Guidance for Industry

Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

DRAFT GUIDANCE

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For questions on the content of the draft document contact (CDER) Min Chen, 301-827-3169 (phone); 301-827-5190 (fax), or (CBER) Miles Braun, 301-827-3974 (phone); 301-827-3529 (fax).

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)
March 2001

01D-0056

GDL 1

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Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4570
Internet at http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448
(Fax) 1-888-CBERFAX or 301-827-3844
(Voice Information) 1-800-835-4709 or 301-827-1800
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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)
March 2001

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Guidance for Industry[1]

Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

This draft guidance, when finalized, represents the Food and Drug Administration's (FDA's) current thinking on this topic. 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 requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist applicants and other responsible parties in fulfilling the FDA's ***existing*** postmarketing safety reporting requirements for human marketed drug and biological products at 21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81.[2] Under these regulations, postmarketing safety reports must be submitted to the Agency for the following:

1. Serious and unexpected adverse experiences from all sources (domestic and foreign)

2. Spontaneously reported adverse experiences that occur domestically and that are:

   - Serious and expected
   - Nonserious and unexpected
   - Nonserious and expected

A. What Does This Guidance Discuss?

This guidance discusses the following postmarketing reports:

[1] This guidance has been prepared by FDA's Safety Reporting Regulations Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

[2] The FDA is planning to propose revisions to these regulations (see section II.C in this guidance). As these proposals are finalized the Agency will revise this guidance to provide industry with assistance in fulfilling the new regulatory requirements.

- 15-Day Reports of Serious, Unexpected Adverse Experiences
- Periodic Reports
- Followup Reports
- Distribution Reports for Biological Products Including Vaccines

This guidance addresses the following regulations for the following products.[3]

Regulation	Product
21 CFR 310.305	Prescription drugs marketed for human use without a an approved application
21 CFR 314.80	Human drugs with approved NDAs
21 CFR 314.98	Human drugs with approved ANDAs
21 CFR 600.80	Human biological products with approved BLAs
21 CFR 600.81	Human biological products with approved BLAs

If you believe the procedures described in this guidance are inapplicable to a particular product or that other procedures are appropriate, you should discuss the matter with the Agency to ensure that your procedures comply with applicable statutes and regulations.

B. What Does This Guidance *Not* Discuss?

This guidance does *not* discuss the following:

- IND Safety Reports (21 CFR 312.32)[4]
- Safety Update Reports for Drugs (21 CFR 314.50(d)(5)(vi)(b))
- Approved NDA Annual Reports (21 CFR 314.81(b)(2))
- Approved BLA Annual Reports (21 CFR 601.28)

This guidance does *not* apply to the following products:

- In vitro diagnostic products
- Whole blood or its components
- Product manufacturing defects (unless the defect is associated with an adverse experience in humans)

C. Good Guidance Practices

The Agency's good guidance practices (GGPs) regulation[5] does not allow the use of mandatory language in guidances unless it is used to describe regulatory requirements. In

[3] NDA means new drug application, ANDA means abbreviated new drug application, and BLA means biologics license application

[4] IND means investigational new drug application

most guidances, we provide the related cite whenever mandatory language is used to indicate the basis for the use of such language. This guidance discusses regulatory requirements in great detail. To avoid including the same regulatory cites repeatedly and to make the guidance user friendly, we will indicate at the beginning of those sections that include extensive discussions of regulatory requirements which cites are particularly relevant. The use of mandatory language (e.g., *must*, *have to*, *required*) will signify a regulatory requirement while the use of words such as *should* and *recommend* will indicate Agency policy.

II. BACKGROUND

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. To date, the Agency has issued a number of final rules and guidances for industry on this topic; several proposed rules are under development.

A. Final Rules

- Expedited Safety Reports for Human Drug and Biological Products

In the *Federal Register* of October 7, 1997 (62 FR 52237), the FDA published a final rule amending its regulations for expedited safety reporting to implement certain definitions, reporting periods, and formats recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These recommendations are discussed in the ICH guidance *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*; March 1, 1995.

- Postmarketing Expedited Increased Frequency Reports for Human Drug and Biological Products

In the *Federal Register* of June 25, 1997 (62 FR 34166), the FDA published a final rule revoking requirements to submit postmarketing increased frequency reports to the Agency in an expedited manner for human drug and biological products.

B. Guidances

With regard to postmarketing safety reporting for human drug and biological products, the FDA has made three final guidances available:

- *Postmarketing Reporting of Adverse Drug Experiences* (March 1992)

[5] The Agency's regulation on good guidance practices published on September 19, 2000 (21 CFR 10.115; 65 FR 56468).

- *Guideline for Adverse Experience Reporting for Licensed Biological Products* (October 1993)

- *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report* (August 27, 1997).

When finalized, this guidance will replace the three guidances listed above and will reflect the new regulatory requirements in the final rules of June 25, 1997, and October 7, 1997.

C. Proposed Rules

The Agency currently is in the process of developing proposed rules to further amend its safety reporting requirements for human drug and biological products. Many of the provisions in these proposed rules will be based on recommendations developed by ICH. For instance, the Agency is planning to propose additional amendments to its expedited safety reporting regulations based on the ICH E2A guidance.

In addition, the FDA is planning, as indicated in the final rule of October 7, 1997, to repropose amendments to its postmarketing periodic safety reporting requirements that were initially proposed in the *Federal Register* of October 27, 1994 (59 FR 54046). The new postmarketing periodic safety reporting proposals will be based on recommendations in the ICH guidance *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* (May 19, 1997).

The Agency also is planning to issue a proposal requiring the electronic submission of postmarketing safety reports consistent with recommendations developed by ICH.[6]

As these proposed rules are finalized, this postmarketing safety reporting guidance for human drug and biological products will be revised to provide industry with assistance in fulfilling the new regulatory requirements.

III. WHO MUST REPORT

According to the regulations, the following persons have postmarketing safety reporting responsibilities:

- *Manufacturers* are required to submit postmarketing expedited safety reports to the FDA for prescription drug products marketed for human use without an approved application (§ 310.305).

[6] See advance notice of proposed rulemaking on electronic reporting of postmarketing adverse drug reactions; request for comments, 63 FR 59746, November 5, 1998.

- *Applicants* (individual or corporate entity that holds an NDA or ANDA) are required to submit postmarketing safety reports to the FDA for human drug products with approved NDAs (§ 314.80) and ANDAs (§ 314.98).

- *Licensed manufacturers* (individual or corporate entity that holds a BLA) are required to submit postmarketing safety reports to the FDA for human licensed biological products with approved BLAs (§§ 600.80 and 600.81).

- Any person whose name appears on the label of a marketed drug as its packer or distributor (§ 310.305(c)(1)(i)) or manufacturer, packer, or distributor (§ 314.80(c)(1)(iii)) has postmarketing safety reporting responsibilities.

- Any person whose name appears on the label of a licensed biological product as its manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing has postmarketing safety reporting responsibilities (§ 600.80(c)(1)(iii)).

For the purposes of this guidance, the term *applicant* includes all persons with postmarketing safety reporting responsibilities under §§ 310.305, 314.80, 314.98, 600.80, and 600.81.

According to the regulations at §§ 310.305(d), 314.80(f), and 600.80(f), if an applicant becomes aware of a reportable adverse experience, the applicant is responsible for preparing a postmarketing safety report and submitting it to the FDA. Applicants should not assume that their responsibilities are fulfilled if they ask the person who pointed out a reportable adverse experience to submit a safety report to the FDA.

IV. WHAT DO I REPORT?

The following paragraphs discuss the types of adverse experiences that must be reported to the FDA under §§ 310.305, 314.80, 314.98, and 600.80. This section also describes the minimum data elements that should be included in an individual case safety report.

An *adverse experience* is any undesirable event that is associated with the use of a drug or biological product in humans whether or not considered product-related by the applicant.[7] An *individual case safety report* describes an adverse experience(s) for a patient or subject. Individual case safety reports of domestic adverse experiences for marketed human drug and biological products, except vaccines, must be submitted to the FDA on FDA Form 3500A; a Vaccine Adverse Event Reporting System (VAERS) form must be used for adverse experiences associated with the use of vaccines. Individual case safety reports of foreign adverse experiences can be submitted on FDA Form 3500A

[7] See Appendix A for definition of *adverse experience*. (See also □□ 310.305(b), 314.80(a) and 600.80(a).)

(VAERS form for vaccines) or, if preferred, on a Council for International Organizations for Medical Sciences (CIOMS) I form. See section VIII in this guidance for discussion of reporting formats for individual case safety reports.

A. Type of Adverse Experiences

1. Adverse Experiences that are Serious and Unexpected from All Sources (Domestic and Foreign)[8]

Serious and unexpected adverse experiences from all sources, whether domestic or foreign, must be submitted to the FDA. Possible sources include, for example, scientific literature, postmarketing studies, or commercial marketing experience.

Scientific literature reports include published and unpublished scientific papers that are known to the applicant (see section VI.A in this guidance for reporting of adverse experiences from the scientific literature).

Postmarketing studies include in vitro, animal, clinical, and epidemiological or surveillance investigations (see section VI.B in this guidance for reporting of adverse experiences from studies). Adverse experiences from studies must only be submitted to the FDA if the applicant believes that there is a reasonable possibility that the drug or biological product caused the adverse experience (see §§ 310.305(c)(1)(ii), 314.80(e)(1) and 600.80(e)(1)).

