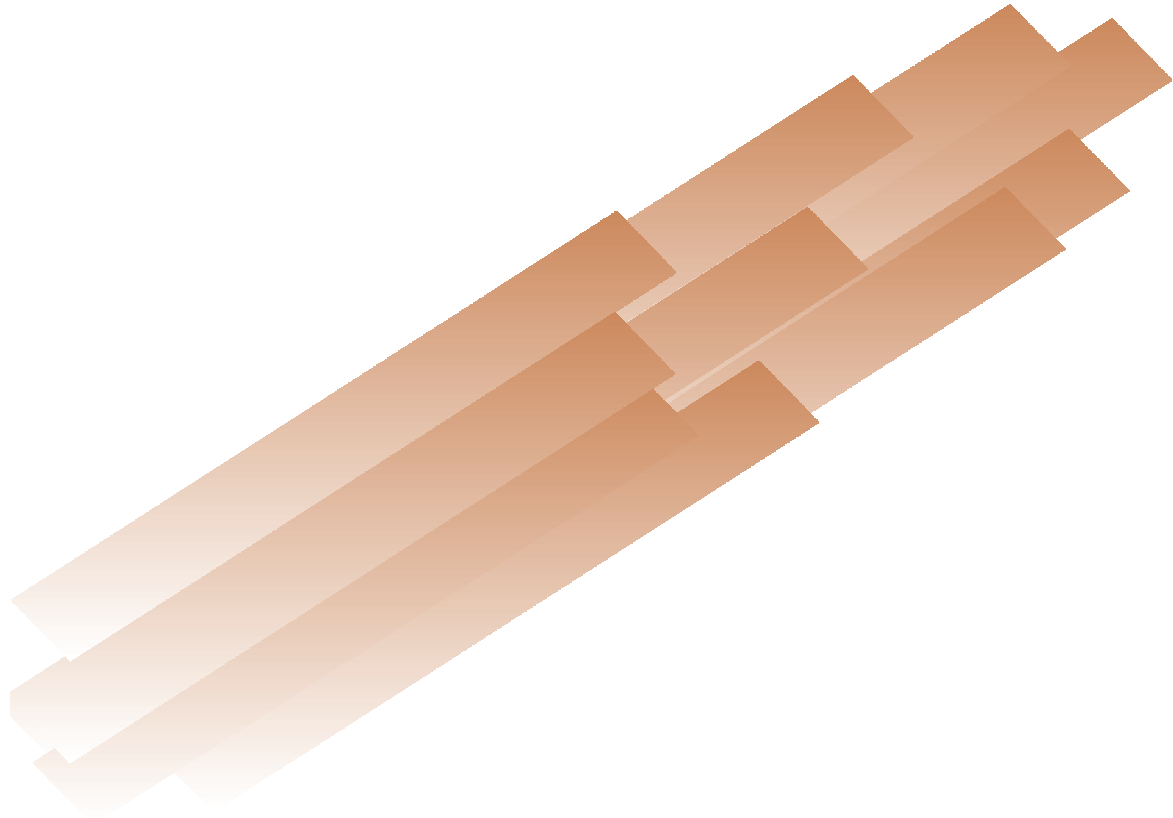


Guidance for Industry

Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
August 1997
CLIN4**

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GUIDANCE FOR INDUSTRY¹

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I. INTRODUCTION

The FDA has undertaken a major effort to clarify and revise its regulations regarding pre- and postmarketing safety reporting requirements for human drug and biological products. With regard to the postmarketing safety reporting regulations for human drug and licensed biological products, the Agency published a proposed rule in the *Federal Register* of October 27, 1994 (59 FR 54046), to amend these requirements, as well as others, to implement international standards, and to facilitate the reporting of adverse experiences. The FDA is still considering comments submitted in response to this proposed rule and will be finalizing the proposed amendments based on those comments as well as on recommendations developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS).

