Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Postmarketing Individual Case 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 the Division of Dockets Management (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@fda.hhs.gov, or telephone (CDER) Roger Goetsch, 301-770-9299 or (CBER) Stephen Ripley, 301-827-6210.

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)

June 2008
Electronic Submissions

Guidance for Industry

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Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-210
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
(Internet) http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
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Technical specifications associated with this guidance will be provided as stand alone documents. They will be updated periodically independent of the guidance. To ensure that you have the most recent versions of the stand alone documents, check the appropriate center's guidance Web page. For CBER, this Web page is http://www.fda.gov/cber/esub/icsr.htm. For CDER, this Web page is http://www.fda.gov/cder/regulatory/ersr/#Postmarketing.

Guidance for Industry[1]
Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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). This guidance consolidates and revises information pertaining to electronic submission of postmarketing individual case safety reports (ICSRs) and attachments to ICSRs (ICSR attachments)[2] in the following guidances:

- Draft guidance for industry *Providing Regulatory Submissions in Electronic Format – Postmarketing Expedited Safety Reports* issued in May 2001 (Expedited Reports draft guidance)
- Draft guidance for industry *Providing Regulatory Submissions in Electronic Format – Postmarketing Periodic Adverse Drug Experience Reports* issued in June 2003 (Periodic Reports draft guidance)

This guidance on ICSRs supersedes the Expedited Reports draft guidance in its entirety and the ICSR and ICSR attachment portion of the Periodic Reports draft guidance. The descriptive

[1] This guidance has been prepared by the Office of Information Technology (OIT) and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER).

[2] See section II of this document for a description of ICSRs and ICSR attachments.

information portion of the Periodic Reports draft guidance is now addressed only in other Agency guidance. [3]

This guidance discusses general information related to the electronic submission of postmarketing ICSRs and ICSR attachments for the following products[4]:

- Drug products marketed for human use with approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs)
- Prescription drug products marketed for human use without an approved NDA or ANDA
- Biological products, including therapeutic vaccines,[5] marketed for human use with approved biologic license applications (BLAs) and submission tracking numbers (STNs)
- Human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated under section 361 of the Public Health Service Act (referred to in this guidance as section 361 HCT/Ps)
- Nonprescription human drug products marketed without an approved application

This guidance does not apply to prophylactic vaccines, whole blood, or components of whole blood.[6]

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[3] This guidance does not address the electronic submission of the descriptive information for periodic reports. For information on submitting the descriptive information in electronic format, see the section on "Periodic safety update reports" in the guidance for industry entitled *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. The discussion of the electronic submission of descriptive information in the eCTD guidance does not apply to vaccines, whole blood, or components of whole blood.

[4] See the postmarketing safety reporting regulations for:

- NDAs in 21 CFR 314.80 and ANDAs in 21 CFR 314.98,
- prescription drug products marketed for human use without an approved NDA or ANDA in 21 CFR 310.305,
- biological products marketed for human use with BLAs and STNs in 21 CFR 600.80,
- section 361 HCT/Ps in 21 CFR 1271.350(a), and
- nonprescription human drug products marketed without an approved application in section 760 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 379aa) (See Public Law 109-462 available on the Internet at http://www.fda.gov/cder/regulatory/public_law_109462.pdf).

Postmarketing safety reports for all of these products may be submitted to FDA in electronic format in place of paper (see memoranda 23 in Docket 1992S-0251, available on the Internet at http:/www.fda.gov/ohrms/dockets/dockets/92s0251/07s0251.htm).

[5] Therapeutic vaccines are used to treat disease (e.g., BCG for treatment of bladder cancer), while prophylactic vaccines are used to prevent disease (e.g., influenza vaccine).

[6] Postmarketing safety reports for prophylactic vaccines are submitted to the Vaccine Adverse Event Reporting System (VAERS). Information on VAERS is available on the Internet at http://www.fda.gov/cber/vaers/vaers.htm. Postmarketing reports of fatalities that are required to be submitted for whole blood and components of whole blood (21 CFR 606.170(b)) are currently submitted to FDA on paper. Information on submitting these reports is available on the Internet at http://www.fda.gov/cber/transfusion.htm.

Changes from the Expedited Reports and Periodic Reports draft guidances include consolidation of all the information pertaining to electronic submission of ICSRs and ICSR attachments into a single guidance with associated technical specifications and updates on the recommendations for making these submissions, including information on the following:

- Data elements and electronic submission formats now being supported by the FDA
- Data to include to enable the Agency to process ICSRs and ICSR attachments;
- How to create the message header for submissions sent to the FDA's Electronic Submission Gateway (ESG)
- Descriptions of Agency acknowledgments for submissions that are sent to the ESG

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. The technical specifications associated with the guidance are being provided as stand alone documents to make them more accessible to the user. **The associated specifications will be updated periodically independent of the guidance. To ensure that you have the most recent versions of the stand alone documents, check the appropriate center's guidance Web page.**

Postmarketing ICSRs and ICSR attachments sent to CDER and CBER for human drug and biological products addressed by this guidance are entered into the FDA's Adverse Event Reporting System (AERS) database. [7] CDER is responsible for oversight of the AERS database and entering of information into it for both CDER and CBER. Applicants sending postmarketing ICSRs and ICSR attachments in ***electronic format*** to the FDA for products regulated by CBER should follow procedures provided for CDER in this guidance and elsewhere.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GENERAL INFORMATION

An ***ICSR*** is a description of an adverse drug experience[8] related to an individual patient or subject.[9] An ICSR is made up of data elements.