2. Other Spontaneously Reported Adverse Experiences (Domestic Only)[9]

Adverse experiences occurring in the United States from commercial marketing experience must be submitted to the FDA if they are spontaneously reported to applicants and are:

- serious and expected
- nonserious and unexpected, or
- nonserious and expected

Applicants can request a waiver of the requirement to submit individual case safety reports of nonserious, expected adverse experiences for drugs and certain biological products (see section XI.A in this guidance on waiver requests).

3. Serious Adverse Experiences[10]

[8] The requirements for reports of serious, unexpected adverse experiences can be found in §§ 310.305(c), 314.80(c)(1) and 600.80(c)(1).

[9] The requirements for reports describing these adverse experiences can be found in §§ 314.80(c)(2) and 600.80(c)(2).

The outcome of an adverse experience must be determined before a report can be identified as *serious*. A serious report must have one or more of the following outcomes:

- Death
- Life-threatening adverse experience
- Initial inpatient hospitalization or prolongation of hospitalization
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event based upon appropriate medical judgment that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious.

A patient admitted to a hospital for 1 or more days as a result of an adverse experience, even if released on the same day, would qualify for the *initial inpatient hospitalization* outcome. An emergency room visit that results in admission to the hospital would also qualify for the *initial inpatient hospitalization* outcome. However, emergency room visits that do not result in admission to the hospital would not qualify for this outcome and, instead, should be evaluated for one of the other outcomes in the definition of *serious* (e.g., life-threatening adverse experience, important medical event).

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.

Important medical events would include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Applicants should mark the "other" box in item B2 of FDA Form 3500A for adverse experiences identified as *important medical events*.

Applicants should actively seek the outcome for a suspected serious adverse experience reported to them. If unable to initially determine the outcome for an adverse experience, an applicant should continue to actively seek information in an attempt to determine an outcome. For a serious adverse experience that was not initially reported to the applicant by a health care professional (e.g., report from a consumer), the applicant should actively pursue contacting the health care

[10] See Appendix A for definition of *serious adverse experience*. (See also §§ 310.305(b), 314.80(a) and 600.80(a).)

277 professional associated with the care of the patient to gather further medical
278 perspective on the case.
279
280 *4. Unexpected and Expected Adverse Experiences*[11]
281
282 The current FDA-approved labeling for the human drug or biological product should
283 be used as the reference document to determine whether an adverse experience is
284 *unexpected* or *expected*. An adverse experience would be considered *unexpected*
285 if it is not included in the product's current FDA-approved labeling and *expected* if it
286 is included in this document.
287
288 *5. Spontaneous Report*[12]
289
290 Spontaneous reports are unsolicited communications from individuals (e.g., health
291 care professional, consumer) to applicants that concern adverse experiences.
292 Spontaneous reports should not include adverse experiences identified from
293 information solicited by applicants such as individual cases or findings derived from
294 a study (e.g., any organized data collection scheme).
295
296 **B. Data Elements to Include in a Postmarketing Individual Case Safety Report**
297
298 Before considering any clinical incident for submission to the FDA in an individual case
299 safety report, applicants should, at a minimum, have knowledge of the following four data
300 elements:
301
302 1. An identifiable patient
303 2. An identifiable reporter
304 3. A suspect drug or biological product
305 4. An adverse experience or fatal outcome suspected to be due to the suspect
306 drug or biological product
307
308 If any one of these basic elements remains unknown after being actively sought by the
309 applicant, a report on the incident should not be submitted to the FDA because reports
310 without such information make interpretation of their significance difficult, at best, and
311 impossible, in most instances. Instead, the applicant should maintain records of its efforts
312 to obtain the basic elements for an individual case in its corporate drug or biological
313 product safety files. If an applicant submits a report to the FDA that lacks any of the four
314 basic elements, it will be returned to the applicant marked *insufficient data for a report*.
315

[11] See Appendix A for definitions of *unexpected and expected adverse experiences*. (See also §§ 310.305(b), 314.80(a) and 600.80(a).)

[12] See Appendix A for definition of *spontaneous report*.

316 An applicant that is actively seeking information on an adverse experience should use
317 direct verbal contact with the initial reporter of the adverse experience (e.g., in person, by
318 telephone or other interactive means such as a videoconference). The applicant should not
319 merely send the initial reporter a letter requesting information concerning the adverse
320 experience. Applicants should use a health care professional (e.g., physician, physician
321 assistant, dentist, pharmacist, nurse) for contacts with initial reporters because such
322 persons should be able to understand the medical consequences of the case and ask
323 appropriate questions to acquire relevant information rapidly to determine the significance
324 of the case.
325
326 With regard to *an identifiable patient*, reports of the type Isome patients got anaphylaxis
327 should be excluded until further information about the patients is obtained. A report stating
328 that Ian elderly woman had anaphylaxis or a Iyoung man experienced anaphylaxis should
329 be included because there is enough information to suspect that specific patients were
330 involved. Patients should not be identified by name or address. Instead, the applicant
331 should assign a unique code (e.g., patient initials) to each report.
332 For spontaneous reports, the applicant should assume that an *adverse experience* or *fatal*
333 *outcome* was suspected to be due to the suspect drug or biological product (implied
334 causality). For clinical studies, an *adverse experience or fatal outcome* need not be
335 submitted to the FDA unless the applicant concludes that there is a reasonable possibility
336 that the product caused the adverse experience or fatal outcome (see §§ 310.305(c)(1)(ii),
337 314.80(e)(1) and 600.80(e)(1)). An *adverse experience* should, at a minimum, consist of
338 signs (including abnormal laboratory findings, if appropriate), symptoms, or disease
339 diagnosis (including any colloquial descriptions obtained) for purposes of reporting. Thus,
340 a report stating that a patient Iexperienced unspecified injury, I or a patient Isuffered
341 irreparable damages should not be included until more specific information about the
342 adverse experience can be determined.
343
344
345 **V. TYPE OF REPORTS**
346
347 The following paragraphs discuss the types of postmarketing safety reports that must be
348 submitted to the FDA based on the regulations as listed.
349
350 **A. 15-Day Reports of Serious, Unexpected Adverse Experiences**[13]
351
352 Individual case safety reports of serious, unexpected adverse experiences from all sources
353 (domestic and foreign) must be reported to the FDA as soon as possible, but in no case
354 later than 15 calendar days of initial receipt of the information by the applicant. See section
355 VIII in this guidance for discussion of reporting formats for individual case safety reports.
356

[13] The requirements for 15-Day Reports can be found in §§ 310.305(a), (c)(1)(i) and (d)(1), 314.80(c)(1)(i) and (f)(1), and 600.80(c)(1)(i) and (f)(1).

An applicant should not wait for the initial reporter of a serious, unexpected adverse experience to send them written information about the experience before submitting a 15-day report to the FDA. An applicant can and should submit a 15-day report to the FDA based only on verbal information.

1. Determination of 15-Day Reporting Period

Serious, unexpected adverse experiences must be submitted to the FDA no later than 15 calendar days of initial receipt of the information by the applicant. For reporting purposes, this information should include, at a minimum, the four basic elements (i.e., an identifiable patient, an identifiable reporter, a suspect drug or biological product, and a serious, unexpected adverse experience). 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 the VAERS form (i.e., this date represents Day 0 of the 15-day time clock).

If the 15th calendar day occurs on a weekend or U.S. Federal holiday, the 15-day report should be submitted the first working day after the weekend or U.S. Federal holiday.

The applicant should exercise due diligence to acquire all the information for an individual case safety report immediately upon receipt of a suspected serious, unexpected adverse experience (e.g., completion of all the applicable elements on FDA Form 3500A). The applicant should maintain records of its efforts to obtain this information and should include in the narrative section of FDA Form 3500A (i.e., item B5), a chronological description of these efforts if there is a delay in obtaining such information.

When an applicant receives a report of a serious, unexpected adverse experience but it is not possible to complete all the applicable elements for an individual case safety report within 15 calendar days, a preliminary report that contains at least the four basic elements should be submitted. Additional followup information should be actively sought and submitted within 15 calendar days after obtaining the new information (see section V.C in this guidance for discussion of followup reports).

For foreign reports, the 15-day time clock begins when the applicant or its foreign affiliate has received the four basic elements for a 15-day report. Applicants should therefore establish effective mechanisms to ensure rapid information transfer from their foreign affiliates.