In response to the President's regulatory reinvention initiative, which directed departments and agencies to eliminate or modify regulations that are outdated or otherwise in need of reform, the FDA recently published a final rule in the *Federal Register* (62 FR 34166; June 25, 1997). This final rule revokes the postmarketing safety reporting requirement to submit expedited increased frequency reports for human drug and licensed biological products.

At this time, the Agency is considering recommendations recently developed by ICH and plans to propose additional amendments to its postmarketing safety reporting regulations. Throughout this effort, the Agency intends to develop guidances for industry to provide recommendations on how industry can best fulfill the postmarketing safety reporting requirements. The FDA plans to prepare a single consolidated guidance document on this topic once the process is concluded.

Over the years, changes in marketing practices in the United States have led to expanded contacts between drug and biologics manufacturers and consumers. This has resulted in the acquisition of new types of safety information not previously obtained by industry. In addition, the FDA has noted an increase in the number of individual case reports of adverse experiences that are

¹This guidance has been prepared by the Adverse Drug Reaction Reporting Regulations Working Group in the Center for Drug Evaluation and Research (CDER) in collaboration with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on reporting of certain postmarketing adverse experiences for human drug and licensed biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

submitted to the Agency with insufficient data to begin the evaluation of a report. Overall, the largest increase has been in the number of reports submitted on adverse experiences classified as *nonserious and labeled* (i.e., listed in the approved labeling for marketed products).

This guidance for industry has been developed to clarify what information should be obtained before an individual case of an adverse experience should be considered for submission to the FDA and how safety information from solicited contacts with patients should be handled. The guidance also informs applicants and licensed manufacturers that the FDA is willing to entertain waiver requests for periodic submission of individual case reports for adverse experiences that are determined to be nonserious and labeled. The Agency believes that the recommendations in this guidance document will improve the quality of postmarketing safety reports and decrease the industry's current safety reporting burden without jeopardizing public health.

This guidance document should be used in conjunction with CDER's *Guideline for Postmarketing Reporting of Adverse Drug Experiences* (March 1992) and CBER's *Guideline for Adverse Experience Reporting for Licensed Biological Products* (October 1993). Hard copies of the guidances of March 1992 and October 1993 are available from CDER's Drug Information Branch and CBER's Office of Communication, Training and Manufacturers Assistance, respectively (addresses above). Electronic versions of these guidances are also available on the Internet at <http://www.fda.gov/medwatch/report/mfg.htm>.

II. DATA ELEMENTS FOR A SAFETY REPORT

Applicants² of approved new drug applications (NDA), abbreviated new drug applications (ANDA), and antibiotic applications, manufacturers³ of marketed prescription drugs for human use without approved NDAs or ANDAs, and licensed manufacturers⁴ of approved biologic product license applications are required to report adverse experiences to the FDA under 21 CFR 310.305, 314.80, 314.98, and 600.80. Before considering *any* clinical incident for submission to the FDA in an expedited or periodic safety report, applicants, manufacturers, and licensed manufacturers should have knowledge of the following four data elements:

- a. an identifiable patient;
- b. an identifiable reporter;

² For purposes of this guidance, the term *applicant* includes manufacturers, packers, and distributors.

³ For purposes of this guidance, the term *manufacturer* includes packers and distributors.

⁴ For purposes of this guidance, the term *licensed manufacturer* includes manufacturers, packers, distributors, shared manufacturers, joint manufacturers, or any other participant involved in divided manufacturing.

- c. a suspect drug or biological product; and
- d. an adverse event or fatal outcome.

In other words, if any of these basic elements remain unknown after being actively sought by the applicant, manufacturer, or licensed manufacturer, a report on the incident should not be submitted to the FDA because reports without such information make interpretation of their significance difficult, at best, and impossible, in most instances. The applicant, manufacturer, and licensed manufacturer should maintain records of their efforts to obtain the basic elements for an individual case in their corporate drug or biological product safety files. If reports lacking any of the four basic elements are submitted to the FDA, they will be returned to the reporter marked "insufficient data for a report." If the reporter is an applicant, manufacturer, or licensed manufacturer, they also will be reminded to actively seek the basic elements for the report and to maintain a record of such efforts.

