "Day 15" falls on a weekend or US Federal holiday will not be considered late if submitted on the first working day after the weekend or Federal holiday. Reports can be submitted prior to Day 15, but the current wording makes it sound as if the report **must** be submitted on that first working day following the weekend or holiday.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
V	Page 10	381	The new policy to include in the narrative of FDA Form 3500A a chronological description of due diligence efforts if there is a delay in obtaining such information is confusing since "delay" has not been defined. This is also incompatible with Agency instruction later in this guidance to keep narratives as concise as possible because the FDA's database for this section is limited. 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. Additionally, in today's global safety systems, the narrative must be fit for purpose for submission to regulators worldwide, and this would not be acceptable to other regulators. This would also be a duplication of effort since companies are already required to maintain records of due diligence efforts, most of which are maintained in detail for the individual case outside of the narrative, and these records are available upon request.
V	Pages 10 & 11	399 - 407	Submitting copies of discharge summaries and autopsy reports/death certificates for serious, unexpected adverse experiences is redundant. Relevant information from these documents is summarized and included in the appropriate boxes on the FDA Form 3500A. The rationale for including a list of relevant documents maintained in the applicant's corporate drug or biologic product safety files is not understood. These records should be on file, but not included as part of the narrative summary. The guidance requests concise narratives due to limited space in AERS database: the narrative section should be limited to pertinent clinical details only. A written request should be submitted to the applicant from the Agency if a copy of any documentation retained by the applicant is required. No other regulatory authority worldwide has requested this information be submitted. This request is inconsistent with the Paperwork Reduction Act and E2B. Please clarify the rationale for including these documents with each serious unexpected AE.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
V	Page 10	401	The new policy to include in reports a listing of available documents (eg, medical records, labs, etc.) would seem to be a duplication of effort, since relevant information drawn from these documents will already be included in the appropriate section of the FDA Form 3500A. Source documents have always been available upon request. This is also incompatible with Agency instruction later in this guidance to keep narratives as concise as possible because the FDA's database for this section is limited. It would seem to be in the best interest of public health if this narrative space is used for a description of relevant medical-safety information rather than for administrative purposes. Additionally, in today's global safety systems, the narrative must be fit for purpose for submission to regulators worldwide, and not simply to one Regulatory Agency.
V	Page 13	486 - 495	In general, it is very discouraging to see no movement towards harmonization with ICH PSUR guidelines in the periodic report requirements; does this indicate what can be expected from the forthcoming final rule on PSURs? Many companies have applied for waivers so they can submit periodic reports in the PSUR format. The subtle changes in the periodic report section, such as the new requirement for a tabulation of reports received from the FDA, will be a significant technological and administrative burden on companies, since this will mean even more US-specific listings will need to be added to the PSUR for submission to the FDA. This would seem to have minimal added value.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
V	Page 16	628	The document states that information from an initial report that is later found to be inaccurate should not be repeated in the follow-up report. Please clarify if elimination of initially reported adverse event terms that were not confirmed on follow-up would be acceptable. Existing guidance states that adverse events be described "using the reporter's own words"; there has been reluctance in industry to delete any terms or information from subsequent follow-up reports.
V	Page 16	629	The new policy of highlighting information in a follow-up report by underlining or bolding new or corrected information is incompatible with the abilities of many adverse event reporting systems, such as Clintrace™, especially if new information is combined with relevant information from the initial report. We currently identify new information with a statement at the bottom of the narrative; we believe this should be an acceptable alternative. Additionally, in today's global safety systems, the narrative must be fit for purpose for submission to regulators worldwide, and not simply to one Regulatory Agency.
V	Page 16	633	The document states that the narrative of follow-up reports should be concise because FDA's database for this section is limited. We would request that the Agency provide information regarding the length to which the section should be limited, preferably consistent with E2B guidance to limit the narrative section to no more than 10,000 characters. The statement is specific to limiting the narrative for follow-up reports. Please clarify that the same statement holds true for narratives in initial reports as well.
V	Page 16	640	The guidance mentions that non-serious reports for which the four basic elements are known do not require any follow-up. Please clarify whether this includes both non-serious expected and non-serious unexpected events.
V	Page 17	669	The document states that follow-up reports should not be submitted if additional relevant information is not obtained for the adverse experience. Regulations state that follow-up reports should be submitted when "new information" is received, and make no distinction regarding **any** new information and **relevant** new information. Please clarify/define "relevant" information.
V	Page 18	731	The reference in the last paragraph should be changed to section VIII. D.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comment
VI	Page 18	742	If an abstract contains enough information to make a report, and translation of the full article is pending, shouldn't the report be submitted with the translated abstract? The translated full-text article could be submitted in follow-up. There is a need for a statement indicating that the MedWatch may be sent without the article if necessary to meet the required 15-day timeframe.
VI	Page 19	747	The guidance states that when multiple identifiable patients are described in an article, a copy of the article should be attached to only one of the FDA Form 3500As, and the other forms should reference the manufacturer report number of the case that the article is attached to. The narrative is not an appropriate location for this information. The case is submitted to regulatory authorities worldwide, and this is not standard practice worldwide. Please clarify where the Agency would expect to see this reference on the FDA Form 3500A.
VI	Page 19	755	A clear definition of "suspect product" is required; a company drug could have been mentioned as a concomitant drug in a publication (the drug may not have been mentioned in the title of the publication).
VI	Page 19	762	The policy to submit literature reports for drugs which contain the same active moiety even when the formulation, indication, etc. are different would seem to lead to duplicate reporting, since NDA's for these may be held by different companies in the US, which means all of the different companies will be sending in the same literature reports. Does the company need to report cases with the same moiety (but other brand names) that are marketed by other companies in the US?
V	Page 19	762 - 764	The policy to submit literature reports for drugs which contain the same active moiety even when the formulation, indication, etc. are different could lead to duplicate reporting. NDA's for these products may be held by different companies in the US, which means all of the different companies will be sending in the same literature reports. We recommend that if the trade name is not known or not specified, then the innovator of the product should submit the report.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
VI	Page 19	768	What is the purpose of submitting the article in duplicate (translated as well as untranslated versions)? This would seem to be a violation of the paperwork reduction act, (reference consistently here) and contrary to the Agency's initiative to move to a paperless environment. If the Agency doubts the verity of the translation, the company could supply it on request.
VI	Page 19	776 - 777	The guidance indicates that adverse experiences incidental to "other types of studies" not involving "monitoring" adverse experiences should be considered spontaneous reports. Please give examples of "other types of studies" and clarify if the use of the word "monitoring" in this context refers to actual site monitoring and other components of GCP (informed consent, case report forms, etc.).
VI	Page 19	785	Please clarify if "reasonable possibility" means cannot be ruled out, as defined in the E2A document. This has not been included in regulations and is a higher standard than that included in 21 CFR 312.32. Otherwise, we suggest changing the phrase "if applicant or investigator believes there is a reasonable possibility...."
VI	Page 20	795	Unblinding should only take place for serious, unexpected and POSSIBLY RELATED AE's.
VI	Page 20	807	This document states that when a foreign report is submitted on a product that is not identical to a product 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 Form 3500A. 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 redundant. Current practice when this 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, along with the notation "non-US product".

