

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Technical Specifications Document

Associated Guidance Document(s):

Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports (June 2008)

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Center for Drug Evaluation and Research (CDER)
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Revision History Table

Date	Version	Summary of Changes
2008-06-11	1.0	Original version
2008-08-06	1.1	Added Filename format info.
2008-10-10	1.2	Updated UTF-8 to ISO-8859-1 encoding; indicated simultaneous acceptance of ICSR and ICSR attachments; provided another acceptable file extension for SGML files; and clarified use of abbreviations (NDA, ANDA, and STN).
2008-10-22	1.3	Provided clarification in Section II; updated footnote 3; and added new paragraph to Section V.C.
2013-07-05	1.4	Updated AERS to FAERS migration changes, removed references to SGML file formatting, incorporated updates from CBER.

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Specifications for Preparing and Electronically Submitting ICSRs and ICSR Attachments to FAERS

This document provides current specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form for marketed drug and biological products, including therapeutic vaccines, to the FDA Adverse Event Reporting System (FAERS). This document does not apply to prophylactic vaccines, whole blood, components of whole blood, human cells, tissues, and cellular and tissue-based products (HCT/P) regulated under section 361 of the Public Health Service Act or Investigational New Drug (IND) Safety Reports.

ICSRs and ICSR Attachments are to be submitted through the FDA Electronic Submission Gateway (ESG)¹. ICSRs are to be prepared in accordance with the ICH E2B(R2) data elements in XML file format for compatibility with the FAERS database. ICSRs are not to be submitted to the electronic Common Technical Document (eCTD) in a portable document file (PDF) format.²

If you have not previously submitted an ICSR in electronic format to the FDA, you should notify the FAERS electronic submission coordinator of your intent at faersesub@fda.hhs.gov. The FAERS coordinator will assist you with submission of a test file.

I. THE ELECTRONIC SUBMISSION

Each initial ICSR or follow-up ICSR may consist of several parts, including structured information and non-structured information, such as ICSR attachments.

In order for FDA to process, review, and archive the ICSRs, prepare your ICSR for electronic submission as follows:

- A. Provide a unique filename for the submission; see section II of this document.
- B. Add a file header and file extension; see section III of this document.
- C. Populate the elements of the ICSR file; see section IV of this document.
- D. If applicable, add ICSR attachments to ICSR files; see section V of this document.

¹ For information on providing submissions using the ESG, refer to <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>

² See FAERS Electronic Submissions at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>

II. FILENAME

A. Each electronic submission of ICSRs or attachments to ICSRS must have a unique filename (e.g., your named file + date time stamp to the second: filenameYYYYMMDDHHMMSS). You may choose your own format to maintain uniqueness.

B. If you do not receive a FAERS acknowledgement within two hours of the ESG message delivery notice of acknowledgement, resubmit, the original submission without changing the filename.

C. If you receive a FAERS acknowledgement with a response of an unsuccessful (failed) acknowledgment:

1. For a single ICSR submission, resubmit the corrected ICSR with a new unique filename.
2. For a submission consisting of multiple ICSRs, and one or more ICSRs in the submission failed to process, separate the failed ICSRs from the successfully submitted ICSRs, correct the failed ICSRs, and resubmit only the corrected ICSRs as a new submission with a unique filename. For example, if there were 50 ICSRs in an original submission and 15 of them failed to process successfully, then only the failed 15 ICSRs must be separated, corrected appropriately, and resubmitted with a new unique filename. The resubmission must not contain any of the successfully processed ICSRs.

