Instructions for Submitting Mandatory Electronic Adverse Event Reports to FDA/CVM

May 21, 2010

1 Introduction

This document provides information and instructions needed by industry stakeholders (Sponsors) to submit electronically generated compliant animal Adverse Event Reports (AER) to the Food and Drug Administration's (FDA) Center for Veterinary Medicine's (CVM) Electronic Submission System (ESS). Industry stakeholders must follow these instructions carefully in order to accomplish the successful transfer of GL42 compliant AERs to CVM. AERs are bundled into Health Level 7 compliant Individual Case Safety Report (ICSR) batches for submission.

2 FDA Contact Information

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

2.1 FDA Electronic Submissions Gateway (ESG) Support

The Email address to obtain assistance with FDA ESG issues and problems is:
    esgprep@fda.hhs.gov

2.2 CVM ESS Support

If you have any technical questions regarding the sending of AER submissions please contact the following:

Margaret Zabriski
Email Address: margaret.zabriski@fda.hhs.gov

2.3 CVM Office of Surveillance and Compliance (OSC) Support

If you need assistance or have questions on GL42 AER issues please send an Email to the following address:

CVMAESupport@fda.hhs.gov

3 Document References

FDA and CVM are providing a number of documents to assist stakeholders in correctly structuring a compliant GL-42 HL7 Individual Case Safety Report (ICSR) submission.
The following documents outline and describe the physical layout of compliant reports including mandatory and optional components of the ICSR. These documents will also describe how FDA/CVM will validate and support the submitted ICSRs.

Title and Web Link	Description
Guidance for Industry - Data Elements for Submission of Veterinary Adverse Event Reports to the Center for Veterinary Medicine http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM213153.pdf	Guidance document on providing information (Data Elements) to the FDA CVM via Form 1932 - Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report
Electronic Transmission Implementation Specifications [Step By Step] http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ReportaProblem/UCM213149.pdf	Technical instructions for building compliant Health Level 7 (HL7) animal ICSRs
Electronic Transmission Implementation Specifications [Validation Procedures] http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ReportaProblem/UCM213150.pdf	Validation procedures for compliant HL7 animal ICSRs
Instructions for Submitting Mandatory Electronic Adverse Event Reports to FDA/CVM http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ReportaProblem/UCM213151.pdf	Instructions to assist in transmitting HL7 FDA CVM complaint ICSRs (This Document)
ICSR Vocabularies http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ReportaProblem/UCM213148.xls	MS Excel spreadsheet listing the vocabularies of compliant GL-42 data elements

Table 1 - FDA AER Document List

4 FDA Electronic Submission Gateway (ESG) Operations

The FDA's ESG is the primary method that stakeholders can use to electronically transmit AERs to FDA. The FDA ESG is a secure, high speed transfer method that is available seven days a week, 24 hours a day that provide stakeholders with the capability to send electronic submissions to the various Centers of the FDA.

The FDA ESG has defined a set of procedures and processes that stakeholders <u>must</u> 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:

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

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

http://www.fda.gov/downloads/ForIndustry/ElectronicSubmissionsGateway/ucm114648.pdf

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

5 CVM Electronic Submission System Registration

CVM has developed and deployed an integrated set of system processes to accept electronic submissions for all Center activities from industry stakeholders. This system is called CVM Electronic Submission System (ESS) has been in operation since 1999 and has gone through a

number of changes over the years. CVM has now added the capability to accept animal adverse event reports from industry sponsors.

Individual stakeholders who are <u>not</u> currently a <u>CVM ESS Registered Stakeholder</u> must notify FDA/CVM of their intent to transmit electronic submissions of Adverse Events reports. This notification process is electronically accomplished and only has to be done one-time per individual submitter. In addition to registering, it is used to satisfy the FDA's Gateway requirement of stakeholders sending in a compliant submission to the "Pre-Production" ESG system prior to sending "Production" quality submissions.

After stakeholders have successfully completed the initial FDA ESG "Pre-Production" Registration process the next step is to transmit to FDA/CVM a "Pre-Production (Test)" of a simple submission that contains a single file of registration information (*See Section 7--FDA/CVM ESS Adverse Event Registration Form*). When CVM has received and validated this information you will be sent an Email on how to establish your FDA ESG "Production" account. Once you have your ESG "Production" account established you may now transmit AER submissions to FDA/CVM.

