LIGAND
PHARMACEUTICALS

Regulatory Affairs and Compliance

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May 11, 2001

Re: Docket No. 01D-0056
Comments on Draft Guidance for Industry

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

Dear Sir or Madam:

Reference is made to the draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, published Monday, March 12, 2001, in the U.S. Federal Register, Vol. 66, No. 48, Docket No. 01D-0056.

Ligand Pharmaceuticals Inc., appreciates this opportunity to submit comments (Attachment 1) for the Agency's consideration as the Guidance proceeds towards finalization. Ligand's comments include some general points related to the Agency's philosophy, as we have interpreted it from the Guidance, as well as several specific comments and suggested changes that are organized by page and line number.

We appreciate your consideration of our comments. If you have any questions, please contact the undersigned or Ann M. Jenkins at 858-550-7600 (fax 858-550-1827).

Sincerely,

Howard T. Holden

Howard T Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance

AMJ/lmc

Enclosure

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Comments on Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (March 2001) [Docket No. 01D-0056]

Overall Comment: The Respondent suggests that the word "unexpected" be replaced with "unlabeled," when referring to adverse events that are listed in a product's labeling. "Unexpected" should be used to refer to adverse events listed in the Investigator's Brochure and/or other written material describing a drug not yet approved.

Item No.	Guidance Citation
1.	Page 6, Line 214 *Adverse Experiences that are Serious and Unexpected from All Sources (Domestic and Foreign)* The Respondent requests clarification on reporting serious and unexpected adverse experiences from postmarketing studies. Are these events to be summarized in the Periodic Safety Update Report (PSUR)?
2.	Page 8, Lines 305-6 *Data Elements to Include in a Postmarketing Individual Case Safety Report* The Respondent requests the text be revised to read as follows: "4. An adverse experience or fatal outcome" and delete "suspected to be due to the suspect drug or biological product." Spontaneous AE reports usually require a temporal association to the use of a suspect drug or biological product; a causal association is not currently required. The draft guidance wording implies that the AE need not be reported if it is thought NOT to be due to the drug or biological product.
3.	Page 9, Lines 332-334 *Data Elements to Include in a Postmarketing Individual Case Safety Report* Suggest deleting "implied causality." Lines 305-6 and 332-334 should be consistent.
4.	Page 10, Line 399 *Supporting Documentation* The Respondent requests that the Agency recognize that supporting documentation may be difficult to obtain due to the confidentiality of records.
5.	Page 11, Line 405 *Supporting Documentation* Respondents should delete patient names from any records submitted to the FDA.

Item No.	Guidance Citation
6.	Page 11, Line 433 *Timing of Postmarketing Periodic Reports* The Respondent notes that compliance with the requirement for submission of quarterly reports within 30 calendar days of the last day of the reporting quarter. However, line 1371 specifies that a similar report, a PSUR, is to be submitted within 60 days (consistent with ICH guidelines). Please also note that ICH guidelines are for semi-annual, not quarterly submission of periodic reports. Sixty days is a more reasonable time frame in which to compile a periodic report. This comment also applies to Item No. 17, below.
7.	Page 13, Line 505 *Content of a Postmarketing Periodic Report* The Respondent requests an explanation of how increased reporting frequency is to be determined.
8.	Page 16, Line 629 *Content of Follow-up Reports* The Respondent requests clarification on how to identify inaccurate information. The Respondent's database does not permit the use of asterisks and underlining. The Respondent's interpretation of this section is to re-write the report to correct the inaccurate information. Should the relevant information from initial report be combined with the new information into an integrated narrative or can additional paragraphs be added? Sometimes if just the correct information is mentioned, it is not clear which parts of the previously provided information were incorrect.
9.	Page 16, Line 652 *Reporting Considerations* The Respondent requests clarification on the change in status of a 15-Day report. Are non-serious, labeled events in temporal association with AEs in the initial 15-Day report, reported as follow-up 15-Day reports? Should further information such as new concomitant medications, discharge data, new data from a diagnostic test (e.g., negative MRI results) be submitted in a follow-up 15-Day report?
10.	Page 17, Line 661-5 *Reporting Considerations* Per the Draft Guidance, for an AE associated with an initial AE, a follow-up report should be submitted (track by patient). For a new AE not associated with an initial AE, an initial report with a new manufacturer report number should be submitted (track by AE). The Respondent notes that it is confusing to use both methods, tracking by AE and tracking by patient and requests that the Agency consider using one method.

Item No.	Guidance Citation
11.	Page 17, Line 681 *Reporting Forms (Item G4)* The Respondent notes that if the date the follow-up information was received is used, then the date of the initial report is lost. The Respondent requests clarification that the date in Item G4 also denotes the start of the 15-Day clock. Also see page 10, lines 368-370 – The initial contact date is lost if all four basic elements not known at that time.
12.	Page 18, Line 738 *Scientific Literature Reports* For serious, unexpected adverse experiences reported in scientific literature, patients often are not identified. Should the Respondent attempt to contact the author for additional information? And, if the information is not obtained, should the Respondent still submit a report, even if it lacks one or more of the four required data elements?
13.	Page 19, Line 779 Postmarketing, Clinical Trial or Surveillance Studies If reports of suspected averse experiences obtained from patient support programs and disease management programs are to be handled as if they were study reports and not as spontaneous reports, please clarify where these reports would be submitted and in what format.
14.	Page 20, Line 794 *Postmarketing, Clinical Trial or Surveillance Studies* The Respondent notes that the Agency expects the study blind to be broken internally. However, this will not be communicated to the Investigator.
15.	Page 20, Line 815 *Death Reports* The Respondent notes that any death, including disease progression, should be reported as a 15-Day Report. Does this include death due to unrelated trauma? Please clarify.
16.	Page 24, Line 993 *Coding of Adverse experiences in Individual Case Safety Reports* The Respondent requests clarification on when the use of MedDRA will be required.
17.	Page 33, Line 1371 *Submission Date and Frequency for PSUR Reports* See comment for Item No. 6, above.