III. ELECTRONIC TRANSPORT FORMAT: XML FILES

FDA accepts the data elements defined in the guidance for industry *E2B(M) Data Elements for Transmission of Individual Case Safety Reports* (April 2002). The E2B(R2) guidance provides additional information and clarification of the previously issued guidances.³

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

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. However it is preferred that ICSRs be submitted with E2B(M) data elements to allow for the most efficient processing of the submissions. For those who wish to use E2B data elements and the corresponding electronic transport format (ICH M2 Electronic Transmission of Individual Case Safety Report Message Specification Final Version 2.3 Document Revision February 1, 2001 (ICH ICSR DTD Version 2.1)), please refer to documentation provided at http://estri.ich.org/icsr/ICH_ICSR_Specification_V2-3.pdf

A. XML Header

1. 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="ISO-8859-1"?>  
<!DOCTYPE ichicsr SYSTEM "http://www.accessdata.fda.gov/xml/icsr-xml-v2.1.dtd">
```

2. FDA supports only the ISO-8859-1 character set for encoding the submission.

B. File Extension

Use “xml” as the file extension for submissions in XML format. 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 “-”.

IV. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS

A. MINIMUM DATA ELEMENTS

An Electronic ICSR should contain the four minimum data elements listed in Table 1.

Table 1: Minimum Data Elements

Element	Data
B.1	Identifiable patient
A.2	Identifiable reporter
B.2	Reaction or event
B.4	Suspect drug

B. ADMINISTRATIVE AND IDENTIFICATION ELEMENTS

So that FDA can successfully process your electronic ICSR submission, populate the administrative and identification elements as indicated in Table 2.

Table 2: 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 (non-expedited)
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.

†The Sender's Safety Report Unique Identifier is comparable to the Manufacturer Report Number (also referred to as the Manufacturer Control Number (MCN)). This is the company's unique case report number, which is used for the life of the case.

C. AUTHORIZATION/APPLICATION NUMBER FORMAT (B.4.k.4.1)

In the section designated for drug information, use the following format for the "Authorization/Application Number" element (B.4.k.4.1) <drugauthorizationnumb> as indicated in Table 3 .

1. For human drug products, include the acronym "NDA" or "ANDA", followed by a space and then the number for the application (e.g., NDA 012345, ANDA 012345). For prescription drug products marketed without an approved application (Rx No Application), use "000000". For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use "999999".
2. For human biological products, include the appropriate acronym "BLA" "STN" or "PLA" followed by a space and the primary six-digit number (e.g., STN 123456).

Table 3: Detailed Description of Application Number Formats

Type of Application	Recommended Format
NDA / ANDA	NDA or ANDA 012345
STN/BLA/PLA	STN or BLA or PLA 123456
Rx No Application	000000
Non-Rx No Application	999999

D. IDENTIFICATION NUMBERS FOR INITIAL AND FOLLOW-UP ICSRs

1. Use the same <safetyreportid> for the E2B(M) elements in section A.1.0.1 for the initial ICSR and any of its follow-up ICSRs; this allows the follow-up report to be linked to the initial report in the FAERS database.
2. A common data element is essential to provide linkage between two reports. If the initial ICSR was submitted on paper but its follow-up ICSR is to be submitted electronically, include the MCN listed in Box G9 of the FDA Form 3500A from the initial report in both A.1.0.1 <safetyreportid> and in A.1.10.2 <companynumb> field in the follow-up electronic submission.
3. Always use the <safetyreportid> that was assigned to the initial ICSR when submitting follow-up reports. If you need to change the <safetyreportid> internally, note the internally reassigned <safetyreportid> in the narrative section of the follow-up report (i.e., element B.5.1) (e.g., “This ICSR has been reassigned the Company ID number COA12345”). Do not use the internally reassigned <safetyreportid> for any follow-up reports.
4. In the event that an incorrect <safetyreportid> has been used in a follow-up report, contact the FAERS electronic submission coordinator at faeresub@fda.hhs.gov so that the follow-up ICSR can be matched to the initial ICSR.

E. MedDRA SPECIFIC ELEMENTS

