Instructions for Electronic Submission of Mandatory Adverse Event Reports to FDA CVM

1 Introduction

This document provides instructions for industry stakeholders (Sponsors) to submit FDA-compliant, electronic animal Adverse Event Reports (AER) to the FDA Center for Veterinary Medicine. These electronic submissions use the Health Level Seven (HL7) Individual Case Safety Report (ICSR) Release 2 Standard and have a specific form and format (ISO/HL7 27953-1). Sponsors must follow these instructions to successfully submit electronic HL7 ICSR compliant AERs to CVM. AERs may be bundled into HL7 ICSR batches for submission.

Sponsors must register with the FDA ESG before they can begin submitting electronic AERs to CVM. Please see the instructions at:
https://www.fda.gov/industry/electronic-submissions-gateway

2 FDA Contact Information

This section contains contact information in the event sponsors need assistance.

2.1 FDA Electronic Submissions Gateway (ESG) Support

For FDA ESG technical questions and account setup, please email:

   ESGHelpDesk@fda.hhs.gov

2.2 CVM Electronic Submission System (ESS) Support

For CVM ESS technical questions or help submitting electronic AERs to CVM, please email:

   CVMDCU@fda.hhs.gov

2.3 CVM Office of Surveillance and Compliance (OSC) Adverse Event (AE) Support

For assistance or questions regarding AER issues related to Form FDA 1932, GFI#188, GFI#214, or GFI#143 please email:

   CVMAESupport@fda.hhs.gov

3 Document References

FDA and CVM provide documents to assist sponsors in correctly structuring the HL7 ICSR-compliant electronic AER submission. These documents can be found under the Supporting Documents sections of the Veterinary Adverse Event Reporting for Manufacturers webpage:

https://www.fda.gov/animal-veterinary/report-problem/veterinary-adverse-event-reporting-manufacturers

Contact CVMAESupport@fda.hhs.gov for the two Electronic Transmission Implementation Specifications technical documents that accompany GFI#214 Electronic Standards for Transfer of Data:

- Step By Step Document
- Validation Procedures Document

These documents describe the details of HL7, ICSR-compliant veterinary adverse event reports, including mandatory and optional components of the electronic ICSR message. One of these documents also describes how FDA/CVM validates electronically submitted ICSR messages.

4   FDA Electronic Submissions Gateway (ESG) Operations

The FDA ESG is the system that sponsors use to electronically transmit AERs to FDA CVM. The FDA ESG is a secure, high speed transfer method that is available seven days a week, 24 hours a day.

The FDA ESG has defined a set of procedures and processes that sponsors must accomplish prior to sending electronic submissions to FDA and CVM. Full information for completing the registration and operation of ESG software is available at the following links:

https://www.fda.gov/industry/electronic-submissions-gateway

The FDA ESG User Guide can be found at the following link:

https://www.fda.gov/industry/about-esg/user-guide

Completion of all FDA ESG requirements must be accomplished prior to transmitting files to FDA CVM.

5   CVM Electronic Submission System (ESS) Notification

CVM ESS is the system used to processes all incoming electronic submissions sent to CVM using the FDA ESG.

Industry sponsors who are already registered with the CVM ESS and have active CVM ESS accounts may submit their electronic AERs using their current FDA ESG Production accounts.

Industry sponsors who are not currently registered with the CVM ESS should follow the process outlined in Guidance for Industry #108: How to Register with the CVM Electronic Submission System to Submit Information in Electronic Format using the FDA Electronic Submissions Gateway at:
https://www.fda.gov/media/70064/download

Industry sponsors who are not currently registered with the CVM ESS must submit the FDA/CVM ESS Adverse Event Registration form. The FDA/CVM ESS Adverse Event Registration form also

satisfies the FDA's Gateway requirement that sponsors send a compliant submission to the "Pre-Production" ESG system prior to sending "Production" submissions.

See *Section 7--FDA/CVM ESS Adverse Event Registration Form* for further instructions on how to complete the notification process and send a simple submission that contains a single file of submitter information. When CVM receives and validates this information, you will be sent an Email notification from the FDA ESG on how to establish your FDA ESG "Production" account. Once your ESG "Production" account is established, you may transmit AER submissions to FDA/CVM.