2. Supporting Documentation

For individual case safety reports of serious, unexpected adverse experiences, the FDA encourages applicants to include relevant hospital discharge summaries and autopsy reports/death certificates. Applicants should also include in their report a

402 list of other relevant documents (e.g., medical records, relevant laboratory data,
403 electrocardiograms, and other concise critical clinical data) maintained in their
404 corporate drug or biological product safety files. The FDA can request that copies
405 of one or more of these documents be provided to the Agency. Applicants should
406 submit copies of these documents to the Agency within 5 calendar days after
407 receipt of the request.
408
409 *3. Report Identification*
410
411 Fifteen-day reports must be submitted in duplicate under separate cover
412 prominently identified as "15-Day Alert Report." For this purpose, the "15-Day Alert
413 Report" identification should be included on the outside envelope.
414
415 For prescription drugs marketed for human use without an approved application, a
416 single copy of the 15-day report and a copy of the U.S. labeling must be submitted.
417 These reports should be marked on the outside envelope with "15-Day Alert Report
418 - 310.305."
419
420 Multiple 15-day reports and 15-day followup reports can be submitted in the same
421 envelope, but they should not be stapled together (see section V.C for discussion of
422 followup reports).
423
424 **B. Periodic Reports[14]**
425
426 The following paragraphs discuss the reporting frequency for submission of periodic
427 reports and the content of these reports. See section XI in this guidance for requests for
428 waivers of the requirement to submit postmarketing periodic safety reports (e.g., waiver to
429 use periodic safety update report (PSUR) format recommended by ICH for periodic report
430 instead of format described in the regulations, waiver to submit individual cases of
431 nonserious, expected adverse experiences in periodic report).
432
433 *1. Timing of Postmarketing Periodic Reports*
434
435 Postmarketing periodic reports are required to be submitted to the FDA for each
436 approved NDA, ANDA, and BLA and are due quarterly for the first 3 years after U.S.
437 approval of the application and annually thereafter. If marketing is delayed, these
438 reports should still be submitted quarterly for the first 3 years of marketing. Upon
439 written notice, the FDA may extend or reestablish the requirement that an applicant
440 submit quarterly reports or require that the applicant submit periodic reports at
441 different time intervals.
442
443 Periodic reports due quarterly must be submitted within 30 calendar days of the last
444 day of the reporting quarter. Reports due annually must be submitted each year

[14] The requirements for periodic reports can be found in ▯▯ 314.80(c)(2) and 600.80(c)(2).

445 within 60 calendar days of the anniversary date of U.S. approval of the application
446 for the drug or biological product (i.e., NDA, ANDA, BLA).
447
448 Periodic submissions should be clearly marked "Periodic Adverse Experience
449 Submission" on the front cover of each volume. Each page of the periodic report
450 should be numbered and include the name and NDA or ANDA number if the
451 periodic report is for a drug product; the name and submission tracking number
452 (STN) should be used if the periodic report is for a biological product (a STN for a
453 biological product can be found on the Internet at www.fda.gov/cber/stn/stn.htm).
454
455 *2. Content of a Postmarketing Periodic Report*
456
457 The regulations require a postmarketing periodic report to contain:
458
459 • a narrative summary and analysis of the information in the report and an analysis
460 of the 15-day Alert reports submitted during the reporting interval
461 • an FDA Form 3500A for each spontaneously reported adverse experience
462 occurring in the United States that was not reported in a 15-day Alert report
463 • a history of actions taken since the last report because of adverse experiences.
464
465 The information contained within a postmarketing periodic report should be divided
466 into four sections in the order described below and should be clearly separated by
467 an identifying tab. If information for one of these sections is not included, the
468 applicant should simply explain why the information is not provided.
469
470 a. Section 1: Narrative summary and analysis
471
472 A narrative summary and analysis of the information in the postmarketing
473 periodic report and an analysis of the 15-day reports (i.e., serious,
474 unexpected adverse experiences) submitted during the reporting period
475 must be provided and should include:
476
477 • The number of non-15-day[15] initial adverse experience reports and
478 the number of non-15-day followup reports contained in this periodic
479 report and the time period covered by the periodic report.
480
481 • A line listing of the 15-day reports submitted during the reporting
482 period. This line listing should include the manufacturer report
483 number, adverse experience term(s), and the date the 15-day report
484 was sent to the FDA.
485

[15] These include serious and expected adverse experiences, nonserious and unexpected adverse experiences, and nonserious and expected adverse experiences.

- A summary tabulation by body system (e.g., cardiovascular, central nervous system, endocrine, renal) of all adverse experience terms and counts of occurrences submitted during the reporting period. The information should be taken from :

  - 15-day reports submitted to the FDA;
  - non-15-day reports submitted in the periodic report;
  - reports forwarded to the applicant by the FDA; and
  - any nonserious, expected adverse experiences not submitted to the FDA but maintained on file by the applicant.

  For the adverse experience term *product interaction*, the interacting products should be identified in the tabulation.

- A summary listing of the adverse experience reports in which the drug or biological product was listed as one of the suspect products, but the report was filed to another NDA, ANDA, or BLA held by the applicant.

- A narrative discussion of the clinical significance of the 15-day reports submitted during the reporting period and of any increased reporting frequency of serious, expected adverse experiences when, in the judgment of the applicant, it is believed the data reflect a clinically meaningful change in adverse experience occurrence. This narrative should assess clinical significance by type of adverse experience, body system, and overall product safety relating the new information received during this reporting period to what was already known about the product. The narrative should also state what further actions, if any, the applicant plans to undertake based on the information gained during the reporting period and include the time period for completing the actions (i.e., when the applicant plans to start and finish the action and submit the information to the Agency).

- The narrative discussion should indicate, based on the information learned during the reporting period, whether the applicant believes either that (1) no change in the product's current approved labeling is warranted or (2) there are safety-related issues that need to be addressed in the approved product labeling. If changes in the approved product labeling are under consideration by the FDA, the applicant should state in the narrative the date and number of the supplemental application submitted to address the labeling changes.

b. Section 2: Narrative discussion of actions taken

A narrative discussion of actions taken must be provided, including any labeling changes and studies initiated since the last periodic report. This section should include:

- A copy of current U.S. product labeling
- A list of any labeling changes made during the reporting period
- A list of studies initiated
- A summary of important foreign regulatory actions (e.g., new warnings, limitations in the indications and use of the product)
- Any communication of new safety information (e.g., a Dear Doctor letter)

c. Section 3: Index line listing

An index line listing of FDA Form 3500As or VAERS forms included in section 4 of the periodic report must be provided. The line listing for each FDA Form 3500A or VAERS form submitted should include:

- Manufacturer report number
- Adverse experience term(s)
- Page number of FDA Form 3500A or VAERS form as located in the periodic report
- Identification of interacting products for any *product interaction* listed as an adverse experience.

d. Section 4: FDA Form 3500As or VAERS forms

FDA Form 3500As or VAERS forms must be provided for the following spontaneously reported adverse experiences that occurred in the United States during the reporting period:

- Serious and expected
- Nonserious and unexpected

572 • Nonserious and expected
573
574 Applicants are encouraged to request a waiver of the requirement to submit
575 individual case safety reports of nonserious, expected adverse experiences
576 for drugs and certain biological products as described below (see section
577 XI.A in this guidance).
578
579 Adverse experiences due to a failure to produce the expected
580 pharmacologic action (i.e., *lack of effect*) should be included in this section
581 (see section VI.F in this guidance).
582
583 For individual case safety reports of serious, expected adverse experiences,
584 the FDA encourages applicants to include relevant hospital discharge
585 summaries and autopsy reports/death certificates, as well as lists of other
586 relevant documents as described for 15-day reports of serious, unexpected
587 adverse experiences (see section V.A.2 in this guidance).
588
589 Initial non-15 day reports should be included in the periodic report in a
590 separate section from non-15 day followup reports (see the following section
591 V.C for discussion of non-15 day followup reports). All initial and followup
592 information obtained for an adverse experience with a given periodic
593 reporting period should be combined and submitted in the periodic report as
594 one initial non-15 day report (i.e., an initial non-15 day report and a non-15
595 day followup report describing the same adverse experience should not be
596 submitted in the same periodic report).
597
598 An FDA Form 3500A or VAERS form for a serious, unexpected adverse
599 experience should not be included in a periodic report because this adverse
600 experience should have been previously submitted to the FDA as a 15-day
601 report.
602
603 If no adverse experiences were identified for the human drug or biological product
604 for the time period involved and no regulatory actions concerning safety were taken
605 anywhere in the world where the product is marketed, the periodic report should
606 simply state this and be submitted to the FDA along with a copy of the current U.S.
607 labeling.
608
609 **C. Followup Reports[16]**
610
611 The following paragraphs discuss the content of and reporting considerations for 15-day
612 followup reports that are submitted in an expedited manner and non-15 day followup
613 reports that are submitted as part of a postmarketing periodic report. A followup report
614 provides information about an adverse experience that has been previously reported as an

[16] The requirements for followup reports can be found in [] 310.305(c)(2), 314.80(c) and 600.80(c).

initial report with a unique manufacturer report number. The followup report should be identified with the same unique manufacturer report number as the initial report.

A 15-day followup report must be submitted within 15 calendar days of receipt of new information on a 15-day report. Followup information to adverse experiences submitted initially in a periodic report can be submitted in the next periodic report.

1. Content of Followup Reports

A followup report should provide a complete picture of the current understanding of the adverse experience. Relevant information from the initial report should be combined with the followup information to present an accurate and comprehensive description of the adverse experience as it is understood at the time of the followup. Information from the initial report later found to be inaccurate should not be repeated in the followup report. All new information including correction of previously submitted inaccurate information that is included in a followup report should be highlighted (e.g., with an asterisk, underlined).

The narrative section of the followup report should be concise (i.e., item B5 of FDA Form 3500A) because the FDA's adverse event reporting database (AERS) is limited for this section of the form.

For serious adverse experiences, applicants should exercise due diligence in obtaining followup information for the purposes of completing all the applicable elements for an individual case safety report (e.g., FDA Form 3500A). For adverse experiences that are determined to be nonserious and for which the four basic elements are known (see section IV.B), additional followup is not necessary.

Any attachments submitted with an initial report (e.g. scientific journal articles, hospital discharge summaries) should not be resubmitted with a followup report.

2. Reporting Considerations

A copy of the initial report or a previous followup report should not be sent with the latest followup report. Fifteen-day followup reports should not be submitted in the same envelope with periodic reports.

