Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Postmarketing Expedited Safety Reports

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document send an e-mail (CDER and CBER) to aersesub@cder.fda.gov, or telephone (CDER) Deborah Yaplee, 301-827-3237 or (CBER) Michael Fauntleroy, 301-827-5101.

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)

May 2001
Electronic Submissions

Guidance for Industry

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Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
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Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
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Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Mail: the Voice Information System at 800-835-4709 or 301-827-1800

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 is one in a series of guidance documents intended to assist applicants making regulatory submissions in electronic format to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in the Food and Drug Administration (FDA). Agency guidance documents on electronic submissions will be updated regularly to reflect the evolving nature of the technology and the experience of those using this technology.

This guidance discusses general issues related to the electronic submission of postmarketing expedited safety reports for (1) drug products marketed for human use with new drug applications (NDAs) and abbreviated new drug applications (ANDAs), (2) prescription drug products marketed for human use without an approved NDA or ANDA, and (3) therapeutic biological products marketed for human use with biologic license applications (BLAs). This guidance does not apply to vaccines.

The guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations* (January 1999*)* discusses issues common to all types of electronic regulatory submissions, such as acceptable file formats, media, and submission procedures (General Considerations guidance of 1999).[2] Information provided in this guidance on electronic submission of postmarketing expedited safety reports supercedes information provided in the General Considerations guidance of 1999 (e.g., number of copies that should be submitted).

[1] This guidance has been prepared by the Office of Information Technology (OIT) and Office of Post-marketing Drug Risk Assessment (OPDRA) in the Center for Drug Evaluation and Research (CDER) in cooperation with the Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER).

[2] The FDA is in the process of revising the General Considerations guidance of 1999 and will issue a draft guidance for public comment summer of 2001.

Postmarketing safety reports sent to CDER and CBER for human drug and biological products are loaded into the FDA's Adverse Event Reporting System (AERS) database. CDER is responsible for oversight of the AERS database and loading of information into it for both CDER and CBER. Applicants sending postmarketing expedited safety reports ***electronically*** to the FDA for products regulated by CBER should follow procedures provided for CDER in the General Considerations guidance of 1999 (as well as subsequent versions of the general considerations guidance).

II. GENERAL ISSUES

Regulations for submission of postmarketing expedited safety reports to CDER and CBER are described in 21 CFR 310.305(c), 314.80(c)(1) and 600.80(c)(1). This section briefly addresses some general issues related to the electronic submission of postmarketing expedited safety reports.

A. Parts of a Postmarketing Expedited Safety Report

For the purpose of electronic submissions, we have divided the postmarketing expedited safety report into two parts: (1) the individual case safety report (ICSR) and (2) the attachments to the ICSR (ICSR attachments).

For purposes of this guidance on electronic submission of postmarketing expedited safety reports, an ICSR contains data elements as defined in the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). The information described in the E2B guidance was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2B working group. In November 2000, this group revised E2B (E2BM). The FDA will implement E2BM in the near future. At that time, the Agency will support use of both the E2B and E2BM data elements.

ICSR attachments include published articles that must accompany ICSRs based on scientific literature (21 CFR 314.80(d) and 600.80(d)) as well as other supporting information such as relevant hospital discharge summaries and autopsy reports/death certificates.

B. Electronic Transport Format

The electronic transport format to be used with the E2B data elements is defined in the ICH document entitled *M2 Electronic Transmission of Individual Case Safety Report Message Specification version 2.24 (ICH ICSR DTD Version 2.0) (M2 Specification version 2.24, DTD version 2.0*), which can be found at www.fda.gov/cder/m2. In November 2000, the ICH M2 working group revised the specifications for electronic submission of individual case safety reports consistent with E2BM.[3] The revised

[3] *M2 Electronic Transmission of Individual Case Safety Reports Message Specification version **2.3** (ICH ICSR DTD Version **2.1**)* (M2 Specification version 2.3, DTD version 2.1).

electronic specifications will be implemented by the FDA concurrently with implementation of E2BM.

C. The Archival Copy

Once we have identified the ICSR and/or ICSR attachments in public docket number 92S-0251 as submission types that we can accept in an electronic format, you can provide them in an electronic format in place of the currently required paper copies.[4] Until that time, if you wish to submit electronically, you must also submit a paper copy for the archival file.[5]

D. Notification of Initial ICSR Submission

Prior to the first time that you submit an ICSR electronically to the FDA, you should notify the AERS electronic submission coordinator of your intent at aersesub@cder.fda.gov. It is not necessary to contact the AERS electronic submission coordinator prior to sending an ICSR to the FDA for subsequent electronic submissions of ICSRs.

E. Sending in the Submission

You can send an ICSR to the FDA using either physical media (i.e., floppy disk, CD-ROM, or digital tape) or the FDA's Electronic Data Interchange (EDI) gateway. We prefer that you send the ICSR using the EDI gateway because this allows the most efficient processing of the reports. ICSR attachments, however, should be sent ***only*** on physical media.

For information on providing submissions using the EDI gateway, contact the AERS electronic submission coordinator at aersesub@cder.fda.gov.

Information on preparing and sending submissions on physical media can be found in the General Considerations guidance of 1999.[6] Current regulations require that postmarketing expedited safety reports bear prominent identification as to their contents (i.e., "15-day Alert report," or "15-day Alert report-followup").[7] When sending a report to the FDA on physical media, applicants should identify the media as described in the current regulations (i.e., "15-day Alert report," or "15-day Alert report-followup").

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[4] See 21 CFR 310.305(d), 314.80(f) and 600.80(f) for requirement to submit postmarketing safety reports on an FDA Form 3500A.

[5] See 21 CFR 11.2(b)(2).

[6] As described previously in section I of this guidance, applicants with approved applications for products regulated by CBER should follow procedures described in the General Considerations guidance of 1999 for CDER.

[7] See 21 CFR 310.305(c)(4), 314.80(c)(1)(iv), and 600.80(c)(1)(iv).

F. Notification of Receipt of Report by the FDA

Once a submission reaches the EDI gateway and is successfully recognized and decrypted, an EDI gateway acknowledgement will be returned to the sender. The date of this acknowledgement will serve as the official receipt date of the submission.

After receipt of the submission, we will load the ICSRs into the AERS database. For submissions sent via the EDI gateway, an automated standard generalized markup language (SGML) acknowledgment message, which gives the status of each report in the transmission, will be returned to you via the gateway.

For submissions sent on physical media, the Agency will determine the receipt date as it does with submissions sent to the FDA on paper (i.e., receipt date is the date it arrives at the Agency). The Agency will only contact you if there are problems with the format of the report or if the report does not load properly into the AERS database. We will contact you by phone or email, describe the problem, and request a resubmission of the report in the proper format. This resubmission should take place as soon as possible.

III. ORGANIZING THE ELECTRONIC SUBMISSION

A. ICSR

The following describes the steps you should take to prepare and send the ICSR in an electronic format.

1. Prepare the Data Using the Appropriate E2B/M2 Format

Whether you are providing the ICSR on physical media or sending it using the EDI gateway, you should provide the ICSR as an SGML file using the data elements and electronic transport format currently accepted by the FDA (e.g., currently, the FDA is accepting E2B data elements with the M2 Specification version 2.24, DTD version 2.0 electronic transport format.[8] See sections II.A and II.B in this guidance).

a. Coding reactions and events

Section B.2 of E2B is designated for reaction/event terms. For these fields, the FDA prefers that applicants use the Medical Dictionary for Regulatory Activities (MedDRA).[9] For the E2B field, B.2.i.1, you should insert the lowest level term (LLT) in MedDRA that most closely corresponds to the term reported by the primary source. For the E2B field,

[8] Once the Agency has implemented them, the FDA will also accept E2BM data elements with the M2 Specification version 2.3, DTD version 2.1 electronic transport format.

[9] 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) .

B.2.i.2, you should insert the preferred term (PT) in MedDRA that corresponds to the LLT used in B.2.i.1.[10] If you do not have access to MedDRA, you should populate the E2B field, B.2.i.2, with a reaction term (e.g., a COSTART term, a WHOART term) and leave the E2B field, B.2.i.1, blank.

b. Identification numbers

Section A.1 of E2B is designated for identification numbers. You should include in the A.1.10 field a concatenation of the country code, sender identification, and report number. E2B fields A.1.10.1, A.1.10.2, and A.1.11.2 should only be filled in if a report is received by one entity (e.g., the FDA, a company) **AND** the entity subsequently transmits the report to one or more other entities. [11]

- E2B field A.1.10.1 should be filled in by the FDA (or other regulatory authority) if:

1. it receives a direct report from a health care professional or consumer **AND**
2. the report is subsequently sent to one or more other entities.

- E2B field A.1.10.2 should be filled in by a company if:

1. it is the first company to receive a direct report from a health care professional or consumer **OR**
2. it is the first company to receive an ICSR from the FDA (or other regulatory authority) **AND**
3. the report is subsequently sent to one or more new entities.

- E2B field A.1.11.2 should be filled in by a company if:

1. it receives an ICSR from another company **AND**
2. the report is subsequently sent to one or more new entities.

The A.1.11.2 field should be used by all companies that receive an ICSR from another company (i.e., this field may contain multiple identification numbers). Possible scenarios for populating fields A.1.10.1, A.1.10.2, and A.1.11.2 are shown in Table 1.

[10] If you are using subsequent versions of *E2B (e.g., E2BM)*, you should follow the explicit guidance for populating the B.2 fields as described in the document.

[11] If you are using subsequent versions of E2B (e.g., E2BM), you should follow explicit guidance for populating the A.1 fields as described in the document.