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
VI	Page 20	817	The guidance states that death is always a serious outcome, whether associated with an unexpected adverse experience, or associated with an expected adverse experience, with labeling that does not specifically state that the adverse experience may be associated with a fatal outcome. Please clarify how to handle an adverse experience when the only information received is "death, unknown cause," especially in instances where the patient is known to have a fatal disease.
VI	Page 21	834	The definition of adverse experience includes any failure of expected pharmacological action that is synonymous with lack of effect. Please clarify if the reporter has to use the terms 'lack of efficacy' in order for the report to be termed 'lack of effect'.
VI	Page 21	839	Lot number is not always provided. Please add: 'The lot number of the suspect product should be included if available in item C6 of FDA Form 3500A.
VI	Page 21	842	Industry does not consider emergency contraception a labeled indication; however, FDA does, and special note of this situation should be made. .
VI	Page 21	842	This paragraph seems not relevant (since, by definition, drugs can not be considered effective in unapproved indications); therefore, the purpose of this paragraph needs to be clarified. A link with product complaints should not be overlooked in the context of lack of effect reports.
VI	Page 21	850	Does an e-mail address alone constitute a valid patient or reporter? Does a chat room "nickname" without a corresponding e-mail address constitute a valid patient or reporter?
VI	Page 21	859 - 862	The FDA is asking that both age and DOB be provided for children <3 years old. This is redundant and inconsistent with E2B recommendations. The document states that for all pediatric patients, weight and dose should be included. This information is not always available. Please change the statement to read "for all pediatric patients, weight and dose should be included, if available."