If the initial report was submitted as a 15-day report, the followup report should be submitted as a 15-day followup report even if the followup information shows that the adverse experience was expected or not serious. All subsequent followup reports for adverse experiences that are expected or not serious should be submitted in periodic reports. A 15-day followup report should be submitted if the adverse experience is found to be serious and unexpected, even if the original report was not submitted as a 15-day report.

If a new adverse experience occurs that is associated with the initial adverse experience, a followup report should be submitted. However, if the new adverse experience is not associated with the initial adverse experience (e.g., occurs after a subsequent administration of the product), an initial report with a new manufacturer report number should be submitted for the new adverse experience. In these cases, the applicant should consider the clinical relevance of the adverse experiences to each other when determining whether an initial report or followup report should be submitted.

Followup reports should not be submitted if additional relevant information is not obtained for the adverse experience. However, as described in the regulations, applicants should maintain records of their efforts to obtain additional information, particularly for serious adverse experiences. FDA may request this documentation.

3. Reporting Forms

For followup reports, particular attention should be paid to completing the following items on FDA Form 3500A:

- Item G3 - Mark *health professional* if at any time a health professional provided information for the report.
- Item G4 - Use the date the followup information was received by the applicant.
- Item G7- Mark *followup*, and indicate whether this is the 1st, 2nd, 3rd, ... followup report.
- Item G9 - Use the same unique manufacturer report number assigned to the initial report. This is essential to prevent duplicate counting of reports and to ensure that the followup information is coupled with the correct initial report.

For followup reports, particular attention should be paid to completing the following items on the VAERS form for vaccines:

- Top right - Indicate the name of the person who provided information for the report.
- Box 24 - Use the same manufacturer report number assigned to the initial report. This is essential to prevent duplicate counting of reports and to ensure that the followup information is coupled with the correct initial report.
- Box 25 - Use the date the followup information was received by the applicant.
- Box 27 - Mark *followup*, and indicate whether this is the 1st, 2nd, 3rd, ... followup report.

704 *4. Report Identification*
705
706 Fifteen-day followup reports must be submitted in duplicate under separate cover
707 prominently identified as "15-Day Alert Report-Followup." For this purpose, the "15-
708 Day Alert Report-Followup" identification should be included on the outside
709 envelope.
710
711 **D. Distribution Reports for Biological Products Including Vaccines**
712
713 This section is based primarily on regulations in § 600.81. These regulations only apply to
714 human biological products with approved BLAs. Unless otherwise notified by the Director,
715 Center for Biologics Evaluation and Research, an applicant must submit at periodic
716 intervals two copies of a report containing information about the quantity of the product
717 distributed domestically (including distributors) under the BLA.
718
719 Distribution reports are due within the first 6 months after approval of a BLA, and,
720 subsequently, at 6-month intervals. Upon written notice, the FDA can require that the
721 applicant submit reports under this section at alternate times.
722
723 The report must include the bulk lot, fill lot, and label lot numbers for the total number of
724 dosage units of each strength or potency distributed (e.g., 50,000 per 10-milliliter vials),
725 labeled date of expiration, and date of distribution of fill lot or label lot. The report must also
726 include information about any significant amount of a fill lot or label lot that may have been
727 returned. Disclosure of financial or pricing data is not required. According to the
728 regulations, the FDA can require submission of more detailed product distribution
729 information, if needed.
730
731 See section VIII.E in this guidance for a suggested reporting format for distribution reports.
732
733
734 **VI. SPECIAL REPORTING SITUATIONS**
735
736 **A. Scientific Literature Reports[17]**
737
738 Serious, unexpected adverse experiences reported in the scientific literature (or in an
739 unpublished scientific paper) that are known to the applicant must be submitted as 15-day
740 reports on an FDA Form 3500A or comparable format. Applicants can use literature
741 search services (e.g., Weekly Reactions) to identify adverse experiences in the scientific
742 literature. A copy of the article or manuscript must be attached to the completed FDA
743 Form 3500A; it is not sufficient to submit only abstracts of articles. All reports from the
744 scientific literature and unpublished scientific papers should be marked *Literature* in item
745 G3 of FDA Form 3500A.

[17] The requirements for scientific literature reports can be found in □□ 314.80(c)(1)(i), 314.80(d), 600.80(c)(1)(i), and 600.80(d).

A separate FDA Form 3500A should be completed for each identifiable patient that experiences a serious, unexpected adverse experience. Thus, if an article describes six patients that experience a given serious, unexpected adverse experience, six FDA Form 3500As should be completed. In such cases, a copy of the article should be attached only to one of the FDA Form 3500As.. All other FDA Form 3500As submitted for the article should reference the manufacturer report number of the FDA Form 3500A that has the copy of the article attached.

If multiple products are mentioned in the article, an FDA Form 3500A should be submitted only by the applicant whose product is the suspect drug. The suspect product is that identified by the article's author and is usually mentioned in the article's title. If the applicant believes that the suspect product is different from the one identified by the author of the article, the applicant should indicate such information in the narrative section of the FDA Form 3500A.

Reports of serious, unexpected adverse experiences 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, strengths, routes of administration, and indications vary.

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.

B. Postmarketing, Clinical Trial, or Surveillance Studies[18]

For the purposes of this section, *a study* refers to the systematic collection of data involving solicitation of adverse experience information (e.g., derived from a clinical trial, patient registry). Adverse experiences incidental to other types of studies not involving monitoring adverse experiences of products should be treated as spontaneous reports (see Appendix A in this guidance for definition of *spontaneous report*). For purposes of safety reporting, 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.

Serious, unexpected adverse experiences that occur during a study must be submitted as 15-day reports. These adverse experiences are only required to be reported if there is a reasonable possibility that the drug or biological product caused the adverse experience.

[18] The requirements for reporting adverse experiences from studies can be found in 310.305(c)(1), 314.80(c)(2)(iii), 314.80(e)(1), 600.80(c)(2)(iii), and 600.80(e)(1).

Adverse experiences occurring with marketed drug or biological products during IND trials must also be submitted, as prescribed under 312.32, to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review office in the Center for Biologics Evaluation and Research that has responsibility for oversight of the IND.

For each adverse experience, a suspect product should be identified. Reports from blinded studies should be submitted only after the code is broken. The blind should always be broken for each patient or subject that experiences a serious, unexpected adverse experience unless arrangements have been made otherwise with the responsible FDA review division. Exceptions to breaking the blind usually involve situations in which mortality or certain serious morbidities are indeed the clinical endpoint. This is consistent with the ICH E2A guidance.

C. Foreign Reports[19]

Foreign reports of serious, unexpected adverse experiences must be submitted as 15-day reports. Other foreign reports, including serious and expected, nonserious and unexpected, and nonserious and expected adverse experiences are not required to be submitted.

Reports of foreign serious, unexpected adverse experiences 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, strengths, routes of administration, and indications vary. When a foreign report is submitted on a product that is not identical to a product marketed in the United States, item C1 of FDA Form 3500A should contain the foreign trade name, the generic name, and the NDA number for the product with the same active moiety that is marketed in the United States.

D. Death Reports

Death is always a serious outcome (see definition of *serious* in Appendix A of this guidance and at 310.305(b), 314.80(a) and 600.80(a)). Thus, if death is associated with an unexpected adverse experience, or if death is associated with an expected adverse experience but the labeling does not specifically state that the adverse experience may be associated with a fatal outcome, a 15-day report should be submitted.

E. Overdose Reports

Reports of overdose should be submitted *only* when the overdose is associated with an adverse experience. If the adverse experience associated with the overdose is serious and unexpected, a l5-day report should be completed. If the adverse experience is serious and expected, nonserious and unexpected, or nonserious and expected, a non-15 day

[19] The requirements for reporting of foreign adverse experiences can be found in 310.305(c)(1)(i), 314.80(c)(2)(iii) and 600.80(c)(2)(iii).

report should be submitted in the periodic report for spontaneously reported domestic cases.

F. Lack of Effect Reports

The definition of *adverse experience* includes *any failure of expected pharmacological action* that is synonymous with *lack of effect* (see definition of *adverse experience* in Appendix A of this guidance and at 310.305(b), 314.80(a) and 600.80(a)). All spontaneously reported cases of a *lack of effect* that occur in the United States should be reported on FDA Form 3500A and submitted in the periodic report with other adverse experiences. The lot number of the suspect product should be included in item C6 of FDA Form 3500A.

If the report of *lack of effect* is for an unapproved indication, the event should not be reported to the FDA as an individual case safety report. Instead, this information should be included in the narrative summary section of the periodic report.

G. Information on the Internet

Adverse experience information that is submitted to an applicant via the Internet (e.g., e-mail) should be reported to the FDA if the applicant has knowledge of the four basic elements for an individual case safety report (see section IV.B in this guidance). Applicants should review any Internet sites sponsored by them for adverse experience information, but are not responsible for reviewing any Internet sites that are not sponsored by them. However, 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.

H. Pediatric Patients

For children under 3 years of age, the child's date of birth and age in days or months (e.g., *15 months*) should be included under item A2 of FDA Form 3500A. The word *days* or *months* should be clearly written. For all pediatric patients, body weight (item A4 of FDA Form 3500A) and dose (item C2 of FDA Form 3500A) should be included.

For reports of a congenital anomaly, the age and sex of the infant should be included. Followup reports for the infant should be considered followup to the initial report; followup for the mother should be submitted as a new initial individual case safety report on a separate FDA Form 3500A. The date that the congenital anomaly is detected should be used as the event onset date (e.g., birth date of the infant, date pregnancy is terminated, date congenital anomaly is detected by ultrasound or other diagnostic technique). This date should be used in item B3 of FDA Form 3500A.

