Guidance for Industry

Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers

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)

July 2013
Electronic Submissions

Guidance for Industry

Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers

Additional copies are available from:

Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
(Tel) 240-276-9300
or

Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
Phone: 800-835-4709 or 301-827-1800

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)

July 2013
Electronic Submissions

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]

Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers

This guidance represents 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 guidance provides firms with information on the appropriate electronic file format to use when electronically submitting to FDA postmarket, non-expedited individual case safety reports (ICSRs) on adverse drug experiences.[2] Non-expedited ICSRs are the case reports required to be submitted at the time firms submit their periodic adverse (drug) experience reports (21 CFR 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B)). This guidance explains that firms that previously submitted non-expedited ICSRs in an electronic format that is not supported by FDA should contact the Center for Drug Evaluation and Research (CDER)[3] or the Center for Biologics Evaluation and Research (CBER) and resubmit their non-expedited ICSRs in a compatible electronic format.

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

[2] For purposes of this guidance, *adverse drug experience* includes an adverse experience associated with use of drug or a biological product, including a therapeutic vaccine.

[3] CDER is responsible for oversight of FDA's Adverse Event Reporting System (FAERS) database and entering information into it for both CDER and CBER. Applicants sending postmarket ICSRs and ICSR attachments in electronic format to FAERS for products regulated by CBER should follow procedures for CDER in the draft guidance for industry *Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports.*

Note: Agency guidance, including on electronic submissions, are updated to reflect the evolving nature of the technology and the experience of those using this technology. To make sure you have the latest version of a guidance, go to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

This guidance does not apply to reports of adverse experiences associated with use of prophylactic vaccines, human cells, tissues, cellular and tissue-based products, whole blood, or components of whole blood.

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.[4]

II. BACKGROUND

FDA regulations at 21 CFR 314.80(c)(2) and 600.80(c)(2) require applicants to submit postmarket periodic safety reports at prescribed intervals. Each periodic safety report must contain a descriptive portion and the non-expedited ICSRs[5] for the reporting interval. The descriptive portion can be submitted as a periodic adverse drug experience report[6]; a periodic adverse experience report[7]; a periodic safety update report[8]; or a periodic benefit–risk evaluation report.[9]

Non-expedited ICSRs can be submitted on paper or electronically.[10] When submitted electronically, the non-expedited ICSRs should be submitted in XML format. This is because FDA is currently able to process electronic submissions of non-expedited ICSRs only in XML, prepared according to International Conference on Harmonisation (ICH) standards for database-

[4] Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), provides that submissions under 505(b), (i), or (j) of the FD&C Act or 351(a) or (k) of the Public Health Service Act be submitted in such electronic format as specified by the FDA in guidance. In section 745A(a), Congress granted explicit statutory authority to FDA to implement the electronic format for submissions requirement by guidance. FDA may consider, at a future date, whether to include information pertaining to providing submissions of postmarket non-expedited ICSRs in electronic format in guidance pursuant to Section 745A(a) of the FD&C Act.

[5] As described in 21 CFR 314.80(c)(2)(ii)(*b*) and 600.80(c)(2)(ii)(B). Non-expedited ICSRs were previously referred to as *periodic ICSRs*.

[6] As described in 21 CFR 314.80.

[7] As described in 21 CFR 600.80.

[8] FDA allows firms with approved waivers (under 21 CFR 314.90 and 600.90) to use the ICH E2C Periodic Safety Update Report format when submitting the descriptive portion of periodic safety reports.

[9] FDA allows firms with approved waivers (under 21 CFR 314.90 and 600.90) to use the ICH E2C(R2) Periodic Benefit-Risk Evaluation Report format when submitting the descriptive portion of periodic safety reports.

[10] On August 21, 2009, FDA issued a proposed rule entitled "Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements" (74 FR 42184). Once finalized, the rule will require that all mandatory postmarketing safety reports for human drug and biological products be submitted in an electronic format that FDA can process, review, and archive, unless a waiver is granted.

to-database transmission of information.[11] When submitted in this compatible electronic format, non-expedited ICSRs can be downloaded into the FDA Adverse Event Reporting System (FAERS) database through the Electronic Submission Gateway.

We have become aware that some firms have submitted non-expedited ICSRs to the electronic Common Technical Document (eCTD) in a portable document file (pdf) format together with the descriptive portion of the periodic safety report.