The FDA/CVM ESS registration process that must be accomplished follows:

1. Register with the FDA ESG
2. Obtain the FDA/CVM ESS Adverse Event Registration Form
3. Fill out the form
4. Access the FDA ESG "Pre-Production" system
5. Submit the filled out FDA/CVM ESS Adverse Event Registration Form to the ESG "Pre-Production" CVM Adverse Event Reports folder
6. If your test submission was properly completed and accepted you will receive two Emails;
   - #1 from FDA/CVM indicating that the requirements for "Production" access have been satisfied
   - #2 from FDA ESG with instructions on how to create your "Production" account
7. Create your FDA ESG "Production" account
8. Your are now ready to transmit GL-42 HL7 ICSR reports

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 or Regulatory Affairs
- Health Level 7 (HL7) Organization or International Standards Organization

6.1   *Required Dun & Bradstreet Data Universal Numbering System (DUNS)*

Dun & Bradstreet assigns and maintains a database of the D-U-N-S® Numbers, which serve as unique identifiers (codes) of business entities. Upon application, each business entity (e.g., registrant, establishment, importer, US agent) is assigned a distinct site-specific 9-digit D-U-N-S® Number. The site-specific D-U-N-S® Number for an entity is a useful resource for FDA in

identifying and verifying certain business information for that entity, e.g., trade 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 D-U-N-S® 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 identifies an establishment within the Food and Drug Administration. This unique number is the identification number 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 firm has more than one location, each location will have a unique FEI.

6.3 HL7 Organizational Object Identifiers (OID)

{Note: for the Initial System Release this requirement has been relaxed. A unique system OID is NOT required. A substitute OID of "1.2.3.4" must be used in lieu of an assigned OID.}

The Health Level 7 (HL7) organization has defined the ICSR format that requires individual stakeholder firms (not individuals within stakeholder firms) to obtain a unique organizational object identifier (OID). This identifier is assigned by either the International Standards Organization (ISO) or the HL7 organization. These organizations ensure that the OID is unique and recorded. The process to obtain an OID can be found at the following web addresses:

HL7
   http://www.hl7.org

   Click the OID Registry Link - http://www.hl7.org/oid/index.cfm

   Click the "Click to Obtain or Register an OID" Link - http://www.hl7.org/oid/Submitter.cfm

Fill out the required fields in the forms and submit the information to obtain an OID.

7   FDA/CVM ESS Adverse Event Registration Form

This section is for stakeholders who wish to electronically submit Individual Case Safety Reports (Adverse Events) to CVM in lieu of forwarding paper-based FDA 1932 forms. As stated previously, if stakeholders currently have an active FDA Gateway account and you are actively registered with CVM's ESS then you do not have to accomplish anything in this section.

Stakeholders who wish to submit electronic ICSRs must have a FDA Gateway account and must have registered their intentions to send these reports. Stakeholders can register their intent to send submissions by obtaining, filling-out and submitting FDA/CVM's Registration Web Form. The Registration Web Form can be obtained from FDA/CVM's Web site at the following address:

http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ReportaProblem/UCM223831.zip

Once you have obtained the Web Form use the following procedure to fill it out and submit it to FDA/CVM.

- Steps to go through to register
    - Obtain the Registration HTML Form
    - Fill out the Form
    - Generate the XML
    - Copy the XML into a file on your computer desktop
    - Send the Register.XML file to CVM Via the Gateway