I. Prescription Drugs Marketed for Human Use Without an Approved Application[20]

For prescription drugs marketed for human use without an approved NDA or ANDA, all serious, unexpected adverse experiences must be reported to the FDA on an FDA Form 3500A within 15 calendar days. These reports must be submitted in SINGLE copy under separate cover. The report should be marked on the outside envelope "15-Day Alert Report - 310.305." A copy of the U.S. product labeling must accompany each report.

Postmarketing periodic reports should not be submitted for these drugs.

J. Another Applicant's Product

Reports of adverse experiences in which the initial reporter identifies the suspect product as one marketed by another applicant should be promptly forwarded to that applicant. An applicant who receives a report of an adverse experience regarding one of its products from another applicant must submit the report to the FDA within the same time constraints applicable to any report received from a third party (see section VI.K in this guidance).

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.

K. Multiple Suspect Products

If a reportable adverse experience involves two or more suspect products from the same applicant, only one FDA Form 3500A should be completed. The FDA Form 3500A should reference only one manufacturer report number. The report should be submitted to the NDA, ANDA, or BLA considered *most suspect* by the initial reporter. If each product is equally suspect, the report should be submitted to the product first in alphabetical order. The adverse experience should also be reported in the narrative summary section of the periodic report for the other product(s).

However, if one suspect product is a licensed non-vaccine biologic and the other is a licensed vaccine, separate reporting forms should be submitted. An FDA Form 3500A should be used for the licensed non-vaccine biologic and a VAERS form should be used for the licensed vaccine.

If a reportable adverse experience involves two or more suspect products and two or more applicants, an applicant may choose to submit an FDA Form 3500A to the FDA on the adverse experience that describes detailed information including the product(s) from the

[20] The requirements for prescription drugs marketed for human use without an approved application can be found in 310.305.

914 other applicant. In such a case, the other applicant should receive a copy of the FDA Form
915 3500A including its manufacturer report number so that the other applicant can reference
916 this report when providing any relevant followup information to the FDA. The other applicant
917 should not submit to the FDA information originally submitted to the Agency by the first
918 applicant.
919
920 **L. Suspect Drugs with Multiple NDAs or ANDAs by the Same Applicant**
921
922 A drug substance can be the subject of more than one approved NDA or ANDA. If an
923 applicant receives a report for a drug and the specific application is identifiable, the report
924 should be submitted to that application. However, if a drug substance has more than one
925 application and it cannot be determined which of the approved applications is involved, the
926 report should be submitted to the application for the drug product that was approved first
927 and that has the same general route of administration as the suspect drug substance. This
928 would usually be the application with the lowest number.
929
930 **M. Two or More Marketers of a Product**
931
932 If two or more companies that co-market a specific drug product have an approved NDA
933 for the product, one of the companies should be identified as having primary responsibility
934 for reporting adverse experiences for the drug product to the FDA to avoid duplicative
935 reporting of adverse experiences. This would also be true for two or more companies that
936 co-market a specific biological product and have an approved BLA for the product.
937
938 **N. Unapproved Indications**
939
940 An adverse experience associated with the use of a product for an unapproved indication
941 should be reported to the FDA as is required for any other spontaneously reported adverse
942 experience occurring in the United States (e.g., 15-day report for a serious, unexpected
943 adverse experience or periodic report for a nonserious, unexpected adverse experience).
944 However, a *lack of effect* report for an unapproved indication should not be reported on an
945 FDA Form 3500A. Instead, such information should be included in the narrative summary
946 section of a periodic report.
947
948 **O. Product Interactions**
949
950 If an applicant receives a report identified as a product interaction, each of the products
951 should be identified as a suspect product in item C1 of FDA Form 3500A.
952
953 **P. Reports from the FDA[21]**
954

[21] The requirements for submitting reports received from the FDA can be found in □□ 310.305(c)(5), 314.80(b), and 600.80(b).

Sometimes FDA forwards individual case safety reports (i.e., FDA Form 3500As) to applicants. For example, applicants can participate in the FDA's MedWatch-to-Manufacturer Program. This program is designed to expedite transmission from the FDA to applicants participating in the program cases of serious adverse experiences reported directly to the FDA voluntarily by initial reporters (e.g., health care professionals, consumers). Details of the program can be found on the Internet at www.fda.gov/medwatch/report/mmp.htm.

Applicants that receive individual case safety reports from FDA are not required to resubmit them to the Agency. However, followup information to these initial reports must be submitted to the FDA (see section V.C in this guidance).

Q. Product Defects

If a product defect results in an adverse experience, the adverse experience should be reported as any other spontaneously reported adverse experience occurring in the United States (e.g., 15-day report for a serious, unexpected adverse experience or periodic report for a nonserious, unexpected adverse experience).

R. Reporting Ambiguities

In some cases, it may be difficult to interpret specific criteria used for reporting. Examples include determining whether an adverse experience is expected or unexpected or whether a patient is identifiable or not. For these and any other ambiguities, the applicant should use a conservative approach and err on the side of reporting the adverse experience to the FDA. Thus, if there is doubt, consider an adverse experience to be unexpected, consider a patient to be identifiable, and so on.

VII. CODING OF ADVERSE EXPERIENCES IN INDIVIDUAL CASE SAFETY REPORTS

Companies currently use a variety of medical terminologies to code adverse experiences in individual case safety reports (e.g., COSTART, WHOART, MedDRA). At this time, the FDA will accept adverse experiences coded with any of these terminologies. However, as recommended by ICH, the Agency encourages companies to use MedDRA for this purpose and as indicated in the FDA's advanced notice of proposed rulemaking on this topic (63 FR 59746; November 5, 1998), the Agency plans to propose to require use of MedDRA as the terminology for coding adverse experiences in individual case safety reports submitted to the FDA.

Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280 (703-345-7799 in Washington D.C. area), fax 703-345-7755, e-mail subscrib@meddramsso.com, Internet at www.meddramsso.com).

1000
1001
1002 **VIII. REPORTING FORMATS[22]**
1003
1004 Individual case safety reports of adverse experiences that occur domestically for marketed
1005 human drugs and biological products, except vaccines, must be submitted to the FDA on
1006 FDA Form 3500A; a VAERS form must be used for vaccines. Foreign adverse
1007 experiences can be submitted either on FDA Form 3500A or, if preferred, on a CIOMS I
1008 form. Foreign adverse experiences associated with the use of vaccines can be submitted
1009 on either a VAERS form or, if preferred, a CIOMS I form. A separate FDA Form 3500A,
1010 VAERS form, or CIOMS I form must be completed for each individual person experiencing
1011 an adverse experience.
1012
1013 The following paragraphs describe how to acquire or generate the various reporting forms
1014 for individual case safety reports and how to obtain information on FDA's pilot program for
1015 electronic submission of these reports. This section also describes a suggested reporting
1016 format for distribution reports for human biological products with approved BLAs.
1017
1018 The following abbreviations should be used when specific information is not available for
1019 an individual case safety report or distribution report:
1020
1021 • NA for not applicable
1022 • NI for no information at this time (but may be available later)
1023 • UNK for unknown
1024
1025 **A. FDA Form 3500A**
1026
1027 See Appendix C of this guidance for a copy of the form.[23]
1028
1029 1. Copies of the FDA Form 3500A can be obtained in the following ways:
1030
1031 • From the Internet at www.fda.gov/medwatch/report/mfg.htm. Print the
1032 form or download it as a PDF file. Form software can also be
1033 downloaded and used to complete the forms using a personal
1034 computer. Completed forms should be mailed to the FDA because
1035 this software does not permit electronic submission of reports. The
1036 software is also available on disk. For a copy of the disk, call 1-800-
1037 FDA-1088 or send an electronic request via the MedWatch comment
1038 page (www.fda.gov/medwatch/report/mfg.htm). Note: this software

[22] The requirements for reporting formats can be found in □□ 310.305(d), 314.80(f) and 600.80(f).

[23] Instructions for completing FDA Form 3500A are available on the Internet at www.fda.gov/medwatch/report/instruc.htm.

contains both FDA Form 3500 for voluntary reporting and FDA Form 3500A for mandatory reporting.

- By Fax - Call 1-800-FDA-1088 and make the following selections:

  Press 1 (health professional)
  Press 2 (obtain a copy of a form)
  Press 4 (obtain fax of FDA Form 3500A).