With regard to *an identifiable patient*, reports of the type "some patients got anaphylaxis" should be excluded until further information about the patients is obtained; a report stating that "an elderly woman had anaphylaxis" or "a young man experienced anaphylaxis" should be included because there is enough information to suspect that specific patients were involved. Patients should not be identified by name or address; instead, the applicant, manufacturer, and licensed manufacturer should assign a code (e.g., patient initials) to each report. An *adverse event* should at a minimum consist of signs (including abnormal laboratory findings), symptoms, or disease diagnosis for purposes of reporting. Thus, a report stating that a patient "experienced unspecified injury," or a patient "suffered irreparable damages" should not be included until more specific information about the adverse event can be determined. With regard to *fatal outcome*, the FDA expects applicants, manufacturers, and licensed manufacturers to submit reports of patient deaths even if the adverse event is unknown.

The four basic elements are consistent with international harmonization initiatives. For more information on these initiatives, refer to section III.B.3 of the International Conference on Harmonization; *Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (ICH E2A document; 60 FR 11284; March 1, 1995) and the definition of *Minimum Standard of Information* in the final report of CIOMS Working Group I (*International Reporting of Adverse Drug Reactions*, 1990) or the definition of *CIOMS Reportable Case Histories (CIOMS Report)* in the final report of CIOMS Working Group II (*International Reporting of Periodic Drug-Safety Update Summaries*, 1992).

III. INDIVIDUAL CASE REPORTS BASED ON SOLICITED INFORMATION

The FDA has determined, for purposes of postmarketing safety reporting under 21 CFR 310.305, 314.80, 314.98, and 600.80, that information concerning potential adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., company-sponsored patient support programs, disease management programs) should be handled as safety

information obtained from a postmarketing study. Applicants, manufacturers, and licensed manufacturers should not report safety information obtained through these types of patient contacts unless the adverse event meets the regulatory definitions of *serious* and *unexpected* and there is a reasonable possibility that the drug or biological product caused the adverse experience (see 21 CFR 310.305(c)(1)(ii), 314.80(c)(2)(iii), 314.80(e), 600.80(c)(2)(iii), and 600.80(e)).

IV. INDIVIDUAL CASE REPORTS OF NONSERIOUS, LABELED ADVERSE EXPERIENCES

The FDA encourages applicants and licensed manufacturers to submit requests to the Agency (address below), under 21 CFR 314.90(a) and 600.90(a), to waive the requirement to submit Form FDA-1639 or FDA Form 3500A to the FDA for each adverse experience that is determined to be both nonserious and labeled (21 CFR 314.80(c)(2) and 600.80(c)(2)). As part of this waiver request, applicants and licensed manufacturers should indicate that individual case reports of adverse experiences with the four basic elements (see section II) that are determined to be both nonserious and labeled would be held in their corporate drug or biologic product safety files. Applicants and licensed manufacturers should also indicate that upon request by the FDA, they would submit one or more of these reports to the Agency within five calendar days after receipt of the request. As described in the guidances of March 1992 and October 1993, the FDA expects applicants and licensed manufacturers to continue to include in their periodic reports a listing by body system of all adverse experience terms and counts of occurrences for nonserious, labeled adverse experiences.

At this time, the FDA does not intend to grant licensed manufacturers waiver requests for new biological molecular entities within one year of licensure or for blood products, plasma derivatives, or vaccines. The Agency believes that it is important to continue periodic review of all reports of adverse experiences for these products to identify safety problems due to lot-to-lot variations and to monitor the safety of new biological products.

Applicants of marketed human drug products should submit written waiver requests, under 21 CFR 314.90(a), to:

Dr. Murray Lumpkin
Deputy Center Director for Review Management
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-2
Rockville, MD 20857

Licensed manufacturers of human licensed biological products should submit written waiver requests, under 21 CFR 600.90(a), to:

Dr. Marcel Salive
Division of Biostatistics & Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, HFM-220
Rockville, MD 20852-1448