FDA does not have a systematic method to identify non-expedited ICSRs that are submitted to the eCTD in pdf format together with the descriptive portion of the periodic safety report. In addition, non-expedited ICSRs submitted to the eCTD in pdf format cannot be downloaded into the FAERS database. Lack of access to non-expedited ICSRs in FAERS hinders FDA's ability to monitor product safety and public health. Furthermore, submission in pdf format prevents public access to the non-expedited ICSRs through FAERS.[12]

III. TECHNICAL QUESTIONS AND ANSWERS

The following technical questions and answers are intended to provide clarity to industry and to facilitate the resubmission of non-expedited ICSRs in a compatible electronic file format.

1. Why is this guidance needed?

Some firms have submitted non-expedited ICSRs to FDA in an electronic file format that cannot be processed into the FAERS database. This guidance explains what steps firms should take if they have submitted ICSRs as pdf-formatted documents or in other non-XML formats. Firms should contact FDA as instructed below if they have previously submitted non-expedited ICSRs in this format.

2. What steps should firms take if they have submitted non-expedited ICSRS in an electronic format other than the XML format?

A general correspondence letter should be sent by email to inform FDA about previous submission(s) of non-expedited ICSRs. Notifications should be sent to the following addresses:

- For CDER-regulated drugs and biologics: contact the CDER Office of Surveillance and Epidemiology (OSE) at: cder-ose-pmktregs@fda.hhs.gov
- For CBER-regulated biologics: contact the CBER Electronic Submissions Program at: esgprep@fda.hhs.gov

[11] See FAERS Electronic Submissions at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.

[12] FAERS data are available to the public as quarterly data files or by written Freedom of Information request to FDA. See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.

The letter should include the inclusive dates of the previous submission(s), the subject product(s) involved, and the numbers of non-expedited ICSRs submitted for each product.

3. What can firms expect after contacting FDA?

FDA will contact firms to verify which non-expedited ICSRs should be resubmitted and to instruct them on how to resubmit these reports. In most cases, FDA will instruct firms that previously submitted non-expedited ICSRs of serious adverse experiences in the pdf format to resubmit these ICSRs in the XML format, or in paper form, if firms do not have XML-format capability.

4. Where can firms find information explaining how to submit electronic non-expedited ICSRs in the XML format?

On November 14, 2011, FDA communicated on its eCTD Web site[13] that non-expedited ICSRs should not be submitted to the eCTD. FDA described how to submit them in an electronically compatible format. The Website has since been updated with the following information[14]:

> **Important Note**
> **Submission of periodic safety reports to the eCTD**
> Periodic safety reports consist of two parts: a descriptive portion and the individual case safety reports (ICSRs). ***Only the descriptive portion of the periodic safety report can be submitted to the eCTD.***
>
> **Descriptive portion:**
> Firms can submit the descriptive portion of the periodic safety report in the following formats: the periodic adverse drug experience report, the periodic adverse experience report or, with an approved waiver, either the periodic safety update report[15] or the periodic benefit-risk evaluation report.[16] The descriptive

[13] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm. The CDER eCTD web page includes Important Notices that are updated periodically. For the most recent information about electronic submissions to CDER, check the eCTD web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm328835.htm.

[14] For instructions on organizing, preparing, and submitting either expedited or non-expedited ICSRs and ICSR attachments in electronic format, see the associated document *Specifications for Preparing and Electronically Submitting Electronic ICSRs and ICSR Attachments to FAERS*. Also, in June 2008, FDA issued draft guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – Postmarketing Individual Case Safety Reports.* Once finalized, that guidance will provide information on how to submit ICSRs in an electronic format that FDA can process, review, and archive.

[15] See FDA guidances for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and *E2C Addendum, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*, available on FDA's Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065004.htm.

portion can be submitted to the eCTD in module 5.3.6 and should indicate that the ICSRs have been submitted electronically as XML files to the FDA Electronic Submissions Gateway (ESG) or that FDA 3500A forms have been mailed to the appropriate document control center.

ICSRs:
Firms can submit ICSRs electronically using ICH E2B(R) standards[17] or by mail using Form FDA 3500A. ***Submission of ICSRs to the eCTD is not acceptable because these ICSRs cannot be processed into the FDA Adverse Event Reporting System (FAERS) database.***

[16] The ICH guideline *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2)* is available at: http://www.ich.org/. FDA has initiated the process to adopt the ICH E2C(R2) step 4 guideline as final FDA guidance.

[17] See FDA guidance for industry *E2B(R) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports, Revision 2*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065004.htm .