- By Mail - Up to 10 copies of FDA Form 3500A can be obtained from:

  Office of Post-marketing Drug Risk Assessment
  Center for Drug Evaluation and Research (HFD-400)
  Food and Drug Administration
  5600 Fishers Lane, Room 15B-31
  Rockville, MD 20857

  OR

  Office of Biostatistics and Epidemiology
  Center for Biologics Evaluation and Research (HFM-210)
  Adverse Experience Reporting
  1401 Rockville Pike
  Rockville, MD 20852-1448

  Additional copies can be obtained from:

  Consolidated Forms and Publications Distribution Center
  Washington Commerce Center
  3222 Hubbard Rd.
  Landover, MD 20785

2. Copies can be created by:

   - Photocopying a blank FDA Form 3500A

   - Producing a computer-generated facsimile of FDA Form 3500A

   In place of using the preprinted forms, a computer-generated facsimile of FDA Form 3500A can be used after approval, in writing, by FDA (□□ 310.305(d)(3), 314.80(f)(3) and 600.80(f)(3)). This computer-generated facsimile of FDA Form 3500A should:

   a. Contain all the elements (i.e., 2-column format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A in

the identical enumerated sequence of the form, except as otherwise noted. For reports in which no suspect medical device is involved, the box Section D. *Suspect Medical Device* on the front page of FDA Form 3500A can be replaced with the box Section G. *All Manufacturers* located on the back page of the form. This would allow reporters of adverse experiences for drug and biological products to use a one-page form for reporting. See Appendix F of this guidance for a sample of a one-page FDA Form 3500A).

b. Have, at least, a 1/4" margin around the entire form so that information is not lost during scanning, copying or faxing of the document (the left-hand margin may be increased up to □ " to permit binding (e.g., hole-punching) of the form) (all other margins have to continue to be at least 1/4").

c. Include the name of the company centered on the top of the front page.

d. Include in the lower left corner of the front page the phrase *3500A Facsimile* instead of the phrase *FDA Form 3500A (date of form [e.g., 6/93]).*

e. Include in the upper right corner of the front page above the *FDA Use Only* box the phrase *FDA Facsimile Approval: [include date of approval by FDA]*, instead of the phrase *See OMB statement on reverse.*

f. Have the data and text contained within the boxes on a computer-generated FDA Form 3500A conform to the following specifications:

- The font size should not be less than 10 point.
- A font type should be selected that is easy to read (e.g., CG Times, Arial) and not condensed. The form may be copied or faxed multiple times. For visual contrast, the font type used for the data and text should, if possible, be different from the font type used to create the FDA Form 3500A.
- Have all data and text contained within each of the boxes (e.g., a box marked with an □x□ should be centered within the box, and narratives should include margins so that letters are not obscured or made ambiguous by lines defining a box.).

- Have the phrase *continued* included at the end of each field that has additional information continued onto another page.

g. Have continuation pages containing additional information for narrative entries conform to the following specifications:

- Each page should be identified as Page _ of _.
- Each page should include the manufacturer report number in the upper right corner.
- Each page should include the name of the company in the upper right corner.
- The section and block number (e.g., Block B5) for each narrative entry should be included.

For approval of computer-generated facsimiles of FDA Form 3500As, companies should mail their requests along with two copies of the computer-generated facsimile, a blank one and one with all the boxes completed with sample data/text, to:

Information Technology Staff
OPDRA/CDER/FDA Room 15B23
HFD-420
5600 Fishers Lane
Rockville, MD 20857

Companies can contact the Information Technology Staff at 301-827-3223 to check on the status of an approval request. Companies that are using a computer-generated facsimile of FDA Form 3500A from a vendor that has already obtained approval, in writing, from the FDA for the form do not have to submit another approval request to the Agency (the vendor's name and approval date should appear in the upper right corner of the form).

B. VAERS Form for Vaccines

See Appendix D of this guidance for a copy of the form.[24]

[24] A guidance for industry entitled *How to Complete the Vaccine Adverse Event Reporting System Form (VAERS-1)* (October 1999) is available on the Internet at www.fda.gov/cber/guidelines.htm or from the Office of Communication, Training and Manufacturers Assistance (HFM-40), CBER, 1401 Rockville Pike, Rockville, MD 20852-1448, (Fax) 1-888-CBERFAX or 301-827-3844, (Voice Information) 1-800-835-4709 or 301-827-1800.

1. Copies of the VAERS form can be obtained by calling 1-800-822-7967.

2. In place of using the preprinted forms, a computer-generated facsimile of the VAERS form can be used after approval, in writing, by FDA (▯ 600.80(f)(3)). To request approval of a computer-generated facsimile of a VAERS form, a printed copy with data to illustrate how each data field will be reported should be submitted to:

   Office of Biostatistics and Epidemiology (HFM-210)
   Center for Biologics Evaluation and Research, FDA
   1401 Rockville Pike
   Rockville, MD 20852-1448

C. CIOMS I Form for Foreign Adverse Experiences

CIOMS, working with several member nations and industry, has developed a format for international adverse experience reporting (CIOMS I form) (see Appendix E of this guidance). Applicants can use an FDA Form 3500A or, if preferred, a CIOMS I form for submission of 15-day reports of foreign adverse experiences to the FDA. Applicants cannot use a CIOMS I form for submissions of adverse experiences that occur within the United States. For these adverse experiences, an FDA Form 3500A must be used.

D. Distribution Reports for Biological Products Including Vaccines

This section on distribution reports only applies to human biological products with approved BLAs. Under ▯ 600.81, distribution reports must include the bulk lot, fill lot, and label lot numbers for the total number of dosage units of each strength or potency distributed (e.g., 50,000 per 10-milliliter vials), labeled date of expiration, and date of distribution of fill lot or label lot. The report must also include information about any significant amount of a fill lot or label lot that may have been returned.

The regulations do not specify a reporting form or format for distribution reports. One suggested report format is shown here:

Product name, strength_____

Biologics License No._____ Product Code_____

Bulk Lot No.	Fill Lot No.	Label Lot No.	Expiration Date	Distribution Date	No. of Doses Distributed	No. of Doses Returned

1205
1206 If there is more than one distribution date for a lot, the report should include each
1207 distribution date and the number of doses distributed. When reporting returned doses, the
1208 number of doses distributed should not be repeated.
1209
1210 For vaccines, if available, distribution of doses can be reported by public, private, or
1211 military sectors.
1212
1213 **E. Electronic Submissions**
1214
1215 The FDA is in the process of developing a system for electronic submission of
1216 postmarketing safety reports. At this time, applicants can submit, under a pilot program,
1217 certain individual case safety reports electronically. Details of this pilot program are
1218 available on the Internet at www.fda.gov/cder/aerssub. The Agency also plans to have a
1219 system for electronic submission of distribution reports for biological products including
1220 vaccines in the near future.
1221
1222
1223 **IX. HOW AND WHERE TO SUBMIT POSTMARKETING SAFETY REPORTS**
1224
1225 All submissions should be legible and typewritten with a minimum acceptable font size of
1226 10 point. Legible photostatic copies can be submitted. However, visual contrast should be
1227 adequate to ensure clear readable archival images. The applicant must submit one or two
1228 copies of each safety report as specified in this section unless a waiver is granted
1229 permitting a different number of copies (see section XI in this guidance).
1230
1231 **A. Human Drug Products**
1232
1233 1. For prescription drugs marketed for human use **without** an approved NDA
1234 or ANDA, postmarketing 15-day reports (initial and followup) should be sent
1235 as *single copies* to:
1236
1237 Office of Post-marketing Drug Risk Assessment (HFD-400)
1238 Center for Drug Evaluation and Research
1239 Food and Drug Administration
1240 5600 Fishers Lane
1241 Rockville, MD 20857
1242
1243 2. For drugs with approved **ANDAs**, postmarketing 15-day reports, (initial and
1244 followup), and periodic reports should be sent as *single copies* to:
1245
1246 Office of Post-marketing Drug Risk Assessment (HFD-400)
1247 Center for Drug Evaluation and Research
1248 Food and Drug Administration
1249 5600 Fishers Lane

Rockville, MD 20857

3. For drugs with approved **NDAs**, postmarketing 15-day reports (initial and followup), and periodic reports should be sent *in duplicate* to:

Food and Drug Administration
Central Document Room
12229 Wilkins Ave.
Rockville, MD 20852

B. Human Biological Products and Vaccines

1. For vaccines, postmarketing 15-day reports (initial and followup), and periodic reports should be sent *in duplicate* to:

VAERS
P.O. Box 1100
Rockville, MD 20849-1100

2. For biological products other than vaccines, postmarketing 15-day reports (initial and followup) and periodic reports should be sent *in duplicate* to:

Office of Biostatistics and Epidemiology (HFM-210)
Center for Biologics Evaluation and Research, FDA
Adverse Experience Reporting
1401 Rockville Pike
Rockville, MD 20852-1448

3. For all biological products and vaccines, distribution reports (▯ 600.81) should be sent *in duplicate* to:

Office of Biostatistics and Epidemiology (HFM-210)
Center for Biologics Evaluation and Research, FDA
Distribution Reports
1401 Rockville Pike
Rockville, MD 20852-1448

X. WRITTEN PROCEDURES FOR POSTMARKETING SAFETY REPORTING

Each applicant must develop written standard operating procedures for the surveillance, receipt, evaluation, and reporting of adverse experiences to the FDA (▯▯ 310.305(a), 314.80(b) and 600.80(b)). The FDA will consider an applicant responsible for information known to its employees, affiliates, and contractors. For this purpose, applicants should

