Guidance for Industry

Providing Submissions in Electronic Format — Postmarketing Safety Reports for Vaccines

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-7800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2014

Contains Nonbinding Recommendations

Draft – Not for Implementation

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The technical specification associated with this guidance is provided in a separate document and is updated periodically. To ensure that you have the most recent version of the technical specifications document, check the CBER ICSR Specifications Web page at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm174963.htm

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Guidance for Industry

Providing Submissions in Electronic Format — Postmarketing Safety Reports for Vaccines

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 appropriate FDA staff. 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 you, an applicant, in making postmarket regulatory submissions in electronic format to the Center for Biologics Evaluation and Research (CBER) at FDA. The guidance provides information and recommendations pertaining to the electronic submission of postmarketing safety reports involving vaccine products, including individual case safety reports (ICSRs) and attachments to ICSRs (ICSR attachments),[1] into the Vaccine Adverse Event Reporting System (VAERS). The guidance is applicable to vaccine products marketed for human use with approved biologics license applications (BLAs) for which CBER has regulatory responsibility.[2] The guidance does not apply to any other biologic product. When finalized, this guidance will supersede the FDA guidance entitled "Guidance for Industry: How to Complete the Vaccine Adverse Event Reporting System Form (VAERS-1)" dated September 1998 (1998 Guidance).

Postmarketing ICSRs and ICSR attachments for biological products, which are not addressed by this guidance, are processed into the FDA Adverse Event Reporting System (FAERS) database.[3] For general information pertaining to electronic submission of postmarketing safety reports, including ICSRs and ISCR attachments for these other products, please refer to the FDA draft guidance entitled, "Guidance for Industry: Providing Submissions in Electronic Format – Postmarketing Safety Reports" dated June 2014.[4] When finalized, this guidance will represent

[1] See section III of this document for a description of ICSRs and ICSR attachments.
[2] If an applicant is not sure where to file, the applicant should contact CBER's OCOD for information.
[3] In September 2012, the FAERS database replaced the previously used Adverse Event Reporting System (AERS) database. The transition to the FAERS database has been an important step in improving FDA's postmarketing surveillance capabilities. Information regarding the FAERS database is available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

our current thinking on this topic. Agency guidance on electronic submissions will be updated as necessary to reflect the evolving nature of the technology and the experience of those using this technology.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the Federal Register of June 10, 2014 (79 FR 33072), FDA issued a final rule entitled "Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements." This final rule requires, among other things, that certain postmarketing safety reports required under Title 21 of the Code of Federal Regulations (CFR) 310.305, 314.80, 314.98, and 600.80 (§§ 310.305, 314.80, 314.98, and 600.80) and section 760 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379aa) be submitted to FDA in an electronic format that the Agency can process, review, and archive. This final rule also adds 21 CFR 329.100 to address electronic submission of safety reports required by section 760 of the FD&C Act. These requirements are effective as of June 10, 2015.[5]

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[4] The draft guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369.pdf. Further information regarding regulations and guidances related to postmarketing safety reporting can be found on the FDA Web site, Postmarketing Safety Reporting Requirements for Drug and Biologic Products, at http://www.fda.gov/Drugs/DrugSafety/ucm299833.htm.

[5] Section 745A(a) of the FD&C Act (21 U.S.C. 379k-1), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), provides that submissions under section 505(b), (i), or (j) of the FD&C Act or section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)) shall be submitted in such electronic format as specified by FDA in guidance. In section 745A(a), Congress granted explicit statutory authority to FDA to implement the electronic format for submissions requirement by guidance. This grant of authority, however, does not preclude FDA from implementing such requirements by notice and comment rulemaking (5 U.S.C. 553). Accordingly, at this time, even though FDA has concluded that certain submissions that are addressed in the final rule are also within the scope of section 745A(a), FDA has determined that it is appropriate to amend the regulations on the submission of postmarketing safety reports to remove references to paper submissions and to specify that such reports be submitted in an electronic format that FDA can process, review, and archive. When finalized, this guidance will represent the Agency's current thinking on certain topics associated with this rulemaking. FDA may consider, at a future date, whether to include information pertaining to submission of postmarketing safety reports in electronic format in guidance pursuant to section 745A(a) of the FD&C Act.

