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Drug Development & Technology
Division of Berlex Laboratories, Inc.

300 Fairfield Road
Wayne, NJ 07470-7358
Telephone: (973) 694-4100

10 May 2001

Dockets Management Branch (HGA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 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Re: Docket No. 01D-0056-FDA Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products including Vaccines (66 Federal Register 14391; March 12, 2001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 or Madam:

Berlex Laboratories, Inc. appreciates the opportunity to provide comments on the draft guidance.

Berlex Laboratories, Inc. is the US subsidiary of Schering AG, Germany, an international pharmaceutical company committed to bringing to the market beneficial preventive, diagnostic and therapeutic medicines in the fields of Dermatology, Diagnostic Imaging, Female Healthcare, Therapeutics and Oncology.

The comments have been prepared by the senior staff of the Medical Affairs and Drug Safety Department, which manages approximately 16,000 adverse experience reports per year. Numbering of the specific comment section corresponds to the numbering used in the draft guidance document.

Section IV – WHAT DO I REPORT?

B. Data elements to Include in a Postmarketing Individual Case Safety Report:

Lines 326-330 also 747-751: *Guidance is provided regarding what constitutes an identifiable patient. Examples are given for "an elderly woman or a young man". Also for "six patients" the guidance states to create six reports.*

C6

01D-0056

- Please provide additional guidance on an identifiable patient when a reporter states '50 patients' without further identifiers, or 'between 20 and 30 patients', without further identifiers.
- Does the Agency recommend a cut-off limit for individual MedWatch reports in this scenario? We propose that in cases where the reporter fails to provide any identifiable patients, but states that '50 patients' or 'between 20 and 30 patients' (without further identifiers) experienced adverse event X that the preparation of a ***single*** "summary Medwatch form" detailing the known aspects of the report be considered sufficient.

V. TYPE OF REPORTS

A. 15-Day reports of Serious, Unexpected Adverse Experiences

1. Determination of 15-Day Reporting Period.

Lines 364-371: Discusses the four basic elements of a report with a serious outcome. *The date the company has knowledge of these four basic elements should be entered into item G4 of FDA Form 3500A or Box 25 of VAERS form (i.e., this date represents Day 0 of the 15-day time clock).*

- Please comment on how to correctly enter the dates when the four basic elements of a non-serious adverse experience are known and the case is scheduled to be reported in the next Periodic report, but then additional information is received which upgrades the report to serious. Is the "initial reporting date" the date of the receipt of the 4 elements or the date of receipt of the information making the case serious?

Line 371:

Clarification that the day of receipt of the four data elements is Day 0 for the purposes of calculating reporting timeframes is appreciated.

Line 373:

Allowance for submitting 15-day reports that are due on weekends to be submitted on the first working day after the weekend or US Federal holiday is appreciated.

2. Supporting documentation

Lines 399-401: *FDA encourages applicants to include relevant hospital discharge summaries and autopsy reports/death certificates.....*

- Attaching supporting documents as a routine practice places an extra burden on the applicant. All relevant information is already summarized within the MedWatch form, kept on file, and available upon request

Lines 406-407: *Applicants should submit copies of these documents to the Agency within 5 calendar days after receipt of the request.*

- We request the Agency to revise this to **15** calendar days, for all applicants, as more time may be needed to obtain these documents from licensing partners and foreign affiliate offices, where translation may be necessary.

B. Periodic Reports

2. Contents of a Postmarketing Periodic Report

a. Section 1: Narrative summary and analysis

Lines 486-571: *Re-orders the presentation format of the Periodic Report*

- This presents differences in current format and may require re-programming, which adds an additional burden to companies.

Line 538:

- Please clarify if the agency wants a list of all studies or the list of studies initiated for safety concerns.

Lines 583-787:

- The guidance encourages applicants to attach relevant hospital discharge summaries and other reports for serious expected reports. This will pose a programming burden for the applicants to incorporate page numbering of documents outside the AE database when generating a Periodic Report. We suggest that all supporting documents are kept on file and available upon request.