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
VI	Page 22	883	This section does not address the scenario where a company drug is mentioned as a concomitant drug in a SAE report from a trial, conducted by another company (sometimes we receive such reports from another manufacturer).
VI	Page 22	886	The guidance states that 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 timeframes for forwarding reports to the applicant, as the regulations specify 5 calendar days, and the draft guidance just says "promptly".
VI	Page 22	891	The document states an applicant should only submit a report of an adverse experience to the FDA for a suspect product marketed by another applicant if the applicant of the suspect product is unknown or the report is for "a serious, unexpected adverse experience occurring during the conduct of a study." Please clarify if this is an option or if it should always be applied when the report is from a clinical study.
VI	Page 22	898	The draft provides guidance regarding various scenarios for reporting multiple suspect drugs. The guidance document states that when two products are equally suspect, only one FDA Form 3500A should be completed, and the report should be submitted to the product first in alphabetical order. Please clarify if this is by trade or generic name. Please clarify if this guidance also applies when a drug product and a licensed non-vaccine biological product are equally suspect. Reports for these products are sent to two different addresses. Please clarify if the Agency will handle the internal processing aspects of this situation, or if the guidance to submit only one FDA Form 3500A does not apply in this situation.

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Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
VI	Page 22	906	A separate form should be submitted for a non-vaccine biological and a vaccine when both are suspect. Industry assumes this also means that there should also be separate reports for a drug and vaccine report, drug and device, device and drug, etc. Please clarify if our understanding is correct.
VI	Page 22	911	The last paragraph in this section is very confusing. Please clarify that exchanging copies of FDA Form 3500As applies only to domestic reports.
VI	Page 23	932	The document discusses the clock start for two companies co-marketing in the US and for affiliates of the same company outside the US; however, international co-marketing agreements are not addressed. In the 1992 guideline, the definition of affiliate included licensees abroad. Please clarify if this is a change in policy.
VI	Page 24	963	The guidance states that applicants who receive individual case safety reports from FDA are not required to resubmit them to the Agency. However, follow-up information to these initial reports must be submitted to the FDA. Please clarify as to whether the report should be identified as "initial" (since it will be the first one submitted by the company) or follow-up (in which case what mechanism should be used to link the follow-up information to the information originally received from the Agency, as there would be no unique manufacturers control number to reference?)
VI	Page 24	969	Please define product defect. Please clarify if product defect would include product tampering.
VIII	Page 25	1018	For the list of abbreviations (NA, NI, and UNK), is the guidance suggesting that all of these must be used with their specific meanings, or can one be chosen as an all-purpose default?
XI	Page 33	1356	The document states summary tabulations should be presented by body system of all adverse experience terms and counts of occurrences and be segregated by type. This section is misleading, since, having received a PSUR waiver, we understood that we must submit a tabulation of Alert Reports submitted to FDA.

Comments for: Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
XI	Page 33	1375	The guidance states applicants can request a waiver to submit PSURs to the FDA at a frequency other than those required under 314.80(c)(2)(i) and 600.80(c)(2)(i). Please clarify whether the waiver of frequency is to permit semi-annual reporting instead of either quarterly or annual periodic reports, to request a 60-day time clock for submission of PSURs after data lock on quarterly reporting, or to allow more frequent submissions.
Appendix A	Page 35	1417	**Adverse Event:** Adverse event is synonymous with adverse drug experience, adverse biological experience, adverse product experience, and adverse event. Please clarify if 'side effect' should be included in this list.
Appendix A	Page 35	1431	**Applicant:** Please define 'divided manufacturing'.
Appendix A	Page 35	1453	In the positive dechallenge definition, clarification as to whether or not this includes situations in which treatment for the observed AE was given, needs to be added.
Appendix A	Page 36	1471	**Initial Reporter:** The definition of the term as used in the FDA Form 3500A, Box E is confusing. For example, if the original reporter is a consumer and a physician gives us 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 one physician and then another physician provides complete information, the physician providing complete information is listed as the initial reporter. More guidance consistent with actual practice regarding information in Box E is needed.
Appendix A	Page 36	1474	**Life-threatening adverse experience:** 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. 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.
Appendix A	36	1498	**Spontaneous Report:** Following "It does not include cases identified from information solicited by the applicant such as individual cases or findings derived from a study," please add that this includes patient assistance programs, and registries.

Comments for: Draft Guidance for Industry on Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
Appendix B	Page 38	1530	1. Add 'identifiable' patient
Appendix B	Page 38	1543	5. Due to patient privacy concerns, it is fairly common practice to exclude the name and address of the initial reporter from box E1 if the initial reporter is the patient or the patient's relative. This is in keeping with the regulations, which state that the names and addresses of individual patients should not be included in the reports. Please clarify that this is acceptable.
Appendix B	Page 38	1550	7. Include publications in the list of attachments.

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