Use the Medical Dictionary for Regulatory Activities (MedDRA) to code medical terminology.⁴ When possible, use the Lowest Level Term (LLT), and record the LLT as the MedDRA numeric code rather than the LLT name (e.g. the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444).

1. Reaction/event
 - a) Reaction/event as reported by the primary source field
Record the original reporter’s words verbatim and/or use short phrases to describe the reaction/event in element (B.2.i.0).
 - b) Reaction/event MedDRA term LLT numeric code or text field
Record the MedDRA LLT that most closely corresponds to the term reported by the original reporter in element (B.2.i.1).
 - c) Reaction/event MedDRA term PT numeric code or text field
Record the MedDRA PT that most closely corresponds to the term reported by the original reporter in element (B.2.i.2).

⁴ Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280; Direct 571-313-2574; fax 571-313-2345; e-mail MSSOhelp@mssotools.com).

2. Other E2B elements

For the E2B elements listed in Table 4, use either MedDRA text or, preferably, the corresponding numeric code.

Table 4: Additional E2B Elements for Preferred MedDRA Coding

Element	DTD Descriptor 2.1	Length
B.1.7.1a.2	<patientepisodename>	250 AN
B.1.8f.2	<patientdrugindication>	250 AN
B.1.8g.2	<patientdrugreaction>	250 AN
B.1.9.2b	<patientdeathreport>	250 AN
B.1.9.4b	<patientdetermineautopsy>	250 AN
B.1.10.7.1a.2	<parentmedicalepisodename>	250 AN
B.1.10.8f.2	<parentdrugindication>	250 AN
B.1.10.8g.2	<parentdrugreaction>	250 AN
B.3.1c	<testname>	100 AN
B.4.k.11b	<drugindication>	250 AN
B.4.k.17.2b	<drugrecruration>	250 AN
B.4.k.18.1b	<drugreactionasses>	250 AN
B.5.3b	<senderdiagnosis>	250 AN

F. DRUG(S) DESCRIPTION AND CASE NARRATIVE ELEMENTS

In order for FAERS to successfully process your electronic ICSR submission, applicants are advised to populate the drug description and narrative elements as indicated in Table 5.

Table 5: Detailed Description of Drug(s) and Narrative Elements*†

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 name
B.5.1	<narrativeincludeclinical>	20000AN	Case narrative

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

†APPENDIX I lists specific examples of correct drug element formats

1. Record multiple drugs by:

- a) listing the proprietary drug product name in element (B.4.k.2.1) and/or as the drug substance name in element (B.4.k.2.2).
- b) listing the characterization of each reported drug's role, such as suspect (primary, secondary), concomitant, or interacting in element (B.4.k.1).

2. Medicinal Product Names (B.4.k.2.1) and Active Substance Name (B.4.k.2.2)

FDA validates medicinal product names to the available Structured Product Labeling (SPL)⁵, the submitted label (as ICSR attachment), and the Substance Registration System (SRS).

- a) When the product has an SPL, use the same naming convention as it appears in the SPL when submitting the ICSR.
- b) When submitting a product label as an attachment to an ICSR, use the name as it appears on the submitted product label.
- c) If no medicinal product is named and only the active substance is named, use the name of the active substance as it appears in the SRS⁶.

3. Case Narrative

a) Initial ICSR

Record all case narrative information including clinical course, therapeutic measures, outcome and all additional relevant information in element (B.5.1). If the information exceeds the field length, consider using abbreviations or describe the information utilizing fewer words.

b) Follow-up ICSR

Record both new information and corrections to previously submitted ICSRs in element (B.5.1.7).

⁵ The Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information.

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

⁶ <http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm>

⁷ See the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-Postmarketing Individual Case Safety Reports*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072369.pdf>

G. OTHER DATA ELEMENTS

1. Dosage information field

Supplement the dosage information captured in the structured fields in element (B.4.k.6) <drugdosagetext>.

2. Pharmaceutical form field

Record the pharmaceutical form in element (B.4.k.7) <drugdosageform>. FDA accepts the European Medicines Agency (EMA) dosage codes or text.⁸

3. Route of administration field

Code the route of administration in element (B.4.k.8) <drugadministrationroute> as described in the E2B(R2) Guidance.

4. Receiver field (A.3.2)

Designate FDA as the receiver using the code or text listed in Table 6.

Table 6: Receiver Information

Element	DTD Descriptor 2.1	Code or Text
A.3.2.1	<receivertype>	2
A.3.2.2a	<receiverorganization>	FDA
A.3.2.2b	<receiverdepartment>	Office of Surveillance and Epidemiology
A.3.2.2d	<receivergivenname>	FAERS
A.3.2.3a	<receiverstreetaddress>	10903 New Hampshire Avenue
A.3.2.3b	<receivercity>	Silver Spring
A.3.2.3c	<receiverstate>	MD
A.3.2.3d	<receiverpostcode>	20993
A.3.2.3e	<receivercountrycode>	US
A.3.2.3l	<receiveremailaddress>	faersesub@fda.hhs.gov

5. Message sender field (M.1.5)

a) Test ICSRs:

<messagereceiveridentifier>ZZFDATST</messagereceiveridentifier>

b) Production ICSRs:

<messagereceiveridentifier>ZZFDA</messagereceiveridentifier>

⁸ For a complete list of dosage form codes and text:

<http://eudravigilance.ema.europa.eu/human/PharmaceuticalDoseFormsUpdate.asp>

V. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS

FDA is able to accept and archive ICSR attachments in PDF format. Currently approved formats for the non-structured component (attachments) of an ICSR are PDF version 1.4 (current ICH standard) or 1.6 (current version in use at FDA). An ICSR attachment may be electronically submitted to FAERS either at the same time or after its ICSR is submitted to FAERS. An ICSR must be successfully received in order to link the ICSR to its attachment(s).

A. CONVERTING THE ICSR ATTACHMENT TO PORTABLE DOCUMENT FORMAT (PDF)

Applicants are to 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. IDENTIFICATION INFORMATION IN THE PDF DOCUMENT INFORMATION FIELDS

Each PDF file contains fields to be filled in by the author of the document. FAERS uses these fields in its system to locate and retrieve the attachments to specific ICSRs. To help match the attachment(s) to the ICSR, applicants should fill in the PDF document information fields with the appropriate E2B(R2) data elements for the ICSR as indicated in Table 7.

Table 7: 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(R2)

In addition:

- Use the ISO-8859-1 character set for the information fields.
- Do not exceed the character length indicated above for each information field.
- Avoid creating any custom fields with names identical to the information fields listed in Table 7.

If you need assistance, you can contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov.

APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMAT

Examples of Application Number Format		Comment
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb> <drugauthorizationholder>COMPANYX</drugauthorizationholder>	
Incorrect	<drugauthorizationnumb>123456/10300</drugauthorizationnumb>	Use the appropriate prefix for the NDA/ANDA/STN/BLA/PLA; do not include additional data after the application number
Incorrect	<drugauthorizationnumb>NDA 12-345;IND12,345 </drugauthorizationnumb>	Omit hyphens and commas in the application number. Do not populate the tag with two application numbers; the IND report needs to be submitted separately to the Office of New Drugs
Incorrect	<drugauthorizationnumb>OTC Product</drugauthorizationnumb>	For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use "999999"
Incorrect	<drugauthorizationnumb>NDA 012345(COMPANYX)</drugauthorizationnumb> <drugauthorizationholder></drugauthorizationholder>	Do not populate the company name in the <drugauthorizationnumb> tag

Examples of Drug Element Format	Comment
Correct <medicinalproduct>TYLENOL</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	The stated proprietary name in the <medicinalproduct> tag is the same as provided for structured product labeling (SPL) listing
Correct <medicinalproduct>MIRACLE WONDER DRUG</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	The stated proprietary name is the same as provided in the product label
Incorrect <medicinalproduct>AMAZING DRUG OTC @</medicinalproduct> <activesubstancename>ACETAMINOPHEN 500 mg </activesubstancename>	Only the brand name and active substance should be listed in the <medicinalproduct> and <activesubstance> tags Any additional information should be captured in the relevant structured fields and not included as prefixes and suffixes in the drug name tags.
Incorrect <medicinalproduct>NEW DRUG 40 mcg/mL </medicinalproduct> <activesubstancename>NEWSUBSTANCE Inj </activesubstancename>	Only the brand name and active substance should be listed in the <medicinalproduct> and <activesubstance> tags Any additional information should be captured in the relevant structured fields and not included as prefixes and suffixes in the drug name tags.
Incorrect <medicinalproduct> MWD </medicinalproduct> <activesubstancename> APAP </activesubstancename>	Do not use abbreviations for the brand name or active ingredients in the <medicinalproduct> and <activesubstance> tags