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[7] Postmarketing safety reports for therapeutic vaccines are included in AERS, but reports for prophylactic vaccines, whole blood, and components of whole blood are not. See footnote #6 for information on submitting safety reports to FDA for prophylactic vaccines, whole blood, and components of whole blood.

[8] For purposes of this guidance, the term *adverse drug experience* includes an adverse experience associated with use of a biological product.

[9] The information provided in an ICSR is information required on an FDA Form 3500A (or, if preferred, on a CIOMS I form for foreign events) for each report of an adverse drug experience (§§ 310.305(d)(1), 314.80(f)(1), and 600.80(f)(1)).

ICSR attachments include supporting information for ICSRs such as relevant hospital discharge summaries and autopsy reports/death certificates. ICSR attachments also include published articles for ICSRs based on scientific literature (§§ 314.80(d) and 600.80(d)).

This section briefly addresses some general information related to the electronic submission of ICSRs and ICSR attachments in:

- 15-day Alert reports (§§ 310.305(c), 314.80(c)(1) and 600.80(c)(1)),
- periodic reports (§§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B)),
- HCT/P adverse reaction reports (§ 1271.350(a)), and
- serious adverse event reports required by section 760 of the Act.[10]

Procedures for electronic submission of ICSRs and ICSR attachments, whether they are part of a 15-day Alert report, HCT/P adverse reaction report, serious adverse event report, or periodic report, are the same.

A. Parts of a Postmarketing Safety Report

1. 15-day Alert Report, HCT/P Adverse Reaction Report, and Serious Adverse Event Report

For the purpose of this discussion of electronic submissions, postmarketing 15-day Alert, HCT/P adverse reaction, and serious adverse event reports are considered to have two parts:

- the ICSR and
- ICSR attachments, if applicable.

2. Periodic Report

For the purpose of this discussion of electronic submissions, a postmarketing periodic report is considered to have three parts:

- the ICSR
- ICSR attachments, if applicable, and
- descriptive information.

3. Followup Report

For the purpose of this discussion of electronic submissions, a postmarketing followup report is considered to have two parts:

- the ICSR and

[10] See footnote #4.

- ICSR attachments, if applicable.

A followup ICSR provides information about an adverse drug experience that has been previously reported as an initial ICSR (a 15-day Alert report, an HCT/P adverse reaction report, a serious adverse event report, or an ICSR in a periodic report). Followup ICSRs should provide a complete picture of the current understanding of an adverse drug experience, rather than providing only the changes and/or updates to an ICSR. Additional information on the content and reporting considerations for followup reports to ICSRs submitted to the Agency is available in guidance for industry.[11]

B. Identification Numbers for Initial and Followup ICSRs

Postmarketing safety reporting often involves submitting a series of reports consisting of the initial ICSR and followup ICSRs, along with any associated attachments, over the life cycle of an individual case. To avoid duplicate ICSRs in the AERS database, each initial ICSR report should have a unique identification number. Because we need to match followup ICSRs with the initial ICSR, it is important that the identification number used for the initial ICSR be used for any followup ICSRs. Thus, the initial ICSR and all of its followup ICSRs will be linked in AERS, regardless of the time or method of transmission.

For example:

- If your initial ICSR is submitted to the FDA on paper with its manufacturer control number as its identification number and you wish to submit followup reports for the ICSR in an electronic format, you should use the manufacturer control number from the initial ICSR report as your identification number for all of the followup reports.

- If your initial ICSR is submitted to the FDA in an electronic format with a concatenation of the country code, sender identification, and report number as its identification number and you wish to submit a followup report for the ICSR on paper, you should use the concatenated number from the initial ICSR report as your identification number for the followup report.

See the section on identification numbers for initial and followup ICSRs in the associated document "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments."

C. Data Elements for Electronic Submissions

[11] FDA issued guidance on *Postmarketing Reporting of Adverse Drug Experiences* in March 1992. In March 2001, FDA issued in draft a revised version of the 1992 guidance entitled *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*. Once finalized, the revised guidance will represent the Agency's current thinking on followup reports.

The data elements currently accepted by FDA for electronic submission of ICSRs are defined in the associated document "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments" (in the section on data elements and electronic transport format for electronic submissions).

D. Electronic Transport Format

The electronic transport format currently accepted by FDA for electronic submission of ICSRs is defined in the associated document, "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments" (in the section on data elements and electronic transport format for electronic submissions).

E. Notification of Initial Electronic ICSR Submission

Before the first time that you submit an ICSR in electronic format to the FDA, you should notify the AERS electronic submission coordinator of your intent at aersesub@fda.hhs.gov. The AERS coordinator will assist you with submission of a test file. It is not necessary to contact the AERS coordinator prior to subsequent submissions of ICSRs in electronic format.