C. Follow-up Reports

1. Content of Follow-up Reports

D. Lines 624-631: *A follow-up report should provide a complete picture of the current understanding other the adverse experience Relevant information from the initial report should be combined with the follow-up..... All new information including correction of previously submitted inaccurate information should be highlighted (e.g., with an asterisk, underlined).*

- Berlex is concerned that this will present difficulty in tracking new information vs. follow-up information in regards to receipt date. Also, this may require reprogramming, as most safety databases cannot support the highlighting.

2. Reporting considerations

Lines 660-667:

Berlex appreciates the clarification of when to create a follow-up report vs. creating a new initial report for adverse experiences occurring in the same patient.

3. Reporting Forms

Lines 679: Item G3 – *Mark health professional if at any time a health professional provided information for the report.*

- We wish to comment on the fairly common situation in which an initial reporter consumer/patient provides hospital records which describe the occurrence and treatment of an adverse experience but do not mention any suspect product. Does this qualify as "medically confirmed"?

VI. Special reporting situation

A. Scientific Literature Reports

Lines 740-742: *Applicants can use literature search services (e.g., Weekly Reactions) to identify adverse experience in the scientific literature……*

- Please clarify if utilizing only this one literature service will be considered sufficient monitoring of the published adverse experience case reports in the scientific literature.

Line 743: *It is not sufficient to submit only abstracts of articles.*

- Berlex agrees that every attempt to obtain the full article must be undertaken. However, there may be times when the 4 elements of an adverse experience report are identifiable in the abstract, but the full article is not available, especially when an article requires translation. In order to meet 15-day reporting deadlines, we suggest that an initial report can be submitted with only the abstract and that a follow-up report be submitted upon receipt of the full (translated) article.
- In addition, there are scientific publications in which only abstracts are presented and published.

Line 747-750: *Thus if an article describes six patients that experience a given serious, unexpected adverse experience, six FDA Form 3500As should be completed.*

This is a situation that occurs quite frequently in literature reports of investigator initiated study results, and further guidance is much appreciated.

- Does the statement "six patients experienced neurotoxicity" - without further descriptors of the patients or the neurotoxicity meet the criteria of "**describing**" six patients in a literature report?
- For general statements like these is there an upper limit of when to create individual MedWatch forms? For example: Would the statement '30 out of 100 patients developed neurotoxicity' - without any further information in the article, result in 30 individual MedWatch forms? Are summary reports acceptable in this situation?
- For published reports of investigator initiated studies, when the authors list all serious adverse experiences that occurred during the course of the study, without a causality discussion (e.g. 20 of 100 patients experienced grade IV renal dysfunction) is the temporal association sufficient to require an individual case submission? We propose that in the future, these submissions would be more appropriately reported to the NDA annual or the narrative summary section of the periodic report or PSUR.

Lines 762-765: *Reports of serious, unexpected adverse experience described in the scientific literature should be submitted for products that have the same active moiety as a product marketed in the United States. This is true even if the excipient, dosage forms, strength, routes of administration, and indications vary.*

- Please clarify if an applicant is responsible for submitting literature reports originating from another country, in which the applicant does not market the formulation described in the article.

Lines 767-770: *When a serious, unexpected adverse experience is based on a foreign language article or manuscript, the applicant should translate the publication into English promptly. The original article or unpublished scientific paper and translation should be attached to the submitted FDA Form 3500A.*

- Berlex agrees that every attempt should be made to have a literature report of a serious unexpected adverse experience translated within 15 calendar days. However, it may not always be possible to accomplish this in the 15-day time period, especially when the submission clock has started because the 4 elements of an AE report are apparent in the English abstract. As a result, we propose that in these situations the initial report may be submitted with the abstract and the original non-English article attached to FDA Form 3500A, with a follow-up report submitted with the full translated article within 15 calendar days of receipt of the translation.

