

DIA DRM SIAC

September 28, 2006

FDA Electronic Submissions Gateway (ESG) Update

Agenda

- **Background**
- **Submission Options**
- **Submission Process**
- **System Requirements**
- **Common Mistakes**
- **Document Signatures**
- **Submission Numbers**
- **Contact Information**

Electronic Submissions Gateway - Background

- **Drug Safety (AERS) reporting through the ESTRI Gateway since 2000**
 - Limited capabilities
 - Needed upgrade
- **PDUFA III – Single point of entry for the receipt and processing of electronic submissions**
- **Contract**
 - Full and open competition (17 proposals)
 - Awarded in January 2005 to GlobalNet Services & Cyclone
- **Infrastructure upgrade/replacement**
- **Testing**
 - Started testing with industry partners in October 2005
 - Held over 20 separate testing days with industry partners from January 2006 through April 2006
- **Production – May 3rd 2006**

Electronic Submissions Gateway – Submission Options

- **FDA ESG Web Interface (WebTrader)**
 - The FDA ESG Web Interface sends submissions via Hyper Text Transfer Protocol Secure (HTTPS) through a web browser according to Applicability Statement 2 (AS2) standards.
 - Low cost option
- **Gateway to Gateway (AS1/AS2)**
 - **Applicability Statement 1 (AS1) Gateway-to-Gateway**
 - An electronic submission protocol that uses secure email for communications.
 - This protocol can be used only to send AERS and AERS attachments.
 - FDA ESG support for the AS1 protocol will be phased out.
 - **Applicability Statement 2 (AS2) Gateway-to-Gateway**
 - An electronic submission protocol that uses HTTP/HTTPS for communications.
 - Header information will be used to route submission

Submission Types Accepted

- **CDER**

- AERS - Adverse Event Reports*
- AERS Attachments (PDF)
- BLA - Biologics License Application (eCTD and eBLA format)
- IDE - Device Exemption
- IND - Investigational New Drug Application (eCTD and eIND format)
- DMF - Drug Master File

- **CDRH**

- AERS - Adverse Event Reports*
- AERS Attachments (PDF)
- ANDA - Abbreviated New Drug Application
- BLA - Biologics License Application (eCTD and eBLA format)
- NDA - New Drug Application (eCTD and eNDA format)
- IND - Investigational New Drug Application (eCTD format)
- DMF - Drug Master File (eCTD format)

* Can accept XML format following the ICH E2B standard

- **OCIO**

- Adverse Events (Pilot phase using HL7 ICSR message)
- Electronic Submissions (CeSub eSubmitter software)
 - Premarket notification applications [510(k)] to the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)
 - Radiation safety Product Reports and Annual Reports for radiation emitting products to the Radiological Health Program.

Submission Registration and Process

- **Transaction partner agreement and registration**
- **Testing required for each submission type before moving into production for that submission type**
- **Sending submissions**
 - **Initial gateway receipt**
 - **Message deposition notification (MDN)**
 - **Only basic validation (destination, submission type)**
 - **Center receipt acknowledgement**
 - **May receive a second Center acknowledgement**

Electronic Submissions Gateway Process - Before You Register

- **Submit a Letter of Non-Repudiation Agreement**
 - A letter of Non-Repudiation Agreement must be submitted to the FDA. The non-repudiation agreement allows the FDA to receive electronically signed submissions in compliance with 21 Code of Federal Regulations (CFR) Part 11.100.
 - Send letter to Office of Regional Operations, (ORO)
 - Send copy to ESG Project Manager
 - Sample letters are on the FDA ESG website.
- **Obtain a Digital Certificate**
 - Must be X.509 V3 compliant
 - If you have Cyclone product you can generate the certificate
- **Determine Submission Method**
 - Web-based
 - Gateway-to-Gateway (B2B) submissions using industry standards for the transport protocol (AS1 and AS2)
 - A separate registration will be required for each option selected.

Electronic Submissions Gateway Process - Before You Register

- **Understand Submission Guidelines**
 - Each FDA Center has specific guidelines that should be followed for preparing electronic submissions.
- **Submission Types**
 - Each FDA center will accept only certain specific types of submissions.
- **Begin the Registration Process**
 - Send an email to esgprep@fda.gov
 - Include your name, phone number and the name of the company you represent.
 - State whether you will be using the Web browser, AS1 Gateway-to-Gateway, or AS2 Gateway-to-Gateway.

Registration Summary

Web Trader Registration Wizard Help

Welcome

Select community

Company information

Select certificate file

Review certificate

Login information

Review registration

Registration summary

Review the information below. Click the finish button to submit this registration or click the back button to make changes.

Once you submit this registration, you can use your user ID and password to log on immediately to WebTrader, but you will not be able to successfully send documents until the sponsor authorizes your registration.