- Obtaining the form
    - Locate the form on CVM's Web Page by using the above URL link
    - Open or copy the form to your PC
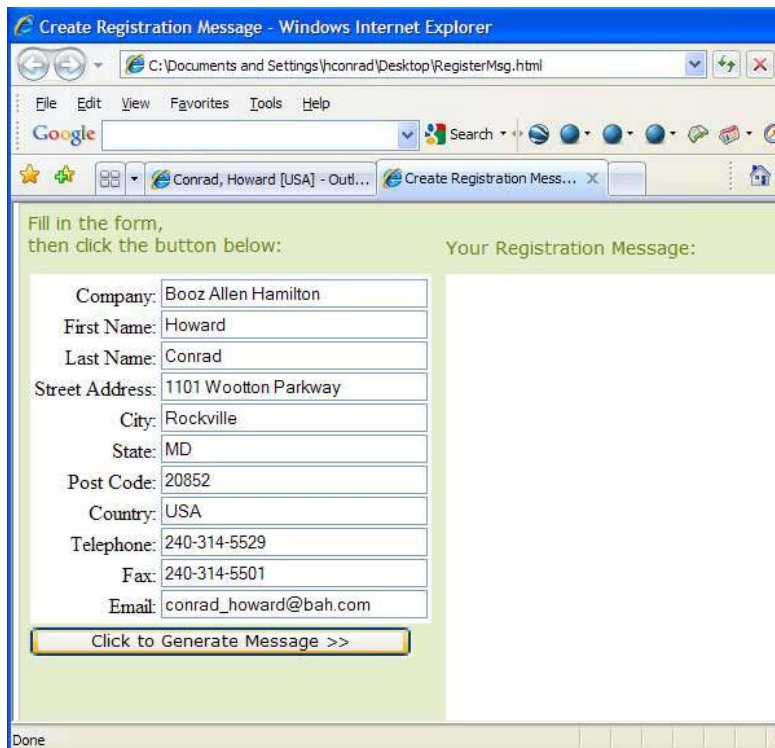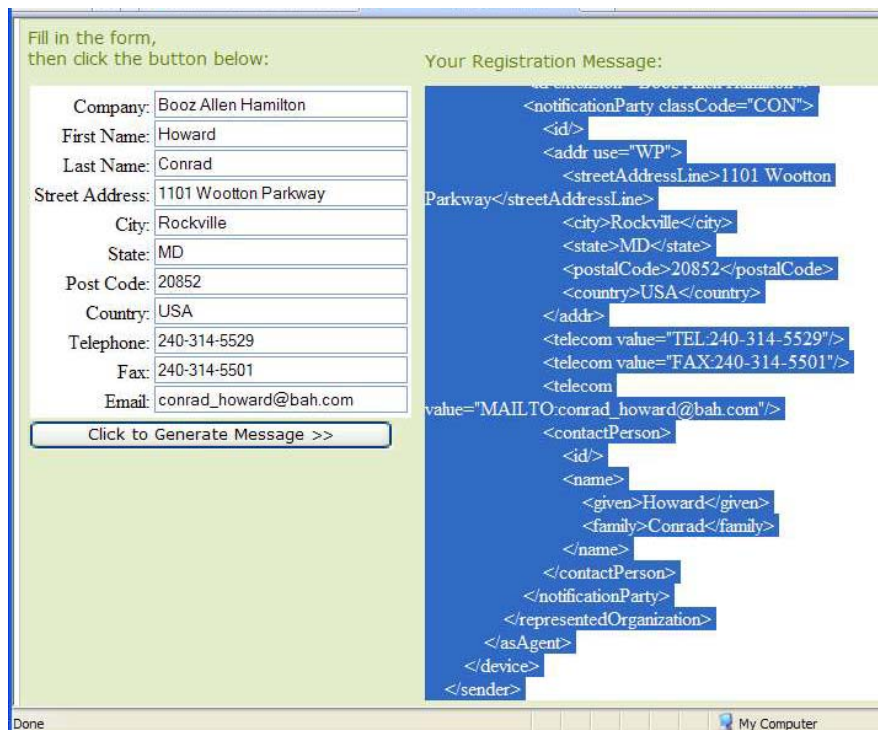