III. GENERAL INFORMATION ABOUT VACCCINE ICSR SUBMISSIONS

For purposes of this guidance, an ***ICSR*** is a description of an adverse experience related to an individual patient or subject that is associated with the use of a vaccine product. More specifically, an ICSR is made up of data elements, such as the date and time of the adverse experience, the name of the suspect vaccine and the name of the manufacturer of a vaccine administered in the 4 weeks prior to the vaccination at issue. These data elements are listed in the relevant regulations at 21 CFR 600.80, most notably § 600.80(g). The information described by the data elements should be included in the ICSR submission if available and applicable to the report. You should submit ICSRs electronically in XML[6] format using the International Conference on Harmonisation's (ICH) E2B(R3) specification. See section III.C of this guidance document for more information about this specification.

ICSR attachments include supporting information for ICSRs, such as relevant medical records, hospital discharge summaries, autopsy reports or other documentation. ICSR attachments also include published articles for ICSRs based on scientific literature (§ 600.80(d)).

Followup ICSRs should provide a complete picture of the current understanding of an adverse experience, rather than providing only the changes and/or updates to an ICSR. Accordingly, followup ICSRs should include information about an adverse experience that has been previously reported as an initial ICSR along with any new information. However, any ICSR attachments submitted with an initial ICSR (e.g., literature articles, hospital discharge summaries) should not be resubmitted with a followup ICSR. See section III.D of this guidance document for information on using unique case identification numbers for the initial ICSR and followup ICSRs to help ensure linkage between the two.

The following sections provide general information related to the electronic submission of initial and followup ICSRs and ICSR attachments. Note that regardless of the type of submission (i.e., those submitted as 15-day Alert reports or reports of adverse experiences that are both serious and expected or nonserious), the electronic submission procedure is the same.

A. Parts of an ICSR Submission

For purposes of this discussion of electronic submissions, an initial or a followup ICSR submission is considered to have two parts:

1. The ICSR itself; and
2. The ICSR attachments, if applicable.

[6] For purposes of this guidance, the term "XML" refers to Extensible Markup Language.

B. Options for Electronic Submission of an ICSR and ICSR Attachments into VAERS

FDA provides two options for electronic submission of ICSRs and ICSR attachments involving vaccine products for processing into VAERS: the direct database-to-database submission method and the eSubmitter tool method. The direct database-to-database submission method is described on CBER's ICSR Specifications Web page.[7] Electronic submission of ICSRs for vaccine products using the FDA eSubmitter tool is described on the CBER ICSR eSubmitter Web page.[8] Both options involve use of XML files that are submitted to FDA through its Electronic Submissions Gateway (ESG). The ESG is the central transmission point for sending information electronically to FDA. Once received through the ESG, the submitted reports are processed into the VAERS database.

C. Technical Specifications for Electronic Submission of ICSRs for Vaccine Products

ICSRs and ICSR attachments must be submitted to FDA in an electronic format that we can process, review, and archive (21 CFR 600.80(h)(1)). For this purpose, CBER will provide associated technical specification documents that will give more information concerning how to create and submit FDA-compliant ICSRs on CBER's ICSR Specifications Web page.

D. Unique Case 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. It is important to note that the unique case identification number must be the same in the initial report and any subsequent followup report(s) (21 CFR 600.80(g)(7)(viii)).[9] Using a unique case identification number allows FDA to link the initial ICSR with any followup reports in the VAERS database, regardless of the time or method of transmission of an individual report. For further information, see the section on identification numbers for initial and followup ICSRs in the FDA ICH E2B(R3) technical specifications document on CBER's ICSR Specifications Web page.

[7] The CBER's ICSR Specifications Web page is available at http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm174963.htm.

[8] The CBER ICSR eSubmitter Web page is available at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm317156.htm.

[9] Note that the unique case identification number replaces the "Manufacturer Report Number" on Form FDA 3500A and the VAERS form.

E. Sending in Submissions

Electronic ICSRs and ICSR attachments should be submitted to FDA through FDA's ESG, which is open 24 hours a day, 7 days a week. ICSR attachments should be submitted to FDA either at the same time that the associated ICSR file is submitted or after the associated ICSR is submitted to FDA. Once received through the ESG, the ICSRs and ICSR attachments will be processed into VAERS.

