
Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Postmarketing Expedited Safety Reports

DRAFT GUIDANCE

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For questions regarding this draft document send an e-mail (CDER and CBER) to aersesub@cder.fda.gov, or telephone (CDER) Deborah Yapple, 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

Providing Regulatory Submissions in Electronic Format — Postmarketing Expedited Safety Reports

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1 **Guidance for Industry¹**
2 **Providing Regulatory Submissions in Electronic Format –**
3 **Postmarketing Expedited Safety Reports**
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8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's)
9 current thinking on this topic. It does not create or confer any rights for or on any person and does
10 not operate to bind FDA or the public. An alternative approach may be used if such approach
11 satisfies the requirements of the applicable statutes and regulations.
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18 **I. INTRODUCTION**
19

20 This is one in a series of guidance documents intended to assist applicants making regulatory
21 submissions in electronic format to the Center for Drug Evaluation and Research (CDER) and
22 the Center for Biologics Evaluation and Research (CBER) in the Food and Drug Administration
23 (FDA). Agency guidance documents on electronic submissions will be updated regularly to
24 reflect the evolving nature of the technology and the experience of those using this technology.
25

26 This guidance discusses general issues related to the electronic submission of postmarketing
27 expedited safety reports for (1) drug products marketed for human use with new drug
28 applications (NDAs) and abbreviated new drug applications (ANDAs), (2) prescription drug
29 products marketed for human use without an approved NDA or ANDA, and (3) therapeutic
30 biological products marketed for human use with biologic license applications (BLAs). This
31 guidance does not apply to vaccines.
32

33 The guidance for industry *Providing Regulatory Submissions in Electronic Format — General*
34 *Considerations* (January 1999) discusses issues common to all types of electronic regulatory
35 submissions, such as acceptable file formats, media, and submission procedures (General
36 Considerations guidance of 1999).² Information provided in this guidance on electronic
37 submission of postmarketing expedited safety reports supercedes information provided in the
38 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.

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

46
47

48 **II. GENERAL ISSUES**

49

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

54

55 **A. Parts of a Postmarketing Expedited Safety Report**

56

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

60

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

69

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

74

75 **B. Electronic Transport Format**

76

77 The electronic transport format to be used with the E2B data elements is defined in the
78 ICH document entitled *M2 Electronic Transmission of Individual Case Safety Report*
79 *Message Specification version 2.24 (ICH ICSR DTD Version 2.0) (M2 Specification*
80 *version 2.24, DTD version 2.0)*, which can be found at www.fda.gov/cder/m2. In
81 November 2000, the ICH M2 working group revised the specifications for electronic
82 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)*.

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

85
86 **C. The Archival Copy**

87
88 Once we have identified the ICSR and/or ICSR attachments in public docket number
89 92S-0251 as submission types that we can accept in an electronic format, you can provide
90 them in an electronic format in place of the currently required paper copies.⁴ Until that
91 time, if you wish to submit electronically, you must also submit a paper copy for the
92 archival file.⁵

93
94 **D. Notification of Initial ICSR Submission**

95
96 Prior to the first time that you submit an ICSR electronically to the FDA, you should
97 notify the AERS electronic submission coordinator of your intent at
98 aersesub@cderr.fda.gov. It is not necessary to contact the AERS electronic submission
99 coordinator prior to sending an ICSR to the FDA for subsequent electronic submissions
100 of ICSRs.

101
102 **E. Sending in the Submission**

103
104 You can send an ICSR to the FDA using either physical media (i.e., floppy disk, CD-
105 ROM, or digital tape) or the FDA’s Electronic Data Interchange (EDI) gateway. We
106 prefer that you send the ICSR using the EDI gateway because this allows the most
107 efficient processing of the reports. ICSR attachments, however, should be sent *only* on
108 physical media.

109
110 For information on providing submissions using the EDI gateway, contact the AERS
111 electronic submission coordinator at aersesub@cderr.fda.gov.

112
113 Information on preparing and sending submissions on physical media can be found in the
114 General Considerations guidance of 1999.⁶ Current regulations require that
115 postmarketing expedited safety reports bear prominent identification as to their contents
116 (i.e., “15-day Alert report,” or “15-day Alert report-followup”).⁷ When sending a report
117 to the FDA on physical media, applicants should identify the media as described in the
118 current regulations (i.e., “15-day Alert report,” or “15-day Alert report-followup”).
119

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).