Figure 1 - CVM AER Registration Web Form

- 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. This is done by using your cursor to highlight all of the data in the generated registration message, pressing the right mouse button and copying the data to your clipboard. See figure below.
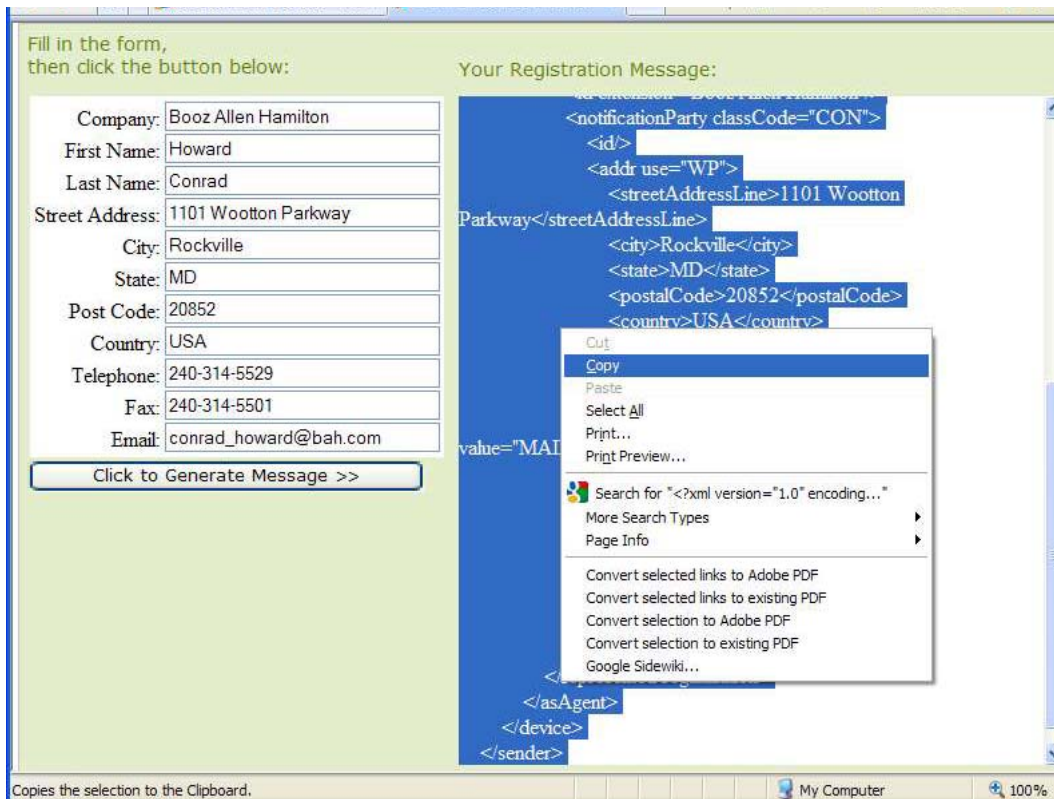
Figure 4 - Creation of Register.XML – Step 1

- 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.
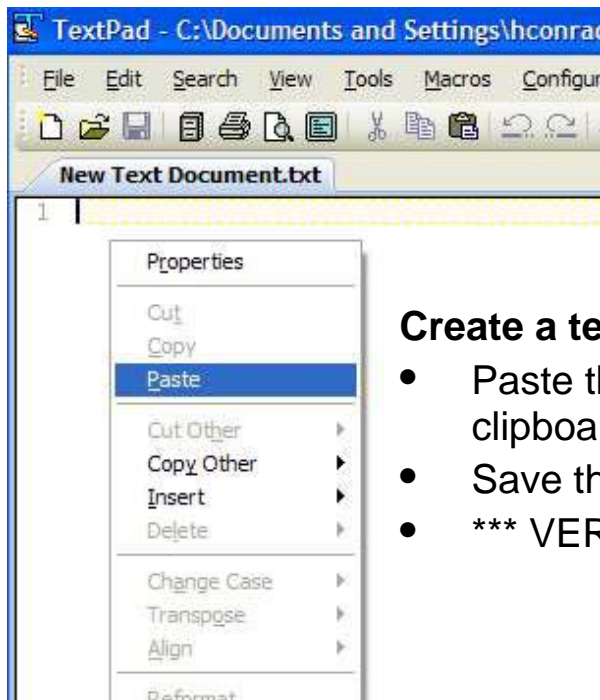
Create a text file
- Paste the contents of the clipboard into the file.
- Save the file as register.xml
- *** VERY IMPORTANT ***

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 via the FDA Electronic Submissions Gateway.

- See Section 8 for procedures on how to transmission your register.xml information file to FDA/CVM.

8   Procedures to Transmit Electronic ICSRs to CVM

8.1   Using the ESG WebTrader Option

WebTrader is a low cost easy use to interface used to send submissions to FDA and CVM. Instructions on its use are contained in documents referenced in *Section 4 - FDA Electronic Submission Gateway (ESG) Operations* found on page 2. In addition, all FDA ESG registration procedures MUST be completed prior to sending submissions to FDA/CVM.

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, stakeholders 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. Stakeholders must also select "Adverse Event Reports"