Table 1: Example Scenarios for Populating Identification Fields

Path of ICSR	Who provides identification number for fields		
	A.1.10.1	A.1.10.2	A.1.11.2
Scenario 1			
A direct report from a health care professional or consumer is sent to the FDA and subsequently transmitted to Company A	FDA	empty	empty
Company A received the report from the FDA and subsequently transmitted it to Company B	FDA	Company A	empty
Company B received the same report from Company A and subsequently transmitted it to Company C and Company D	FDA	Company A	Company B
Scenario 2			
A direct report from a health care professional or consumer is sent to Company A and subsequently transmitted to Company B	Empty	Company A	Empty
Company B received the report from Company A and subsequently transmitted it to Company C and Company D	Empty	Company A	Company B
Company D received the report from Company B and subsequently transmitted it to Company E	Empty	Company A	Company B Company D

The identification numbers used for followup reports should remain unchanged from those included in the original report. Once a field is populated, you should not change the information contained in it for any subsequent report. If you wish to make a correction, you should provide corrected information in a new field. For example, if the FDA (or any other regulatory authority) is not the sender of the original report, the field in A.1.10.1 should not be populated in any followup reports. You should capture your identification number in A.1.10.2 or A.1.11.2.

2. Add EDI Header and Trailer to the ICSR

We use an EDI header and trailer to process the ICSR whether you provide the ICSR on physical media or send it using the EDI gateway. For this reason, you should add an EDI header and trailer to all ICSR files.

EDI headers and trailers are made up of a series of data elements separated by plus (+) signs. A colon should separate segments of the individual data elements. An apostrophe should be used to terminate the header, body of the message, and the trailer.

The ICSR should be preceded by the EDIFACT UNB header and followed by the UNZ trailer. The data that should be used in headers and trailers are shown in the following tables:

Table 2 EDIFACT UNB Header Information

Description	Code	Comments
Identification of the start of the UNB header	UNB	The code for the start of the UNB header should be UNB in upper case letters
Version of the standard of the UNB header	UNOB:1	The current version code should be UNOB in upper case letters
Interchange sender identification code and sender code qualifier	xxxxxxx:01	xxxxxxx should be the number assigned to your company by Dun and Bradstreet Information Services. (For industry sending to the FDA, the sender code qualifier is 01.)
Interchange recipient	FDAEDI.xxxx:zz	xxxx should be the code for the receiving center (CDER, CBER, CDRH, CVM, CFSAN)
Date and time of preparation	yymmdd:hhmm	For now, a two-digit designation should be used for the year
Interchange control reference	Up to 14 alphanumeric characters	You should assign a unique reference number for each interchange. Otherwise the system will not recognize the transmission as new

Table 3 UNZ Trailer Information

Description	Code	Comments
Identification of the start of the trailer	UNZ	The code for the start of the trailer is UNZ in upper case letters
Interchange control count	Up to 6 numerical characters	Counts either the number of messages or the number of functional groups within the interchange. Usually, this is 1
Interchange control reference	Up to 14 alphanumeric characters	This should be the same as the interchange control reference in the UNB header

The following is an example of a complete message with a UNB header and UNZ trailer. The message “this is a test text” was sent to CDER on April 27, 2000 at 11 AM. The company DUNS number was 000000000. The reference number for the message was 10001

```
UNB+UNOB:1+000000000:01+FDAEDI.CDER:zz+000427:1100+10001
'this is a test text'
UNZ+1+10001'
```

3. Send the ICSR File with the EDI Header and Trailer

If you choose to submit the ICSR on physical media, you should use *edi* as the extension for each file. The name of the file should be 40 characters or less excluding the three-digit extension. You should place the *edi* files on the physical media along with any ICSR attachment files. You should follow the General Considerations guidance of 1999 for preparing and sending physical media.[12]

If you choose to submit the ICSR over the EDI gateway, contact the AERS electronic submission coordinator at aersesub@cder.fda.gov for additional guidance.

B. ICSR Attachments

The following describes the steps you should take to prepare and send attachments to an ICSR in an electronic format.

1. Convert the ICSR Attachment to Portable Document Format (pdf)

We are able to archive ICSR attachments in pdf format. You should provide an individual pdf file for each attachment to an ICSR. If there is more than one piece of information in an ICSR attachment, include each piece of information in the same pdf file and provide a pdf bookmark to each piece of information. For example, if there is a hospital discharge summary and an autopsy report for a single ICSR, you should include both in a single pdf file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

2. Enter Identification Information in the pdf Document Information Fields

Each pdf file contains fields that can be filled in by the author of the document. We use these fields in our system to locate and retrieve the attachments to specific ICSRs. To help us match the attachment to the ICSR, you should fill in the pdf document information fields with the appropriate E2B/E2BM data elements included in the ICSR as described in table 4.

[12] As described previously in section I of this guidance, applicants with approved applications for products regulated by CBER should follow procedures described in the General Considerations guidance of 1999 for CDER.

Table 4: Document Information Fields in ICSR Attachments

Document information field	**What information should be included in the field***
Title	Sender's identification number (A.1.10.2)
Subject	FDA identification number (A.1.10.1) and Sender's identification number (A.1.10.2)
Author	Other identification number (A.1.11.2)
Keywords	Date of receipt of the most recent information for this ICSR (A.1.7)

* The information in the parentheses refer to the data elements in *E2B*

3. Naming the ICSR Attachment

To help us match the attachment to the ICSR, you should use the manufacturer's control number for the ICSR as the file name for the ICSR attachment with *pdf* as the extension.