Before submitting an ICSR in electronic format to FDA for the first time, you should submit your request to the CBER Electronic Submissions Program via e-mail at esgprep@fda.hhs.gov. The VAERS Coordinator will assist you with submission of a test file. For subsequent submissions in electronic format, it is not necessary to contact the VAERS Coordinator before submitting the ICSR. For additional information on providing submissions using the ESG, refer to FDA's ESG Web page at http://www.fda.gov/esg.

F. Notification of Receipt of Submissions by the FDA

Once a submission (one or more ICSRs or ICSR attachments) reaches the ESG and is successfully recognized and decrypted, an ESG message delivery notice (MDN) will be sent to the sender. The date of this ESG MDN will serve as the official FDA receipt date of each successfully transmitted ICSR and ICSR attachment in the submission. See FDA's ESG Web page for further information about receipt of submissions through the ESG.

After receipt of the submission, CBER will process the ICSRs and ICSR attachments and a second automated acknowledgement message (CBER receipt acknowledgment) will be sent to the sender via the ESG. The CBER receipt acknowledgement will serve to inform the sender that the ICSR submission(s) have successfully reached the center. We expect that you will receive your ESG MDN and CBER receipt acknowledgement within 24 hours after you have submitted an ICSR, including any associated ICSR attachments to the ESG. A third automated acknowledgment message (VAERS file validation and load acknowledgment) will be sent to the sender to provide file validation and load status for each ICSR submission. For additional information on VAERS acknowledgement message files and format, refer to the FDA ICH E2B(R3) technical specifications document at CBER's ICSR Specifications Web page.

Even though the ICSR and ICSR attachments can be received by FDA on different days, they must be submitted to the Agency within the time periods specified in 21 CFR 600.80(c). Please plan your submissions accordingly.

Additional information on the receipt date of submissions is available in the FDA guidance entitled "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Receipt Dates" dated February 2014.[10]

G. Contingencies If the ESG Is Temporarily Unavailable

As stated previously, we expect that you will receive your ESG MDN and CBER receipt acknowledgement within 24 hours after you have submitted an ICSR or ICSR attachment(s) to the ESG. If you do not receive these messages within 24 hours, we recommend that you first check the FDA ESG Web page to determine whether we are experiencing any problems with the ESG.

- **If the ESG is functional**, and you have not received the CBER receipt acknowledgement within 24 hours after the end of the transmission, contact ESGHELPDESK@fda.hhs.gov for assistance. Please be prepared to provide the Core ID, which is the ID assigned by the FDA ESG for submission tracking, as well as the company name on the account and the date and time the submission was sent.

- **If the ESG is not functional** for more than 24 hours**,** FDA will post a notice on the FDA ESG Web page to provide further guidance concerning alternative submission methods. If the ESG is not functional for more than 48 hours, the FDA ESG e-mail distribution list (listserv) will be used to communicate procedures on how to proceed with your submission. If you follow these procedures, it is important that you do **not** resubmit the ICSRs or ICSR attachment(s) to FDA using the ESG when it becomes functional. Note that when you follow the alternate submission method, the official FDA receipt date of the ICSRs or ICSR attachment(s) will be the date when the submission is received by the CBER Document Control Room (DCC) or VAERS program (for example, if the submission is faxed, the receipt date will be the date on the timestamp of the successful fax).

If you submit ICSRs or ICSR attachment(s) that we are unable to load into the VAERS database because you did not use the correct data elements or an electronic transport format that CBER supports, the third automated VAERS acknowledgement message will indicate that we could not load these ICSRs (or ICSR attachment(s)) into VAERS. The acknowledgement also will indicate which, if any, ICSRs or ICSR attachment(s) that you sent to the ESG at the same time were processed into VAERS. You should resubmit to us only those ICSRs or ICSR attachment(s) that were not processed into VAERS. Your

10 The draft guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072385.pdf.

resubmission should be given a different file name than the original submission and should take place within the required reporting timeframe. The date of the ESG MDN acknowledgement for the resubmission will serve as the official FDA receipt date of the ICSR or ICSR attachment(s).

