The DEGGE GROUP, LTD

Drug Safety Research
and Information

VIA FEDERAL EXPRESS

May 10, 2001

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

Re: Draft Guidance on Postmarketing Safety Reporting
Docket No. 01D-0056

Dear Madam/Sir:

This letter is to provide comments on the Draft Guidance on Postmarketing Safety Reporting published on March 12, 2001.

The majority of our comments are provided in a tabulated format that references the specific Section and line referenced. However, we would like to comment that this Draft Guidance would be greatly enhanced by two structural changes in the document as presented:

1. An outline or flow chart or similar diagram that guides the reader to the overall reporting scheme would be helpful. A precedent for this is found in the new guidelines for annual reports of required postmarketing studies (Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997, April 2001).
2. Placement of the definitions at the beginning of the guidance. This will aid in reviewing the requirements.

We hope these comments are constructive and helpful. Our drug safety group draws upon some considerable experience within the FDA and the regulated industry and we respectfully suggest that attention to these points may assist the Agency in developing a clear, comprehendible guideline.

Sincerely,

Judith K. Jones, MD, PhD.
The Degge Group, Ltd.

01D-0056

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Comments on FDA Draft Guidance:
Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Page	Line #	Reference	Comment
6	203-204	*Adverse Experiences that are Serious and Unexpected from All Sources (Domestic and Foreign)*	Clarifying these are 15-day reports would be very useful whenever the phrase *Serious and Unexpected* was used. It should always be written together.
6	221, 227-229	*Other Spontaneously Reported Adverse Experiences (Domestic Only)* . . . 1) serious and expected 2) nonserious and unexpected 3) nonserious and expected	Clarifying these are NON-15-day reports and as above, whenever any of the phrases (1-3) are used, the statement should be written together.
7	260-263	"Persons incarcerated because of actions allegedly caused by a drug (e.g., psychotropic drugs and rage reactions) have sustained a substantial disruption in their ability to conduct normal life functions. Thus these adverse experiences would qualify for the *significant or persistent disability/incapacity* outcome."	Careful thought should be given to use of applying this language, especially in the context of people who actively and purposefully abuse certain prescription drugs and then become incarcerated. Making the determination that these adverse experiences "qualify for the significant or persistent disability/incapacity outcome" because of a person being incarcerated could place an unfair burden on industry for individual's behavior. Further, alleged disability has significant broader implications as relates to insurance, workman's compensation and legality of incarceration. Because there are legitimate adverse event experiences of this nature that are of concern, perhaps they would be better categorized as *important medical events, and marked as "other" on the 3500* form as such.
7	274-276	For serious AE not initially reported by a HCP	What specific actions would be considered acceptable as "actively pursue[d]".
8	292-294	Reporting requirements for studies	This section is confusing and seems conflicting with previous statement re: studies (IV. A. 1. lines 214- 219) and section VI.B in this guidance for reporting of adverse experiences from studies, further clarification would be useful. For instance, "information solicited by applicants such as individual cases..." is not at all clear. For example, mentions of cases to applicant drug representatives or in calls to medical affairs for information can result in "solicited cases". Are these not spontaneous reports?

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9	316-324	An applicant that is actively seeking information on an adverse experience should use direct verbal contact with the initial reporter. Contact should be by a health professional.	While direct verbal contact is often the best way to get follow-up information, it is not always possible. Applicants should be able to obtain follow-up information in any manner that best works with their departmental operations. In addition, not all AEs require such intensive follow-up. Is this guidance for follow-up suggested for all AEs?
9	326	Comments on identifiable patient - reports of the type "some patients got anaphylaxis" should be excluded until further information is obtained.	Since the number of patients in this example is unclear, many companies have adopted the practice of just sending in one report until more information is obtained, since the report implies that at least one patient was involved. Is the Agency now suggesting that no report should be sent in this example? In addition, how should companies handle a report that says "9 patients got anaphylaxis" with no information on any of the 9 patients?
9	332-334	Spontaneous reports and implied causality	A spontaneous report with an adverse experience or fatal outcome suspected to be due to the suspect drug or biological product **should not** automatically imply "causality."
9	340-342	A report stating that a patient who experienced an unspecified injury should not be included	This is a classic example of a legal case. In the past these reports have been submitted as "reaction nonspecific" because there is an identifiable patient, reporter, and ?AE. Is this a change in Agency policy?
10	359-360	Minimum reporting	Should clarify whether or not a submission of a 15-day report based on only verbal information, still needs to meet the four basic elements (see 385-388).
10	392-395	For foreign reports, 15 day time clock begins when applicant or foreign affiliate has received the four basic elements for a 15 day report.	Would appreciate more guidance from Agency on when the clock starts in joint venture/partnership agreements. When does the clock start when one partner receives the report but the other partner is the NDA holder?
13	491	15-day reports submitted to FDA	Should the format of the tabulation clearly distinguish foreign 15-day from domestic 15-day? Foreign 15-day reports may have different drug formulations or context and should be differentiated.
13	494-495	Summary tabulation information for Periodic Report	Please clarify whether reports which are subject to an approved waiver must still be submitted in the summary tabulation.
14	562	d. Section 4: FDA Form 3500As or VAERS forms	Add language: " : for *Non-15-day Reports*" for clarification