F. Sending in the Submission

You can send an ICSR and/or ICSR attachment to the FDA using either appropriate physical media or the FDA's Electronic Submission Gateway (ESG). We prefer that you send the ICSR and ICSR attachment using the ESG because this allows the most efficient processing of the submissions. 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."

For efficient processing, an ICSR submission should precede the submission of any attachments for that ICSR.

G. Notification of Receipt of Submissions by the FDA

Once a submission (one or more ICSRs or ICSR attachments) reaches the Electronic Submission Gateway (ESG) and is successfully recognized and decrypted, an ESG message delivery notice (MDN) will be sent to the sender. The date of this MDN will serve as the official FDA receipt date of the submission.

After receipt of the submission, we will enter each ICSR into the AERS database. For submissions sent via the ESG, a second automated acknowledgment message (AERS acknowledgement) will be sent to the sender via the ESG. The AERS acknowledgment will give the sender the status of each ICSR or ICSR attachment in the transmission. For information on acknowledgement message files and formats, see the general section of the associated document "Acknowledgement Messages and Formats."

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 our systems. We will contact you by phone or email within 3 working days after we receive your report, describe the problem, and request a resubmission of the report in the proper format. This resubmission should take place as soon as possible. The receipt date of the resubmission will serve as the official FDA receipt date of the report. If you are not able to resubmit your report in an electronic format in a timely manner, you should submit it to the FDA by other means (e.g., on paper) to meet your regulatory requirements.

If your ICSR is submitted to us using the ESG and your ICSR attachments are submitted to us on physical media, the ESG MDN acknowledgment for the ICSR will serve as the official FDA receipt date of the ICSR and the date that we receive the physical medium containing the ICSR attachments will serve as the official FDA receipt date of the ICSR attachments. Even though the ICSR and ICSR attachments may be received by the FDA on different days, they are required to be submitted to the Agency within the time periods specified in our statutes or regulations.[12] Please plan your submissions accordingly.

H. Contingencies if the ESG or AERS Is Temporarily Unavailable

We expect that you will receive your ESG MDN and AERS acknowledgments within 24 hours after you have submitted an ICSR to the ESG. If you do not receive these acknowledgments within 24 hours, you should first check our Web site on the Internet at www.fda.gov/esg/default.htm (ESG and AERS system status) to determine whether we are experiencing any problems with the ESG and/or AERS.

- **If both the ESG and AERS are functional**, you should contact the electronic submission coordinator at aersesub@fda.hhs.gov to determine why you have not received your acknowledgments.

- **If the ESG is not functional** (whether or not AERS is functional) and you decide to meet your regulatory requirements by submitting your ICSRs on physical media, you should **not** resubmit the ICSRs to us using the ESG when it becomes functional. In this case, the official FDA receipt date of the ICSRs is the date the physical media arrives at the Agency.

[12] The ICSRs and ICSR attachments for 15-day Alert reports and HCT/P adverse reaction reports are due within 15 calendar days of initial receipt of the information (see §§ 310.305(c)(1)(i), 314.80(c)(1)(i), 600.80(c)(1)(i), and 1271.350(a)). The ICSRs and ICSR attachments for periodic reports are due within 30 days of the close of the quarter for postmarketing periodic reports due quarterly and within 60 days of the anniversary date of approval of the application for postmarketing periodic reports due annually (see §§ 314.80(c)(2)(i) and 600.80(c)(2)(i)). The ICSRs and ICSR attachments for serious adverse event reports are due within 15 business days of receipt of the report (see section 760(c) of the Act).

- **If the ESG is functional but AERS is not functional**, you should **not** submit your ICSRs to us by other means (i.e., physical media or paper). We will load your ICSRs into AERS as soon as AERS is functional. At that time, you will receive an AERS acknowledgment.

If the ESG or AERS is not functional, a resubmission could affect FDA receipt dates. When appropriate, we will work with you to reset the receipt date, and you should keep relevant documentation for compliance purposes.

If you submit ICSRs to the ESG that we are not able to load into the AERS database because you have not used the data elements and electronic transport formats that the FDA is currently supporting,[13] the AERS acknowledgment will indicate that we could not load these ICSRs into AERS. The acknowledgment will also indicate which, if any, ICSRs that you sent to the ESG at the same time were loaded into AERS. You should resubmit to us only those ICSRs that were not loaded into AERS. Your resubmission should be given a different file name than the original submission and should take place as soon as possible. The date of the ESG MDN acknowledgment for the resubmission will serve as the official FDA receipt date of the ICSR. If you are not able to correct and resubmit your ICSR in an electronic format in a timely manner, you should submit it to the FDA by other means (e.g., on paper) to meet your regulatory requirements.

III. PREPARING AND SUBMITTING ELECTRONIC ICSRS AND ICSR ATTACHMENTS

Electronic ICSRs and ICSR attachments should be submitted to FDA in an electronic format that we can process, review, and archive. For instructions on organizing, preparing, and submitting ICSRs and ICSR attachments in electronic format, see the associated document "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments."

[13] See the data elements and electronic transport format for electronic submissions section of the associated document "Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments."