Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Revision History

Date	Version	Summary of Changes
2008-05-01	1.0	Original version

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Table of Contents

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This document provides current FDA specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form for marketed drug and biological products (including therapeutic vaccines, but excluding prophylactic vaccines, whole blood, and components of whole blood).

I. ORGANIZING THE ELECTRONIC SUBMISSION

Submitting an ICSR often involves submitting a series of information consisting of the original ICSR and followup information over the life cycle of the individual case. Each original ICSR or followup ICSR may consist of several parts including structured information and nonstructured ICSR attachment information. Organize your electronic ICSR and ICSR attachment submission in the format described in the following sections so that FDA can process, review, and archive it.

Prepare your ICSR for submission in an electronic format as follows:

1. Whether you are providing the electronic ICSR on physical media or using the FDA Electronic Submission Gateway (ESG),[1] use one of the file formats currently accepted by the FDA (SGML/or XML; see section II of this document).

2. Add the appropriate header, trailer, and file extension for the file format that you have selected. For files in an SGML format, see section III of this document. For files in an XML format, see section IV of this document.

3. Populate the elements for the ICSR file. See section V for instructions on populating specific elements.

4. If applicable, add an ICSR attachment to your ICSR file. See section VI of this document for instructions on submission of electronic ICSR attachments.

II. DATA ELEMENTS AND ELECTRONIC TRANSPORT FORMAT FOR ELECTRONIC SUBMISSIONS

FDA is currently accepting data elements for the transmission of ICSRs as defined in the guidance for industry *E2BM Data Elements for Transmission of Individual Case Safety Reports* (April 2002) (E2B(M)). The information in the guidance was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for

[1] For information on providing submissions using the ESG, refer to http://www.fda.gov/esg. For information on sending ICSRs and ICSR attachments on physical media, see the associated document "Transmitting Electronic ICSRs and ICSR Attachments on Physical Media"

Human Use (ICH) E2B working group.[2] The E2B(M) guidance provides additional information and clarification of the ICH E2B guidance that was issued by the FDA in 1998.[3]

FDA is currently accepting ICSRs in either SGML or XML format. The E2B(M) data elements are used for both SGML and XML files. In addition, our electronic submission processing supports the character set ISO-8859-1.

III. PREPARING SGML FILES

The electronic transport format for SGML files is described in the associated document "M2 Electronic Transmission of Individual Case Safety Report Message Specification" (ICH ICSR DTD Version 2.1).

A. Add an Electronic Data Interchange (EDI) Header and Trailer to the ICSR File

The addition of an EDI header and trailer enables FDA to process ICSRs in an SGML format successfully. For this reason, add an EDI header and trailer to all ICSR files in an SGML format.

EDI headers and trailers are made up of a series of data elements separated by plus (+) signs. Separate segments of the individual data elements with a colon. Use an apostrophe to terminate the header, body of the message, and the trailer.

The ICSR should be preceded by the EDIFACT UNB header. Use the protocol described in Table 1 to create the header:

[2] The ICH E2B working group continues to work on updating the data elements for transmission of ICSRs. This working group has issued an updated draft guidance on this topic. See the draft guidance for industry entitled *E2B(R) Data Elements for Transmission of Individual Case Safety Reports* (September 2005). The ICH E2B working group also intends to collaborate, as part of an international consortium agreement with the International Standards Organization (ISO), the European Center for Standardization (CEN), and Health Level Seven (HL7), to develop a new international adverse event reporting standard that would support the safety reporting requirements for all FDA-regulated products. The FDA will update these specifications as the Agency adopts and implements new standards.

[3] See the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). FDA currently supports use of E2B data elements in addition to the E2B(M) data elements, but prefers that ICSRs be submitted with E2B(M) data elements because this allows the most efficient processing of the submissions. For those who wish to use E2B data elements and the electronic transport format used with these data elements (M2 Electronic Transmission of Individual Case Safety Report Message Specification 2.24 (ICH ICSR DTD Version 2.0)), please refer to documentation provided at http://www.fda.gov/cder/aerssub/default.htm.

Table 1: 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 is UNB in upper case letters
Version of the standard of the UNB header	UNOB:1	The current version code is UNOB in upper case letters
Interchange sender identification code and sender code qualifier	xxxxxxx:01	xxxxxxx is 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 is the code for the receiving center (CDER, CBER, CDRH, CVM, CFSAN)
Date and time of preparation	yymmdd:hhmm	For now, a two-digit designation is used for the year
Interchange control reference	Up to 14 alphanumeric characters	Assign a unique reference number for each interchange. Otherwise the system will not recognize the transmission as new

The ICSR should be followed by the UNZ trailer. Use the protocol described in Table 2 to create the trailer:

Table 2: 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 is 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'
```

B. Add the File Extension

Use “edi” as the file extension for submissions in an SGML format, whether the ICSR is sent via physical media or the ESG. The name of the file should be 200 characters or less excluding the three-digit extension. We do not support file names with multiple “.” (periods) as well as the use of any special or foreign characters except “_” (underscore) and “-” (dash).

IV. PREPARING XML FILES

The electronic transport format for XML files is described in the associated document “XML Formatted DTD” (DTD Version 2.1).

A. Add XML Header

The addition of an XML header enables FDA to process ICSRs in an XML format successfully. For this reason, add the following XML header to the ICSR file:

```
<?xml version="1.0" encoding="UTF-8"?>
<!DOCTYPE ichicsr SYSTEM "http://www.fda.gov/cder/aerssub/icsr-xml-v2.1.dtd">
```

FDA only supports UTF 8 encoding standards for the submissions.

B. Add the File Extension

Use “xml” as the file extension for submissions in XML format, whether the ICSR is sent via physical media or the ESG. The name of the file should be 200 characters or less excluding the three-digit extension. We do not support file names with multiple “.” (periods) or the use of any special or foreign characters except “_” (underscore) and “-” (dash).

V. SPECIFICATIONS FOR POPULATING SPECIFIC ELEMENTS OF AN ICSR — SGML AND XML FILES

At a minimum, an ICSR should include the following four data elements.

Element	*E2B(M) section*
Identifiable patient	B.1
Identifiable reporter	A.2
Reaction or event	B.2
Suspect drug	B.4

Information to be provided for specific elements of an ICSR is the same whether an SGML or XML file format is used. The values to be provided for certain elements are described in this section.

A. Administrative and Identification Elements

So that FDA can successfully process your electronic ICSR submission, populate the administrative and identification elements listed in Table 3 as indicated:

Table 3: Detailed Description of Administrative Tags*

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
A.1.9	<fulfillexpeditecriteria>	1N	1=yes (expedited) 2=no (periodic)
A.1.0.1	<safetyreportid>	100AN	Sender's (Case) Safety Report Unique Identifier
A.1.10.1	<authoritynumb>	100AN	Regulatory authority's case report number
A.1.10.2	<companynumb>	100AN	Other sender's case report number
A.3.1.2	<senderorganization>	60AN	Sender identifier

* Include either <companynumb> or <authoritynumb> values. FDA cannot process the ICSR without one of these element values.

B. Authorization/Application Number Format

In the section designated for drug information, use the following format for the "Authorization/Application Number" element (E2B(M) element B.4.k.4.1):

- For ***human drug products***, use the abbreviation "NDA" or "ANDA" followed by a space and then the number for the application (e.g., NDA 12345, ANDA 12345). For an over-the-counter product marketed without an approved application, use "000000". For a prescription drug product marketed without an approved application, use "999999".
- For ***human biological products***, use the six-digit submission tracking number (STN) (e.g., 123456), which is the BLA number, for this purpose. Use the same format as described for human drug products (e.g., STN 123456). For human cells, tissues, and cellular and tissue-based products regulated under section 361 of the Public Health Service Act, use "tissue".

C. Identification Numbers for Initial and Followup ICSRS

Use the same identification numbers for the E2B(M) elements in section A.1 for the initial and any followup ICSRs so that we can match followup ICSRs with the initial ICSR. Thus, the initial ICSR and all of its followup reports will be linked in AERS.

If you need to change an identification number internally, note the reassigned internal identification number in the narrative section of the followup report (i.e., E2B(M) element B.5.1)

(e.g., "This ICSR has been reassigned Company A ID number COA12345"). Do not use the reassigned internal identification number for any followup reports; always use the identification number that was assigned to the initial ICSR.

If you use an incorrect identification number in a followup report, contact the AERS electronic submission coordinator at aersesub@fda.hhs.gov so that the followup ICSR can be matched to the initial ICSR.

D. Reactions and Events Elements

Section B.2 of E2B(M) is designated for reaction/event terms. For elements in section B.2, the FDA prefers that applicants use the Medical Dictionary for Regulatory Activities (MedDRA).[4]

- For the E2B(M) element B.2 "Reaction(s)/event(s)," the FDA prefers that you use terms in MedDRA.

- For the E2B(M) element B.2.i.0 "Reaction/event as reported by the primary source," insert the original reporter's words and/or short phrases used to describe the reaction/event.

- For the E2B(M) element B.2.i.2 "Reaction/event MedDRA term (Preferred Term)," insert the preferred term (PT) in MedDRA that most closely corresponds to the term reported by the original reporter.

- If you wish to include the lowest level term (LLT) in MedDRA that most closely corresponds to the term reported by the original reporter, insert this term in the E2B(M) element B.2.i.1 "Reaction/event in MedDRA terminology (Lowest Level Term)."

MedDRA terms should be provided as code. Elements that AERS accepts as code or text include:

<patientmededicalepisodename>
<patientdrugindication>
<patientdrugreaction>
<patientdeathreport>
<patientdetermineautopsy>
<parentmedicalepisodename>
<parentdrugindication>
<parentdrugreaction>
<primarysourcereaction>

[4] Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280 (703-345-7799 in the Washington, D.C., area), fax 703-345-7791, e-mail mssosubscribe@ngc.com, Internet at www.meddramsso.com .)

<reactionmeddrapt>
<reactionterm>
<drugindication>
<drugrecuraction>
<drugreactionasses>
<senderdiagnosis>

AERS accepts only text for <testnames>.

If you do not have access to MedDRA, populate the E2B(M) element B.2.i.2 with a reaction term from a standardized dictionary (e.g., a COSTART term, a WHOART term) and leave the E2B(M) element B.2.i.1 blank.

E. Drug(s) Description and Narrative Elements

So that FDA can successfully process your electronic ICSR submission, populate the drug description and narrative elements as indicated in Table 4.

Table 4: Detailed Description of Drug(s) and Narrative*

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
B.4.k.1	<drugcharacterization>	1N	1=Suspect 2=Concomitant 3=Interacting
B.4.k.2.1	<medicinalproduct>	70AN	Proprietary medicinal product name
B.4.k.2.2	<activesubstancename>	100AN	Drug substance names
B.5.1	<narrativeincludeclinical>	20000AN	Case narrative

* Include <medicinalproduct> and/or <activesubstancename >. FDA cannot process the ICSR without at least one of these elements.

If more than one drug is included in an ICSR, then for each drug identify:

- A suspect drug and/or active ingredient and
- An indication whether drug type is suspect (primary, secondary), concomitant, or interacting

For narrative information, the element "Case narrative including clinical course, therapeutic measures, outcome and additional relevant information" should contain a narrative description of the adverse drug experience. Do not include this narrative description in any other element. If the information that you have for this element (or any other element) exceeds the maximum allowable length, consider alternative ways to convey the information so that it will fit (e.g., use abbreviations, describe the information using fewer words).

For new information or corrections of previously submitted inaccurate information in followup reports, instead of highlighting the information (e.g., with an asterisk, underline) as described in the guidance for industry entitled *Postmarketing Safety Reporting for Human Drug and*

Biological Products Including Vaccines,[5] make a note of this information in the narrative section of the followup report (E2B(M) element B.5.1).

VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS

We are able to archive ICSR attachments in pdf format. Currently approved formats for the nonstructured component (attachments) of an ICSR are PDF version 1.4 (current ICH standard) or 1.6 (current version in use at FDA). For efficient processing, FDA expects an ICSR submission to precede the submission of any attachments for that ICSR. The following describes the steps you should take to prepare and send attachments to an ICSR in an electronic format.

A. Convert the ICSR Attachment to Portable Document Format (PDF)

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, include both in a single pdf file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

B. Enter Identification Information in the PDF Document Information Fields

Each pdf file contains fields to 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, fill in the pdf document information fields with the appropriate E2B(M) data elements included in the ICSR as described in Table 5.

[5] A draft version of the Postmarketing guidance was issued in March 2001. Once finalized, it will represent the Agency's current thinking on followup reports.

Table 5: Document Information Fields in ICSR Attachments

PDF Document Information Field	Include/ Optional	Use the Following Information* To Fill In the PDF Document Information Field	Length
Title	Include	A.1.0.1 <safetyreportid> Sender's (Case) Safety Report Unique Identifier	100AN
Subject	Include	A.1.10.1 <authoritynumb> Regulatory Authority's Case Report Number OR A.1.10.2 <companynumb> Other Sender's Case Report Number	100AN
Author	Optional	A.1.11.2 <duplicatenumb> Other identification number	100AN
Keywords	Optional	A.1.7b <receiptdate> Date of receipt of the most recent information for this ICSR	8N

* The information refers to the data elements in *E2B(M)*

In addition:

- The length of the data in the above fields should be same as their corresponding E2B(M) elements length.
- Avoid creating any custom fields with identical names as the above fields.
- Use ISO-8859-1 character set for the data fields.

C. Naming the ICSR Attachment

To help us match the attachment to the ICSR, use the SafetyReportId as the file name for the ICSR attachment with *pdf* as the extension.