IV. POSTMARKETING SAFETY REPORTS OTHER THAN ICSRs

Under 21 CFR 600.80(c)(2), you must submit postmarketing periodic safety reports at prescribed intervals. Among other things, each periodic safety report must contain a descriptive portion and the ICSRs for all adverse experiences other than those submitted as 15-day Alert reports or followup reports to 15-day Alert reports for the reporting period (i.e., reports of adverse experiences that are both serious and expected or nonserious).[11] The descriptive portion can be submitted as a periodic adverse experience report,[12] a periodic safety update report,[13] or a periodic benefit–risk evaluation report.[14]

For purposes of this discussion of electronic submissions, a postmarketing periodic safety report (§ 600.80(c)(2)) is considered to have three parts:

1. Descriptive information;
2. ICSR(s); and
3. ICSR attachment(s), if applicable

Submission of ICSR(s) and ICSR attachment(s) are addressed in section III above. The *descriptive information* portion of the periodic safety report required under § 600.80(c)(2)(ii)(A) should be submitted separately as a portable document file (or PDF) to section 5.3.6 of the Electronic Common Technical Document (eCTD).[15] Firms should not submit non-expedited ICSRs to the eCTD in a PDF format together with the descriptive portion of the periodic safety report.

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[11] As described in 21 CFR 600.80(c)(2)(ii)(B). Non-expedited ICSRs were previously referred to as *periodic ICSRs*.
[12] As described in 21 CFR 600.80.
[13] FDA allows firms with approved waivers (see 21 CFR 600.90) to use the ICH E2C Periodic Safety Update Report format when submitting the descriptive portion of periodic safety reports. See the guidance document entitled "Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" dated March 2001, including section XI concerning waiver requests. The draft guidance is available at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092257.pdf. This draft guidance, when finalized, will represent FDA's current thinking on this topic.
[14] FDA allows firms with approved waivers (see 21 CFR 600.90) to use the ICH E2C(R2) Periodic Benefit-Risk Evaluation Report format when submitting the descriptive portion of periodic safety reports. See the guidance document entitled "Guidance for Industry: Providing Submissions in Electronic Format –Postmarket Non-Expedited ICSRs Technical Questions and Answers" dated July 2013. The guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362174.pdf.
[15] Information regarding the eCTD is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

V. WAIVER REQUESTS

Under 21 CFR 600.90, an applicant required to submit a postmarketing safety report under § 600.80 may ask FDA to waive temporarily the requirement that the safety report be submitted in electronic format. We anticipate that temporary waivers for licensed vaccine products regulated by CBER will be needed only in rare circumstances. Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA for technical assistance rather than submitting a waiver request. Companies that normally use the direct database-to-database method to submit reports to FDA could use the eSubmitter tool we have made available as a backup method during short-term, temporary outages.

A. Content of Waiver Requests

An applicant's request to waive the electronic format requirement must include one of the following as supporting documentation: An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved (e.g., acts of nature, widespread internet outages, temporary issues with the applicant's adverse event database(s)); a description of an alternative submission that satisfies the purpose of the requirement; or other information justifying a waiver (21 CFR 600.90(a)).

We recommend that this request be submitted to FDA in writing by mail. The request should reference all products that are to be covered by the waiver. If not already provided as justification for the waiver for purposes of meeting the requirements under § 600.90(a), we recommend that the waiver request include the reason for the request (i.e., the nature of the inability to comply), as well as the anticipated time to recover, and a company contact. The waiver request also should include a proposed end date for the waiver and a description of any proposed alternative reporting method, as relevant to the circumstances. Potential alternative reporting methods could include (but are not limited to) physical media and fax. The waiver request should be clearly titled "**WAIVER REQUEST – POSTMARKETING SAFETY REQUIREMENTS**" in bold capital letters at the top of the first page of the submission.

B. Where to Submit Waiver Requests

For licensed vaccine products regulated by CBER, waiver requests should be addressed to:

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Document Control Center
10903 New Hampshire Avenue
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002.

C. FDA Response to Waiver Requests

FDA reviews waiver requests on a case-by-case basis. FDA intends to respond in writing to the requestor,[16] stating whether or not the waiver is granted. If the waiver is granted, FDA intends to also include in its response letter a description of the acceptable alternate format(s) for the safety report. **Waivers of the requirement to submit reports in electronic format, if granted, will be temporary.**

[16] To follow up with the company, FDA intends to contact the individual who submitted the waiver request unless an alternate contact person is provided.