120 **F. Notification of Receipt of Report by the FDA**

121
122 Once a submission reaches the EDI gateway and is successfully recognized and
123 decrypted, an EDI gateway acknowledgement will be returned to the sender. The date of
124 this acknowledgement will serve as the official receipt date of the submission.
125

126 After receipt of the submission, we will load the ICSRs into the AERS database. For
127 submissions sent via the EDI gateway, an automated standard generalized markup
128 language (SGML) acknowledgment message, which gives the status of each report in the
129 transmission, will be returned to you via the gateway.
130

131 For submissions sent on physical media, the Agency will determine the receipt date as it
132 does with submissions sent to the FDA on paper (i.e., receipt date is the date it arrives at
133 the Agency). The Agency will only contact you if there are problems with the format of
134 the report or if the report does not load properly into the AERS database. We will contact
135 you by phone or email, describe the problem, and request a resubmission of the report in
136 the proper format. This resubmission should take place as soon as possible.
137

138
139 **III. ORGANIZING THE ELECTRONIC SUBMISSION**

140
141 **A. ICSR**

142
143 The following describes the steps you should take to prepare and send the ICSR in an
144 electronic format.
145

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

147
148 Whether you are providing the ICSR on physical media or sending it using the EDI
149 gateway, you should provide the ICSR as an SGML file using the data elements and
150 electronic transport format currently accepted by the FDA (e.g., currently, the FDA is
151 accepting E2B data elements with the M2 Specification version 2.24, DTD version 2.0
152 electronic transport format.⁸ See sections II.A and II.B in this guidance).
153

154 a. Coding reactions and events

155
156 Section B.2 of E2B is designated for reaction/event terms. For these fields, the FDA
157 prefers that applicants use the Medical Dictionary for Regulatory Activities (MedDRA).⁹
158 For the E2B field, B.2.i.1, you should insert the lowest level term (LLT) in MedDRA that
159 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@meddramssso.com, Internet at www.meddramssso.com).

160 B.2.i.2, you should insert the preferred term (PT) in MedDRA that corresponds to the
161 LLT used in B.2.i.1.¹⁰ If you do not have access to MedDRA, you should populate the
162 E2B field, B.2.i.2, with a reaction term (e.g., a COSTART term, a WHOART term) and
163 leave the E2B field, B.2.i.1, blank.

164
165 b. Identification numbers

166
167 Section A.1 of E2B is designated for identification numbers. You should include in the
168 A.1.10 field a concatenation of the country code, sender identification, and report
169 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
170 received by one entity (e.g., the FDA, a company) **AND** the entity subsequently transmits
171 the report to one or more other entities.¹¹

- 172
173 • E2B field A.1.10.1 should be filled in by the FDA (or other regulatory authority) if:
174 1. it receives a direct report from a health care professional or consumer **AND**
175 2. the report is subsequently sent to one or more other entities.

- 176
177 • E2B field A.1.10.2 should be filled in by a company if:
178 1. it is the first company to receive a direct report from a health care professional or
179 consumer **OR**
180 2. it is the first company to receive an ICSR from the FDA (or other regulatory authority)
181 **AND**
182 3. the report is subsequently sent to one or more new entities.

- 183
184 • E2B field A.1.11.2 should be filled in by a company if:
185 1. it receives an ICSR from another company **AND**
186 2. the report is subsequently sent to one or more new entities.

187
188 The A.1.11.2 field should be used by all companies that receive an ICSR from another
189 company (i.e., this field may contain multiple identification numbers). Possible scenarios
190 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.

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192

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 |

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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.

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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 |

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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 |

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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

227
228 UNB+UNOB:1+000000000:01+FDAEDI.CDER:zz+000427:1100+10001
229 'this is a test text'
230 UNZ+1+10001'
231

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

233
234 If you choose to submit the ICSR on physical media, you should use *edi* as the extension
235 for each file. The name of the file should be 40 characters or less excluding the three-
236 digit extension. You should place the *edi* files on the physical media along with any
237 ICSR attachment files. You should follow the General Considerations guidance of 1999
238 for preparing and sending physical media.¹²
239

240 If you choose to submit the ICSR over the EDI gateway, contact the AERS electronic
241 submission coordinator at aersesub@cderr.fda.gov for additional guidance.
242

243 **B. ICSR Attachments**

244
245 The following describes the steps you should take to prepare and send attachments to an
246 ICSR in an electronic format.
247

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

249
250 We are able to archive ICSR attachments in pdf format. You should provide an individual
251 pdf file for each attachment to an ICSR. If there is more than one piece of information in
252 an ICSR attachment, include each piece of information in the same pdf file and provide a
253 pdf bookmark to each piece of information. For example, if there is a hospital discharge
254 summary and an autopsy report for a single ICSR, you should include both in a single pdf
255 file with a bookmark to the hospital discharge summary and a bookmark to the autopsy
256 report.
257

258 *2. Enter Identification Information in the pdf Document Information Fields*

259
260 Each pdf file contains fields that can be filled in by the author of the document. We use
261 these fields in our system to locate and retrieve the attachments to specific ICSRs. To
262 help us match the attachment to the ICSR, you should fill in the pdf document
263 information fields with the appropriate E2B/E2BM data elements included in the ICSR as
264 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.

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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) |

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* 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.