1294 develop procedures that allow for expedited handling of adverse experience reports.
1295 Records of due diligence should be maintained. This applies to surveillance and
1296 processing for both domestic and foreign reports of adverse experiences.
1297
1298
1299 **XI. REQUESTS FOR WAIVERS TO POSTMARKETING SAFETY REPORTING**
1300 **REQUIREMENTS**
1301
1302 Under □□ 314.90(a) and 600.90(a), applicants may ask the FDA to waive any
1303 postmarketing safety reporting requirement that applies to the applicant under □□ 314.80
1304 and 600.80. The following paragraphs discuss certain postmarketing periodic safety
1305 reporting requirements for which the FDA is currently granting waivers.
1306
1307 **A. Submission of FDA Form 3500A for Nonserious, Expected Adverse**
1308 **Experiences**
1309
1310 Applicants are encouraged to request a waiver for submission of FDA Form 3500As for
1311 individual case safety reports of nonserious, expected adverse experiences that, at a
1312 minimum, contain the four basic elements (see section IV.B in this guidance). In such
1313 cases, applicants should maintain records of these nonserious, expected adverse
1314 experiences in their corporate drug or biological product safety files. The FDA may
1315 request that an applicant submit to the Agency FDA Form 3500As of one or more of these
1316 adverse experiences. The agency would expect these forms to be submitted within 5
1317 calendar days after receipt of the request.
1318
1319 Applicants who obtain a waiver for the requirement to submit individual case safety reports
1320 of nonserious, expected adverse experiences would still be expected to submit information
1321 on these adverse experiences to the FDA in the summary tabulations section of
1322 postmarketing periodic reports (see section V.B.2.a in this guidance).
1323
1324 At this time, the FDA does not intend to grant waiver requests for new biological molecular
1325 entities within one year of licensure or for blood products, plasma derivatives, or vaccines.
1326 The Agency believes that it is important to continue periodic review of all individual case
1327 safety reports of adverse experiences for these products to identify safety problems due to
1328 lot-to-lot variations and also to monitor the safety of newly approved biological products.
1329
1330 **B. Submission of PSUR format for the Periodic Report**
1331
1332 Applicants can request a waiver of the requirement to submit postmarketing periodic
1333 safety reports in the format described in the regulations. Instead, applicants can prepare
1334 these reports using the PSUR (Periodic Safety Update Report) format described in the
1335 ICH E2C guidance. In addition, the Agency recommends the following:
1336
1337 • If all dosage forms and formulations for the active substance, as well as
1338 indications, are combined in one PSUR, this information should be

separated into specific sections of the report when such separation is appropriate to accurately portray the safety profile of the specific dosage forms. For example, one should not combine information from ophthalmic drop dosage forms and solid oral dosage forms. One copy of the PSUR should be submitted for each approved NDA or ANDA whose product is covered in the PSUR as well as an additional copy for review by the postmarketing pharmacovigilance office.

- Copies of the FDA Form 3500A or VAERS form that are required by the regulations must be included.[25] These forms should be included with the PSUR as an appendix. You can request a waiver for submission of certain nonserious, expected adverse experiences on an FDA Form 3500A as described in the previous section.

- A summary tabulation should be included as an appendix listing all spontaneously reported U.S. individual case safety reports from consumers if such cases are not already included in the PSUR. Summary tabulations should be presented by body system of all adverse experience terms and counts of occurrences and be segregated by type (i.e., serious/unexpected; serious/expected; nonserious/unexpected; and nonserious/expected),

- A narrative should be included as an appendix that references the changes, if any, to the approved U.S. labeling for the dosage forms covered by the PSUR based on new information in the PSUR. A copy of the most recently approved U.S. labeling for the product(s) covered by the PSUR should be included.

C. Submission Date and Frequency for PSUR Reports

Applicants can request a waiver to submit PSURs to the FDA based on the month and day of the international birth date of the product instead of the month and day of the anniversary date of U.S. approval of the product.[26] The waiver request should specify that these PSURs would be submitted to the FDA within 60 calendar days of the data lock point (i.e., month and day of the international birth date of the product or any other day agreed on by the applicant and the FDA).[27]

Applicants can also 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).

---

[25] See □□ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B).

[26] The international birth date for a product is the date the first regulatory authority in the world approved the first marketing application for a human drug product containing the drug substance or a human biological product.

[27] The data lock point is the date designated as the cut-off date for data to be included in a PSUR.

D. How and Where to Submit Waiver Requests

1. Marketed human drug products

For waivers under ▯ 314.90(a), applicants should submit a written waiver request (include the product's name(s), date(s) of U.S. approval, and the application number(s)) to:

Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-400
Rockville, MD 20857

2. Licensed biological products

For waivers under ▯ 600.90(a), applicants should submit a written waiver request (include the product name(s), date(s) of U.S. approval, and the application number(s)) to:

Director
Office of Biostatistics & Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, HFM-220
Rockville, MD 20852-1448

XII. VALIDATION OF ADVERSE EXPERIENCE COMPUTER SYSTEMS

If an electronic record of an adverse experience is created, modified, maintained, archived, retrieved, or transmitted, the applicant is required, among other things, to employ procedures to ensure that records are trustworthy, reliable, and consistent with FDA's ability to promote and protect public health (21 CFR part 11). Those procedures must include validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

APPENDIX A: GLOSSARY

Adverse Experience - Any adverse event associated with the use of a drug or biological product in humans, whether or not considered product-related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Reporting an adverse experience does not necessarily reflect a conclusion by the applicant or the FDA that the product caused or contributed to the adverse experience. Adverse experience is synonymous with *adverse drug experience*, *adverse biological experience*, *adverse product experience*, and *adverse event*.

Affiliate - Any individual or entity related by employment or organizational structure to the applicant, including all subsidiaries, whether domestic or foreign.

Applicant - An individual or entity who holds the new drug application (NDA), abbreviated new drug application (ANDA), or the biologics license application (BLA). For purposes of this guidance, this term includes any person whose name appears on the label of a marketed drug or licensed biological product as its manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any participant involved in divided manufacturing.

Causality Assessment - Determination of whether there is a reasonable possibility that the product is etiologically related to the adverse experience. Causality assessment includes, for example, assessment of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, and physiologic plausibility.

Challenge - Administration of a suspect product by any route.

> **Dechallenge** - Withdrawal of a suspect product from a patient's therapeutic regimen.
>
> **Negative Dechallenge** - Continued presence of an adverse experience after withdrawal of the suspect product.
>
> **Positive Dechallenge** - Partial or complete disappearance of an adverse experience after withdrawal of the suspect product.
>
> **Rechallenge** - Reintroduction of a suspect product suspected of having caused an adverse experience following a positive dechallenge.

Negative Rechallenge - Failure of the product, when reintroduced, to produce signs or symptoms similar to those observed when the suspect product was previously introduced.

Positive Rechallenge - Reoccurrence of similar signs and symptoms upon reintroduction of the suspect product.

Disability - A substantial disruption in one's ability to conduct normal life functions.

Expected Adverse Experience - Adverse experience listed in the current FDA-approved labeling for the drug or licensed biological product. This would include any section of the labeling that refers to adverse experience information.

Initial Reporter - The original source of information concerning an adverse experience (e.g., consumer, healthcare professional).

Life-threatening Adverse Experience - An adverse experience that, in the view of the initial reporter, places the patient at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

Serious Adverse Experience - An adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse experience
- Initial inpatient hospitalization
- Prolongation of hospitalization
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus);
- Important medical events, based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Spontaneous Report - A communication from an individual (e.g. health care professional, consumer) to a company or regulatory authority that describes a suspected adverse experience. It does not include cases identified from information solicited by the applicant such as individual cases or findings derived from a study.

1503 **Study** - Any organized data collection system (e.g., adverse experience information
1504 derived from a clinical trial, patient registry including pregnancy registries). Reports from
1505 company sponsored patient support programs and disease management programs should
1506 be handled as if they were study reports and not as spontaneous reports.
1507
1508 **Suspect Product** - Drug or biological product associated with an adverse experience as
1509 determined by the initial reporter, regardless of the opinion of the applicant.
1510
1511 **Unexpected Adverse Experience** - Adverse experience not included in any section of
1512 the current FDA-approved labeling for the drug or licensed biological product. This
1513 includes an adverse experience that may differ from a labeled adverse experience
1514 because of greater severity or specificity (e.g., abnormal liver function versus hepatic
1515 necrosis). Adverse experiences listed as occurring with a class of drugs or biological
1516 products but not specifically mentioned with a particular drug or biological product are
1517 considered unexpected (e.g., rash with antibiotic X would be unexpected if the labeling
1518 said "rash may be associated with antibiotics"). This is because the labeling does not
1519 specifically state "rash is associated with antibiotic X." Reports of death from an adverse
1520 experience are considered unexpected unless the possibility of a fatal outcome from that
1521 adverse experience is stated in the labeling.
1522

APPENDIX B: REPORT CHECKLIST

Before mailing your postmarketing safety reports to the FDA, you should make sure that the following questions have been addressed:

A. For All FDA Form 3500A Reports

1. Have you completed a separate FDA Form 3500A for each patient?

2. Have you included the manufacturer report number in item G9 on FDA Form 3500A? (Note: For followup reports, this number should be identical to the manufacturer report number on the initial report.)

3. Have you clearly marked the report "Periodic" or "15-Day" as appropriate in item G7 on FDA Form 3500A?

4. Have you clearly marked the report "Initial" or "Followup" as appropriate in item G7 on FDA Form 3500A? Do not package and send a 15-day followup report with a non-15 day followup report.

5. Have you included the name, address, and telephone number of the initial reporter in item E1 on FDA Form 3500A?

6. Have you left all the boxes in item B2 of the FDA Form 3500A blank for a nonserious adverse experience? A box should only be checked in item B2 if the outcome for the adverse experience is serious.

7. Have you included all relevant attachments and eliminated unnecessary attachments?

Attachments can include copies of:

- hospital discharge summaries
- autopsy/biopsy reports
- death certificates
- relevant office visit notes
- summaries of relevant laboratory tests and other diagnostic procedures, particularly pre- and post-drug values.

Each page of an attachment should identify the manufacturer report number (i.e., reported in item G9 on FDA Form 3500A) for that case.

In general, attachments should not include:

- lengthy legal records

- complete medical records

8. If two or more products produced by your company were suspected by the initial reporter:

   - Have you completed only one FDA Form 3500A? (You should not prepare more than one FDA Form 3500A even if more than one of the suspect products was produced by your company.)