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16	654-656	15-Day Follow-up Reports -	Find this section very confusing. Suggest not changing reporting status once a report becomes a 15 day report, regardless of number of follow-ups. "Once a 15 day report, always a 15-day report." Also, Agency should provide guidance on completion of Date Received by Manufacturer box when follow-up information is obtained, particularly when multiple follow-up reports are submitted
18	736	Scientific literature reports	Clearer criteria of the agency's expectations of what is considered adequate and sufficient review of the literature would be useful.
18	741-743	Literature search services	Is Weekly Reactions sufficient as the only search service or does it need to be supplemented by another service such as MedLine?
19	747- 748	Identifiable patients in an article	In most cases it is likely that the other 3 minimum data elements (303-306) are also present for each identifiable patient, but if they are not should an individual report be submitted?
19	755-760	Multiple products in an article	Guidance states that suspect product is that identified by the article and is usually mentioned in the article. While this is generally true for case reports, it is not necessarily true for efficacy studies where a treatment is being evaluated in conjunction with other treatments or as part of a treatment regimen. If an AE occurs in a literature article of a study, is that also reportable even if it may not be mentioned in the title, or it is not clear what the specific suspect drug is because it is part of a treatment regimen, e.g. chemotherapy?
19	767-770	Requirement for translation of an article	Translation often takes several weeks even if submitted to a service promptly. How does this impact the 15-day report requirement. Should the applicant hold up the submission of a 15-day report while it is awaiting translation, or should information from an English abstract be submitted in the interim?
19	780-781	Requirements for handling AEs in patient support programs	Would Agency agree that similar policy also applies to Actual Use Studies conducted for OTC switch programs?

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20	807-813	Active moiety requirement	Would appreciate Agency guidance on handling multi-ingredient products where only one active ingredient is the same active moiety as in the US, but other ingredients are not marketed in US or are not in the same combination of actives as other US products?
21	834-840	Lack of effect requirement	Request that Agency reconsider this policy to require that only reports from health professionals be submitted for lack of efficacy. Reports from consumers are typically request for refunds and have no medical merit, yet are high volume. Furthermore, additional guidance is required on the definition of a lack of effect report. Do these words have to be used or is the development of an infection following prophylactic antibiotic use also qualify as lack of effect?
21	859	Age of pediatric patients	Why is it necessary to have both birth date and age? Not required for adults and inconsistent with E2B.
22-23	911-918	Multiple suspect drugs and applicants	Statement that if one applicant receives a report of multiple suspect products from another applicant, the second applicant should not submit the report to FDA unless there is follow up information. This appears to be a new requirement. Previously, the applicant was required to report any information it received where one of its products was considered suspect, unless it came from a regulator. Please clarify.
23	932-936	Two or more marketers of a product	Agency should provide guidance on when the clock starts for 15 day report for these type of arrangements, e.g., if company A is the reporting entity, does clock start when it receives the report or when company B does?
25	1021-1023	Abbreviations for information that is not available	This is extremely confusing. The distinctions between NI and UNK are not clear.
30	1243-1244	Submission of ANDA 15 day reports	Is the requirement to submit a single copy new? I thought this was only applicable to those drugs without an approved application (I.e. 310.305)

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