within the "Submission Type" pull down selection. An example, the following figure shows the proper selections and filled in fields to transmit the CVM Adverse Event Registration Web Form.
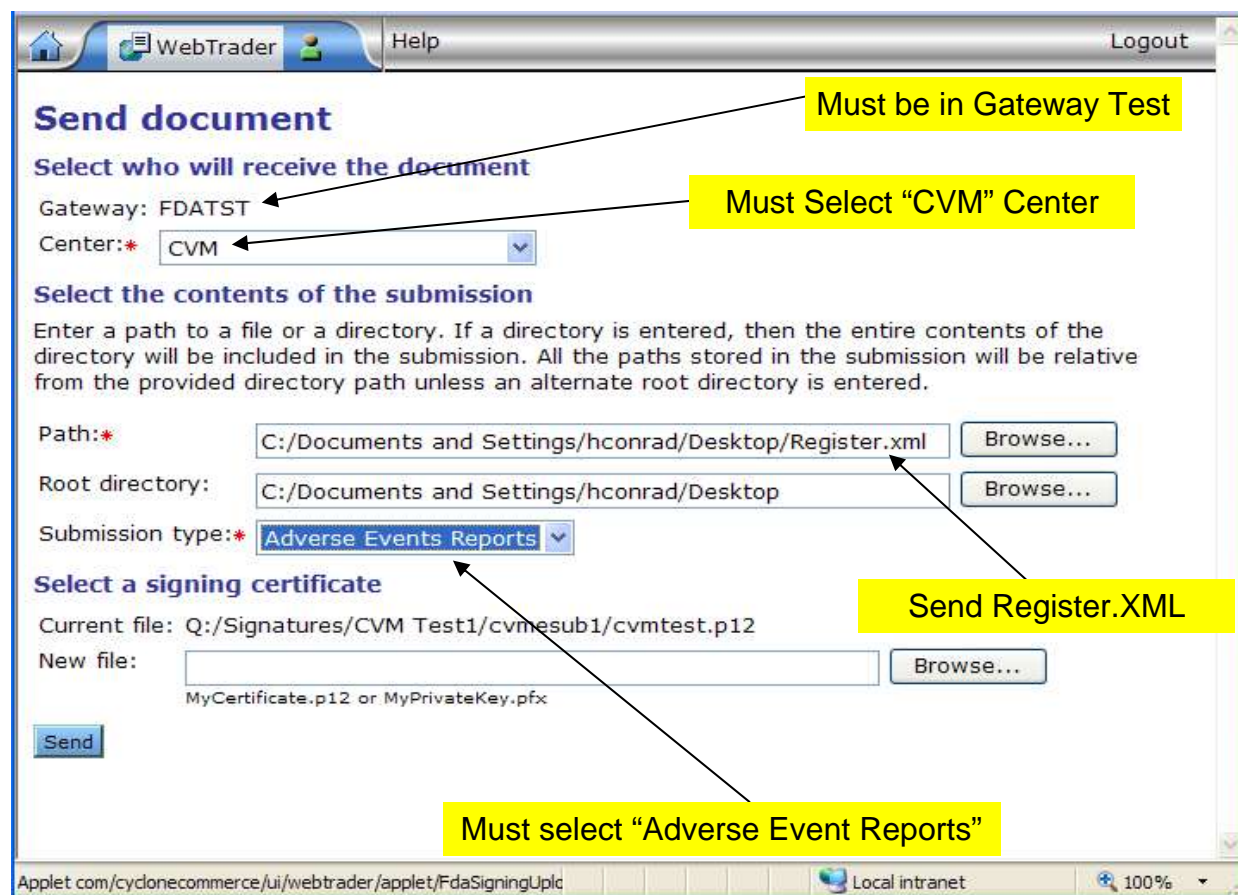
Figure 6 - FDA WebTrader Send File Screen

8.2   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 Section 5 -- AS2 Gateway-to-Gateway Electronic Submissions – Dated February 9, 2010).

- Method 1 requires you to add custom AS2 header attributes that indicate where and the type of submission to be sent within the FDA. The following custom header attributes must be set exactly:

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

- Method 2 uses a unique Routing ID for sending adverse event reports to CVM. The Routing ID for CVM AERs is *CVM_AERS*

9   Electronic ICSR Submission Format

Electronic submissions of ICSRs have a specific form and format. The Electronic Transmission Implementation Specifications [Step By Step] details the submission format. The Step By Step manual specifies that the content of the submission file must start with the header from the ICSR schema specified as the "MCCI_IN200100UV". The following figure depicts a sample ICSR submission.