B. Postmarketing, Clinical Trial, or Surveillance Studies

Lines 779-781: *Reports of suspected adverse experiences obtained from company sponsored patient support programs and disease management programs should be handled as if they were study reports and not as spontaneous reports.*

- Please clarify that all contacts between patients and company sponsored support program personnel are to be handled as phase IV study AE reports.

Lines 794-799: *Regarding breaking of the blind for serious, unexpected adverse experience.*

- Please comment on whether this refers only to serious unexpected, causally related events.

G. Information on the Internet

Lines 848-855: *If an applicant becomes aware of an adverse experience on an Internet site that it does not sponsor, the applicant should review the adverse experience and determine if it should be reported to the FDA.*

- Please provide further guidance regarding what constitutes an identifiable reporter for adverse experiences identified on Internet sites, such as a chat room nickname or an e-mail address.

H. Pediatric Patients

Line 865-867: *Follow-up reports for the infant should be considered follow-up to the initial report; follow-up for the mother should be submitted as a new initial individual case safety report on a separate FDA Form 3500A.*

- Please clarify how to report if a congenital anomaly is detected in a fetus, should this also be a separate case report from the mother? How will the age of the fetus be reported?
- Please clarify how to report in situations involving a fetus or embryo when the histology after abortion shows an abnormality.

K. Multiple Suspect products.

Lines 898-902: ..... *If each product is equally suspect, the report should be submitted to the product first in alphabetical order.*

- Please clarify if this is for product Trade name or generic name.

Lines 906-909: *However, if one suspect product is a licensed non-vaccine biologic and the other is a licensed vaccine, separate reporting forms should be submitted…*

- The guidance states using separate forms (VAERS and FDA Form 3500A) for equally suspect licensed vaccines and licensed non-vaccine biologics. Please clarify that this is also suggested for equally suspect licensed vaccines and a drug product.

Lines 911-918: New guidance on handling reports from another applicant, which has already submitted our product as a multiple suspect. *The other applicant should not submit to the FDA information originally submitted to the Agency by the first applicant.*

- The second applicant cannot ensure that the first applicant has actually submitted the report to the Agency. Please clarify that the first applicant is held accountable for submitting the report to the agency.
- Please clarify if the second applicant is expected to include the initial report in the Periodic Report line listings, tabulations and narrative discussion.

Appendix A: Glossary Definitions: 1446-1447: Definition of dechallenge. Berlex recommends adding: Withdrawal ***or dose reduction*** of a suspect product from a patient's therapeutic regimen.

Lines 1471-1472: Definition of Initial Reporter

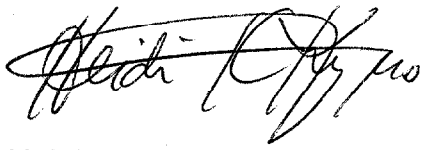
This has been an ongoing question among many applicants and clarification will be most appreciated.

- If the initial reporter is a consumer and medical confirmation is then obtained before the report has been submitted to the Agency, should the consumer or the Health Care Professional appear in Box E?
- If the initial reporter is the consumer/patient who then provides copies of hospital records (without the health professional's knowledge) will the initial reporter remain the consumer/patient, even though FDA Form 3500A box G3 will be marked health professional?
- If the initial reporter is a health professional who provides limited information and then complete information is obtained from another health professional before the report is submitted to the Agency, which reporter information is entered into Box E as initial reporter?
- Due to patient privacy concerns, and regulations which state that the names and addresses of individual patients should not be included in reports, if an initial reporter is a consumer (the patient or a relative) the reporter's identifying information is not displayed on FDA form 3500A. We request that the guidance state that this is acceptable practice. For privacy concerns regarding foreign reports, is it acceptable not to include reporter information?

- Please clarify how to handle the following: Another company sponsors a study with their drug, our product is a concomitant medication (not a study drug) and is mentioned as a second suspect drug by the investigator. Would this be considered a spontaneous report? Should report source "study" also be utilized?

Thank you for the opportunity to comment on the draft guidance. We look forward to the Agency's response.

Yours truly,



Heidi K. Krenz, M.D.
Director, Medical Affairs and Drug Safety

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