6   Sponsor Unique Identifiers

The submitted AER requires a number of mandatory unique identifying elements that must be supplied by the Manufacturer Authorized Holder (MAH) and/or the submitter of the AER. These identifiers are from the following three organizations/sources:

- Dun & Bradstreet
- Food and Drug Administration – Office of Regulatory Affairs
- Food and Drug Administration – Office of Surveillance and Compliance

6.1   Dun & Bradstreet Data Universal Numbering System (DUNS)

Dun & Bradstreet assigns and maintains a database of the Data Universal Numbering System (DUNS) numbers, which serve as unique identifiers (codes) of business entities. On application, each business entity (e.g., registrant, establishment, importer, US agent) is assigned a distinct site-specific 9-digit DUNS number. The site-specific DUNS number is used by FDA in identifying and verifying certain business information for a given entity, e.g., proprietary names used by the entity, addresses, additional ownership information, such as the name of each partner or the name of each corporate officer and director, and the state of incorporation. If the DUNS number for a location has not been assigned, a business may obtain one for no cost directly from Dun & Bradstreet (http://www.dnb.com).

6.2   FDA Establishment Identifiers (FEI)

The FEI is a multi-digit number that the FDA uses to identify a given establishment. This number is the unique identifier for the establishment and must never be changed or reused to identify another establishment. The number is assigned to an establishment at a specific location. If a sponsor has more than one location, each location will have a unique FEI.

6.3   MAH Identifier (MAH ID)

The MAH ID is the eight-character code assigned for the specific identification of each sponsor and validation against the application numbers of any submitted AERs. Please contact CVMAESupport@fda.hhs.gov to register your MAH ID and its association with your products.

7   FDA/CVM ESS Adverse Event Registration Form

If you wish to submit electronic AERs, you must have a FDA ESG Production account and must have notified CVM of your intentions to submit electronic AERs to CVM.

You can notify CVM by submitting the FDA/CVM ESS Adverse Event Registration Form. The Registration Form can be found on FDA/CVM's Web site at the following address:

http://www.fda.gov/media/78823/download

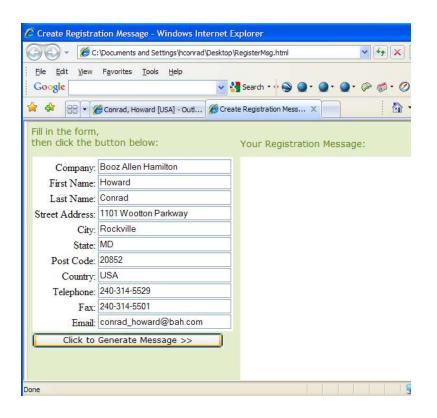See the examples below that illustrate these specific steps:
- o   Fill out the Form
- o   Generate the XML
- o   Copy the XML into a file on your computer desktop
- o   Send the Register.XML file to CVM Via the Gateway

Figure 1 - CVM AER Registration Web Form

- Fill out the form with all the requested information.

Figure 2 - Filled in Registration Web Form

- When you have completed filling out the registration information in the Web form then press the "Click to Generate Message >>" button. You should see the following:
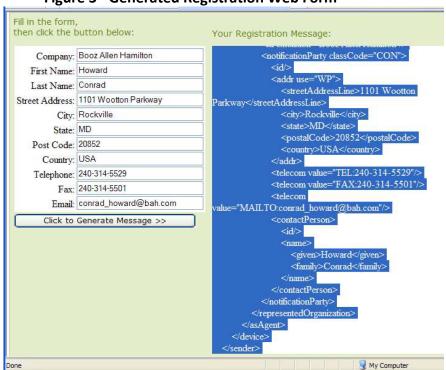
Figure 3 - Generated Registration Web Form

- After generating the message you now need to copy the generated XML data into a text document. Use your cursor to highlight all of the data in the generated registration message, press the right mouse button and copy the data to your clipboard. See figure below.
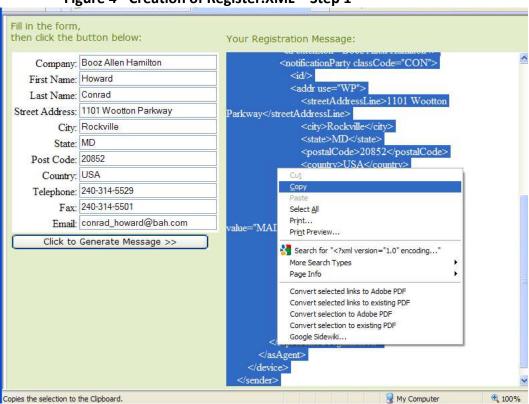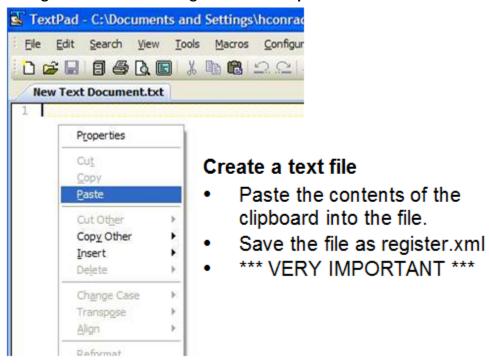
Figure 4 - Creation of Register.XML – Step 1

- Once the data has been copied into your clipboard, navigate to your desktop and create a text file (using Notepad, TextPad, etc.). Paste the data from the clipboard into the text file.