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

http://www.accessdata.fda.gov/icsr/schema/cvm/Schemas/MCCI_IN200100UV.xsd

A sample snapshot of a compliant HL7 ICSR submission follows in the next figure.

```
<?xml version="1.0" encoding="UTF-8" ?>
<!-- edited with XMLSpy v2008 sp1 (http://www.altova.com) by Center for Veterinary
Medicine (Center for Veterinary Medicine) -->
- <MCCI_IN200100UV xmlns="urn:hl7-org:v3" xmlns:mif="urn:hl7-org:v3/mif"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:schemaLocation="urn:hl7-org:v3
http://www.accessdata.fda.gov/icsr/schema/cvm/Schemas/MCCI_IN200100UV.xsd"
ITSVersion="XML_1.0">
<!-- ******************************************** 
B.7.3 Batch ID -->
<id root="GAPINDSY" extension="batch-12345" />
<!-- ******************************************** 
B.7.8 Message Date -->
<creationTime value="20071016" />
<responseModeCode />
<!-- ******************************************** 
B.7.10 and 11 Message Version Number + Release Number -->
<versionCode code="V3200909" />
<interactionId />
+ <message xsi:type="PORR_IN049006UV.MCCI_MT000100UV01.Message">
+ <receiver>
+ <sender>
</MCCI_IN200100UV>
```

ICSR HL7 Schema URL

Batch Identifier

Schema Version

Figure 7 - Sample ICSR Submission

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 Electronic Submission System (ESS) Responses

CVM ESS is responsible for validating and either accepting the submission for processing or rejecting the submission for data errors. The message that a submitter receives has detailed information that shows the status of the submitted batch along with statistics of accepted cases versus rejected cases. Remember that if any case within the batch submission has a detected error the complete batch submission of cases are rejected. What follows is a message showing a submission that was rejected and one submission that was accepted.

10.3 CVM's Adverse Event System Responses

What follows are two messages that you can receive from CVM's ESS Adverse Event processing system (IERS). Message number one is an example of a submission in which errors were detected. CVM's system will attempt to validate every case and inform you of all the data inconsistencies that can be found.

```
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: 05-13-2010 05:42:08
IERS Version: V2010-03-31-1.0
ESG Core Id: ci1273743435665.47124@llntap02_te
Received On: 05-13-2010, 05:41:53
Received From: ABC Drug Inc.
Document ID: N/A


Batch ID#:  537
Submission Contact Person:   Richard Johnson
==========================================================================================================
Validator Version: DTS_Validator_05112010


==========================================================================================================Message
Number:  1 <UAER ID number: USA-FDASENDR-2009-US-00023> <ICSR Record Identifier: 1102214>
==========================================================================================================
B.2.6.3) Number of Defective Units Translation (package type) code and is not in the CVM vocabulary.
B.2.6.4) Number of Returned Units Translation (package type) code and is not in the CVM vocabulary.
Message Number:  2 <UAER ID number: USA-GAPINDUS-55T5> <ICSR Record Identifier: 1102214>
==========================================================================================================
Message Number:  3 <UAER ID number: USA-abcdefgh-1234> <ICSR Record Identifier: 1102298>
==========================================================================================================
B.2.1) The values of Registered or Brand Name, Active Ingredients, Strength (Numerator and Denominator), Strength Units (Numerator and
Denominator), ATC Vet Code, Active Ingredient Code and Registration ID must be present for at least one product.

ICSRs Submitted: 3
ICSRs in Error: 2

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

Figure 8 - IERS Rejection Message

The above submission consisted of three cases. Two cases had errors that were detected by IERS (Message 1 & 3) and one case that passed validation (Message 2). Again, notice that all cases were rejected including Message number 2.

The next message is a submission of three ICSR cases that IERS validated and found no errors.

```
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: 05-10-2010 08:56:22
IERS Version: V2010-03-31-1.0
ESG Core Id: ci1273495943345.91658@llntap01_te
Received On: 05-10-2010, 08:53:00
Received From: ABC Drug Inc.
Document ID: A200008
Submission ID: L60


Batch ID#:  2010-05-10 - 08.54.40.0638
Submission Contact Person:   Glenn Peterson

=======================================================================================
Validator Version: DTS_Validator_05062010


=======================================================================================
Message Number:  1 <UAER ID number: USA-GAPINDUS-42Q3>  <ICSR Record Identifier: 1102212>
=======================================================================================
Message Number:  2 <UAER ID number: USA-GAPINDUS-55T5>  <ICSR Record Identifier: 1102214>
=======================================================================================
Message Number:  3 <UAER ID number: USA-USFDACVM-33TY>  <ICSR Record Identifier: 1102215>
=======================================================================================

No errors in ICSR message.


ICSRs Submitted: 3
ICSRs in Error: 0

<<<<<< NOTICE:  All reports have passed data quality control validations. >>>>>>
```

Figure 9 - IERS Acceptance Message