   - Have you identified all the suspect products in item C1 on FDA Form 3500A?

   - Have you indicated on FDA Form 3500A the product considered most suspect by the initial reporter and prepared the report accordingly? (If the initial reporter ranked them equally, you should submit an FDA Form 3500A to the file of the first suspect product in alphabetical order. You should list the adverse experience(s) for each of the other suspected product(s) in the narrative summary section of the periodic report.)

9. Have you completed an FDA Form 3500A for another applicant's drug? (You should send the report to the FDA 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. For all other cases, you should send the report to the applicant holder of the suspect drug and not to the FDA.)

B. For 15-Day Reports

1. Have you clearly marked "15-Day Report" in item G7 on the FDA Form 3500A?

2. Have you packaged the 15-day report (FDA Form 3500A initial or followup) separately? (Do not package and send an initial 15-day report with a 15-day followup report. You should not submit copies of 15-day reports with a periodic report.)

3. Have you submitted the report in duplicate? (Exceptions: for prescription drugs marketed for human use without an approved application and for drugs with approved ANDAs, only a single copy should be sent.)

4. Have you clearly marked the outside mailing envelope "15-Day Report"?

1610
1611 **C. For Periodic Reports**
1612
1613 1. Have you included the four types of information required for a periodic report
1614 and clearly separated the four sections with marked tabs?
1615
1616 2. Have you submitted the report in duplicate? (Exception: For drugs with
1617 approved ANDAs, only a single copy should be sent).
1618
1619 3. Have you eliminated all unnecessary attachments to FDA Form 3500As?
1620
1621 **D. For Followup Reports**
1622
1623 I. Have you included the manufacturer report number in item G9 on FDA Form
1624 3500A? (Note: this number should be identical to the manufacturer report
1625 number on the initial report).
1626
1627 2. Have you marked followup in item G7 on FDA Form 3500A and indicated
1628 what number followup report it is?
1629
1630

APPENDIX C

Form Approved: OMB No. 0910-0291 Expires: 12/31/98
See OMB statement on reverse

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Mfr report #

UF/Dist report #

FDA Use Only

Page ____ of ____

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: _____ or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: _____ lbs or _____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death _____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: _____
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 #2
2. Dose, frequency & route used #1 #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 ☐ yes ☐ no ☐ doesn't apply #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 ☐ yes ☐ no ☐ doesn't apply #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: _____
5. Expiration date (mo/day/yr)
6. model # _____ catalog # _____ serial # _____ lot # _____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) ☐ yes ☐ no ☐ returned to manufacturer on _____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address — phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

FDA Form 3500A

Medication and Device Experience Report
(continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

Page ____ of ____

FDA Use Only

F. For use by user facility/distributor–devices only

1. Check one ☐ user facility ☐ distributor
2. UF/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event (mo/day/yr)
7. Type of report ☐ initial ☐ follow-up # _____
8. Date of this report (mo/day/yr)
9. Approximate age of device
10. Event problem codes (refer to coding manual)
   patient code ____ - ____ - ____
   device code ____ - ____ - ____
11. Report sent to FDA? ☐ yes _____ (mo/day/yr) ☐ no
12. Location where event occurred ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: _____ specify ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. Report sent to manufacturer? ☐ yes _____ (mo/day/yr) ☐ no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& filling site for devices)
2. Phone number
3. Report source (check all that apply) ☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other: _____
4. Date received by manufacturer (mo/day/yr)
5. (A)NDA # _____ IND # _____ PLA # _____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply) ☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ initial ☐ follow-up # ____
8. Adverse event term(s)
9. Mfr. report number

H. Device manufacturers only

1. Type of reportable event ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: _____
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code: _____
4. Device manufacture date (mo/yr)
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual)
   method ____ - ____ - ____ - ____
   results ____ - ____ - ____ - ____
   conclusions ____ - ____ - ____ - ____
7. If remedial action initiated, check type ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: _____ ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/adjustment
8. Usage of device ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative and/or 11. ☐ Corrected data

The public reporting burden for this collection of information has been estimated to average one-hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

APPENDIX D

VACCINE ADVERSE EVENT REPORTING SYSTEM

VAERS

24 Hour Toll-free information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (____)_____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (____)_____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (____)_____

1. State
2. County where administered
3. Date of birth ___/___/___ (mm dd yy)
4. Patient age
5. Sex M F
6. Date form completed ___/___/___ (mm dd yy)

7. Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date ___/___/___ mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination ___/___/___ (mm dd yy) Time _____ AM PM

11. Adverse event onset ___/___/___ (mm dd yy) Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks of date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other /unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for children 5 and under

22. *Birth weight* _____ lb. _____ oz.

23. *No. of brothers and sisters*

Only for reports submitted by manufacturer/immunization project

24. *Mfr. / imm. proj. report no.*

25. *Date received by mfr. / imm. proj.*

26. *15 day report?* ☐ *Yes* ☐ *No*

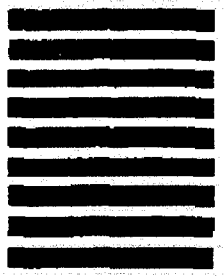
27. *Report type* ☐ *Initial* ☐ *Follow-Up*

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Vaccine Injury Table.
Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS -1

"Fold in thirds, tape & mail - DO NOT STAPLE FORM"

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO



BUSINESS REPLY MAIL

FIRST CLASS MAIL PERMIT NO. 1906 ROCKVILLE, MD

POSTAGE WILL BE PAID BY ADDRESSEE

VAERS
c/o Ogden BioServices Corporation
P.O. Box 1100
Rockville MD 20849-1100

DIRECTIONS FOR COMPLETING FORM

(Additional pages may be attached if more space is needed.)

GENERAL

- Use a separate form for each patient. Complete the form to the best of your abilities. Items 3, 4, 7, 8, 10, 11, and 13 are considered essential and should be completed whenever possible. Parents/Guardians may need to consult the facility where the vaccine was administered for some of the information (such as manufacturer, lot number or laboratory data.)
- Refer to the Vaccine Injury Table (VIT) for events mandated for reporting by law. Reporting for other serious events felt to be related but not on the VIT is encouraged.
- Health care providers other than the vaccine administrator (VA) treating a patient for a suspected adverse event should notify the VA and provide the information about the adverse event to allow the VA to complete the form to meet the VA's legal responsibility.
- These data will be used to increase understanding of adverse events following vaccination and will become part of CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems". Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.
- Postage will be paid by addressee. Forms may be photocopied (must be front & back on same sheet).

SPECIFIC INSTRUCTIONS

Form Completed By: To be used by parents/guardians, vaccine manufacturers/distributors, vaccine administrators, and/or the person completing the form on behalf of the patient or the health professional who administered the vaccine.

Item 7: Describe the suspected adverse event. Such things as temperature, local and general signs and symptoms, time course, duration of symptoms diagnosis, treatment and recovery should be noted.

Item 9: Check "YES" if the patient's health condition is the same as it was prior to the vaccine, "NO" if the patient has not returned to the pre-vaccination state of health, or "UNKNOWN" if the patient's condition is not known.

Item 10: and 11: Give dates and times as specifically as you can remember. If you do not know the exact time, please indicate "AM" or "PM" when possible if this information is known. If more than one adverse event, give the onset date and time for the most serious event.

Item 12: Include "negative" or "normal" results of any relevant tests performed as well as abnormal findings.

Item 13: List ONLY those vaccines given on the day listed in Item 10.

Item 14: List ANY OTHER vaccines the patient received within four weeks of the date listed in Item 10.

Item 16: This section refers to how the person who gave the vaccine purchased it, not to the patient's insurance.

Item 17: List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.

Item 18: List any short term illnesses the patient had on the date the vaccine(s) was given (i.e., cold, flu, ear infection).

Item 19: List any pre-existing physician-diagnosed allergies, birth defects, medical conditions (including developmental and/or neurologic disorders) the patient has.

Item 21: List any suspected adverse events the patient, or the patient's brothers or sisters, may have had to previous vaccinations. If more than one brother or sister, or if the patient has reacted to more than one prior vaccine, use additional pages to explain completely. For the onset age of a patient, provide the age in months if less than two years old.

Item 26: This space is for manufacturers' use only.

APPENDIX E

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

APPENDIX F

Form Approved: OMB No. 0910-0291 Expires: 01/31/01
See OMB statement on reverse

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ___ of ___

Mfr report #

UF/Dist report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ___ lbs or ___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ___ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ___
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 / #2
2. Dose, frequency & route used #1 / #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 / #2
4. Diagnosis for use (indication) #1 / #2
5. Event abated after use stopped or dose reduced #1 ☐ yes ☐ no ☐ doesn't apply; #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known) #1 / #2
7. Exp. date (if known) #1 / #2
8. Event reappeared after reintroduction #1 ☐ yes ☐ no ☐ doesn't apply; #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office – name/address (& mfring site for devices)
2. Phone number
3. Report source (check all that apply)
   - ☐ foreign
   - ☐ study
   - ☐ literature
   - ☐ consumer
   - ☐ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: ___
4. Date received by manufacturer (mo/day/yr)
5. (A)NDA # ___ IND # ___ PLA # ___ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply)
   - ☐ 5-day ☐ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☐ follow-up # ___
8. Adverse event term(s)
9. Mfr. report number

E. Initial reporter

1. Name & address
2. phone #
3. Health professional? ☐ yes ☐ no
4. Occupation
5. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.