Figure 5 - Creation of Register.XML – Step 2

- Save the file with the following file name "register.xml". This is important as our system will only recognize the name "register.xml".

- After completing the above steps you now must forward the register.xml registration file to FDA/CVM using the FDA ESG (See Section 8).

8   Procedures to Transmit Electronic AERs to CVM

All FDA ESG registration procedures MUST be completed prior to sending submissions to FDA/CVM.

8.1   Using the ESG WebTrader Option

WebTrader is a low-cost, easy use-to-interface used to send submissions to FDA CVM. Instructions on its use are contained in documents found on the ESG webpage:

https://www.fda.gov/industry/about-esg/esg-chapter-4-fda-esg-web-interface-electronic-submissions#toc

The Web Trader software is generic tool that can be used to send information to any Center within the Agency. To ensure that information is routed to the correct FDA location stakeholders must select the proper transmission options within Web Trader.

When sending transmissions to FDA/CVM, you must select "Send Document" and then fill out the "Send Document" Web Trader screen. Highlighted areas show that "CVM" must be selected within the "Center" pull down selection. You must also select "Adverse Event Reports" within the "Submission Type" pull down selection. As an example, the following figure shows the proper selections and filled in fields to transmit the CVM Adverse Event Registration Web Form.

Figure 6 - FDA WebTrader Send File Screen

Using the ESG AS2 Gateway-to-Gateway Option

If you are using the FDA ESG AS2 to AS2 Gateway-to-Gateway capability you have two methods to setup routing controls to forward submissions through the ESG.

See the FDA ESG User Guide:

https://www.fda.gov/industry/about-esg/esg-chapter-5-as2-gateway-gateway-electronic-submissions#toc

Section 5 -- AS2 Gateway-to-Gateway Electronic Submissions, Section 5.3 Send a Test Submission:

- Appendix G, AS2 Header Attributes, requires you to add custom AS2 Header Attributes that indicate the type of submission to be sent and where it is to be sent within the FDA. The following custom header attributes must be set exactly:

- o FDASubmissionType = ***Adverse_Event_Reports***
- o FDACenter = ***CVM***

- Appendix K, AS2 Routing IDs, uses a unique Routing ID for sending adverse event reports to CVM. The Routing ID for CVM Adverse Event Reports is ***CVM_AERS.***

9   Electronic AER Submission Format

Electronic submissions of AERs have a specific form and format. Refer to the Electronic Transmission Implementation Specifications Step By Step technical document for details about the submission format. The Step By Step technical document specifies that the content of the submission file must start with the header from the ICSR schema specified as the "MCCI_IN200100UV01".

 The schema location has been published on FDA's External Web site located at:

http://www.accessdata.fda.gov/icsr/schema/cvm/schemas/vich/multicacheschemas/MCCI_IN200100UV01.xsd

10 Responses from FDA and CVM Regarding Transmitted ICSR Submissions

10.1   FDA ESG Responses

The FDA ESG returns two messages for each submission transmitted. The first message indicates that the FDA ESG has received your submission error free. This includes the decryption of the message along with the digital certificate validation. The second message from the ESG notifies the sender that the FDA ESG has successfully transferred the submission to the FDA/CVM processing system responsible for validating and inserting the submission into the ICSR processing system.

10.2   CVM ESS Responses

The CVM ESS will validate and process the incoming AERs and will either accept individual ICSR for processing or reject individual messages because of data errors. CVM ESS will attempt to fully validate every ICSR message and inform you of the problems identified. The message that a submitter receives has detailed information that indicates the status of the submitted batch along with statistics of accepted and rejected ICSRs.

10.3   CVM's Adverse Event System Responses

Here are several examples of messages that you might receive from CVM's ESS Adverse Event processing system (IERS):

Figure 8 - IERS Passed Acceptance Message

This sample message is a submission of two ICSR AERs for which no errors were found on IERS validation.

```
Validation Processing Report:

FDA/CVM Adverse Event Processing System
Validation Report for ICSR Batch Submission

Your submission has been received and accepted for review.

Date/Time this validation report was generated: 03-02-2015 13:04:07
IERS Version: V2013-06-21-1.0
ESG Core Id: ci1273495943345.91658@llntap01_te
Received On: 03-02-2015, 12:56:54
Received From: GAPINDUS
Document ID: A200008
Submission ID: L60


Batch ID#:  54321
Batch Sender: Jane  Doe
=========================================================================================
Validator Version: DTS_Validator_05312013
Batch Wrapper Validation Results:
No errors in batch wrapper.


=========================================================================================
Message Sequence:  1 <UAER ID number: USA-GAPINDUS-42Q3> <Message Number: GAPINDUS-86903192580-42Q3>
=========================================================================================
Message Sequence 2 <UAER ID number: USA-GAPINDUS-55T5> <Message Number: GAPINDUS-86903192581-55T5>
=========================================================================================

No errors in ICSR message.

ICSRs Submitted: 3
ICSRs in Error: 0

<<<<<< NOTICE:  All reports have passed data quality control validations. >>>>>>
Your submission has been received and valid messages have been accepted for review
```

Figure 9 - IERS Partially Passed Acceptance Message

This sample message is for a submission consisting of three ICSR AERs. One AER (Message 2) had errors that were detected by IERS such that the AER was rejected. Two AERs (Messages 1 and 3) passed validation and were accepted.

```
Validation Processing Report:

FDA/CVM Adverse Event Processing System
Validation Report for ICSR Batch Submission

Your submission has been received and accepted for review.

Date/Time this validation report was generated: 03-02-2015 13:04:07
IERS Version: V2013-06-21-1.0
ESG Core Id: ci1273495943345.91658@llntap01_te
Received On: 03-02-2015, 12:56:54
Received From: GAPINDUS
Document ID: A200008
Submission ID: L60


Batch ID#:  12345
Batch Sender: Jane  Doe
=========================================================================================
```

```
Validator Version: DTS_Validator_05312013
Batch Wrapper Validation Results:
No errors in batch wrapper.


===================================================================================================
Message Sequence:  1 <UAER ID number: USA-GAPINDUS-42Q3> <Message Number: GAPINDUS-86903192580-42Q3>
No errors in ICSR message.


===================================================================================================
Message Sequence:  2 <UAER ID number: USA-GAPINDUS-55T5> <Message Number: GAPINDUS-86903192581-55T5>
Error: VICH_GL42_B.7.1_BR1:The AER must contain a valid value for "Attached Document Filename".


===================================================================================================
Message Sequence:  3 <UAER ID number: USA-USFDACVM-33TY> <Message Number: GAPINDUS-86903192582-33TY>
No errors in ICSR message.


===================================================================================================


ICSRs Submitted: 3
ICSRs in Error: 1

<<<<<< NOTICE:
-"Error" identifies messages that must be corrected and resubmitted.
-"Warning" identifies messages that should be reviewed by the sender for necessary follow-up submissions.
-Messages containing both "Error" and "Warning" validation results must be corrected and resubmitted.
>>>>>>>

Your submission has been received and valid messages have been accepted for review.
```

Figure 10 - IERS Rejection Message

This sample message is for a submission that consisted of one AER and had errors that were detected by IERS such that the AER was rejected.

```
Validation Processing Report:

FDA/CVM Adverse Event Processing System
Validation Report for ICSR Batch Submission

Your submission has been rejected. Please correct the following errors and submit the report again.

Date/Time this validation report was generated: 02-10-2015 05:42:08
IERS Version: V2010-06-21-1.0
ESG Core Id: ci1273743435665.47124@llntap02_te
Received On: 02-10-2015, 05:41:53
Received From: GAPINDUS
Document ID: N/A



Batch ID#:  537
Submission Contact Person:   John Doe
===================================================================================================
Validator Version: DTS_Validator_05312013
Batch Wrapper Validation Results:
No errors in batch wrapper.


===================================================================================================
 Message Sequence:  1 <UAER ID number: USA-FDASENDR-2009-US00023> <Message Number: FDASENDR-1102214-2009-US00023>
===================================================================================================
Error: USFDACVM_GL42_A.4.4.3_BR5: When the "Profile Identifier" is "Adverse Event" and the "Type of Submission" is "EXPEDITED", "PERIODIC", or
"OTHER", the value of "Type of Information in Report" must be from the vocabulary list d.Type of Information as identified in the Rule Description
above.

ICSRs Submitted: 1
ICSRs in Error: 1
```

```
<<<<<< NOTICE:  The complete batch of submitted reports has been rejected. >>>>>>
```

Figure 11 - IERS Rejection Message Schema Violation

This sample message shows a validation failure for the reason that a compliant XML schema was not formed. This type of error prevents further validation of the message. For that reason, other errors might subsequently be identified after initial correction and resubmission.

```
Validation Processing Report:

FDA/CVM Adverse Event Processing System
Validation Report for ICSR Batch Submission

Your submission has been rejected. Please correct the following errors and submit the report again.

Date/Time this validation report was generated: 02-10-2015 05:42:08
IERS Version: V2010-06-21-1.0
ESG Core Id: ci1273743435665.47124@llntap02_te
Received On: 02-10-2015, 05:41:53
Received From: GAPINDUS
Document ID: N/A

Your submission has been rejected.  The batch XML is not an ISO27953-1 ICSR schema compliant XML.
```