Company information

Company name: Acme Drug Company
Sponsor: FDA
User ID: adrugco50
Certificate: CN=Micheal Fauntelory, O=FDA

Primary contact

Contact name: Annie Rice
Phone number: 103-777-0987
E-mail address: arice@adc.com

Alternate contact

Contact name: Jack Payne
Phone number: 103-777-0988
E-mail address: jpayne@adc.com

I hereby certify that the information provided herein is true and that I am authorized to register with the FDA.



Electronic Submissions Gateway Process – Test Submission

- **Becoming a Trading Partner & Sending a Test Submission**
 - **Need letter of non-repudiation on file at FDA**

 - **Step 1 – Request an account on the test environment**
 - Executed using a web-based interface
 - Provide contact information
 - Register a valid X.509 v3 security certificate with the FDA ESG

 - **Step 2 – FDA activates the account**
 - Letter of non-repudiation on file at FDA
 - FDA verbally validates the registration information

 - **Step 3 – Send a Test Submission**
 - Send submission up to 7.5 GB
 - Receive a positive Message Delivery Notification (MDN) confirming that the FDA ESG received the submission
 - Receive an acknowledgement from the designated Center confirming that the test submission meets FDA regulatory standards

Electronic Submissions Gateway Process – Production Submission

- **Register with the FDA ESG for Production Submissions**
 - **Step 1 – Request an account on the production environment**
 - Executed using a web-based interface
 - Provide contact information
 - Register a valid X.509 v3 security certificate with the FDA ESG
 - **Step 2 – FDA activates the account**
 - Letter of non-repudiation on file at FDA
 - FDA verbally validates the registration information
 - Valid Test Submission results on file
 - **DONE!** – You are ready to send digitally-signed electronic submissions using the web interface or by using your gateway.
 - **Step 3 – Send Production Submissions**
 - Initial gateway receipt
 - Center receipt acknowledgement
 - May receive a second Center acknowledgement

Sending a Web-based Submission

WebTrader Help Logout

Send document

Select who will receive the document

Gateway: FDA
Center:*

Select the contents of the submission

Enter a path to a file or a directory. If a directory is entered, then the entire contents of the directory will be included in the submission. All the paths stored in the submission will be relative from the provided directory path unless an alternate root directory is entered.

Path:* Browse...

Root directory: Browse...

Submission type:*

Select a signing certificate

Current file: No certificate selected

New file: Browse...
MyCertificate.p12 or MyPrivateKey.pfx

Send

Document Inbox for Web-based Submissions

The receipt for the submission is displayed here. Click on the **Details** link to view its details. This page also displays notifications of any errors encountered in submission and any acknowledgements sent by FDA.

The screenshot shows a web browser window with a navigation bar at the top containing a home icon, 'WebTrader', a user profile icon, 'Help', and 'Logout'. Below the navigation bar is the title 'Documents in Inbox' and an 'Open folder' dropdown menu set to 'Select a folder'. The main content area features a table with the following data:

<input type="checkbox"/>	Name	From	Size	Date ▲	
<input type="checkbox"/>	Receipt for submissiontest.doc <i>New</i>	FDA	3 KB	May 24, 2005 11:24:12 AM	Details

Below the table is a 'Move to trash' link and a summary '1 document'.

Document Inbox for Web-based Submissions

The receipt for the submission is displayed here. Click on the **Details** link to view its details. This page also displays notifications of any errors encountered in submission and any acknowledgements sent by FDA.

The screenshot shows a web browser window titled 'Cyclone - srini webtrader/srinivas on esgtest.fda.gov - Microsoft Internet Explorer'. The address bar contains the URL 'https://esgtest.fda.gov/ui/webtrader/FolderView?name=webtrader.folder.inbox'. The page content is titled 'Documents in Inbox' and features a table of submission receipts. Each row includes a checkbox, a name (often with a 'New' indicator), a 'From' field (usually 'FDATST'), a 'Size' field, a 'Date' field, and a 'Details' link. The table lists various receipts from May 5, 2006, to June 1, 2006.

<input type="checkbox"/>	Name	From	Size	Date	
<input type="checkbox"/>	Receipt for test.txt	FDATST	3 KB	Jun 1, 2006 5:36:19 PM	Details
<input type="checkbox"/>	1147275557944.2331@lntap02.txt <i>New</i>	FDATST	422 bytes	May 10, 2006 11:43:59 AM	Details
<input type="checkbox"/>	1147275721659.2351@lntap02.txt <i>New</i>	FDATST	421 bytes	May 10, 2006 11:43:59 AM	Details
<input type="checkbox"/>	Receipt for AERS_TEST3_wEDI%.XML <i>New</i>	FDATST	3 KB	May 10, 2006 11:42:02 AM	Details
<input type="checkbox"/>	Receipt for alerts_xml%.txt <i>New</i>	FDATST	3 KB	May 10, 2006 11:39:18 AM	Details
<input type="checkbox"/>	1146865048617.834@lntap02.txt <i>New</i>	FDATST	422 bytes	May 5, 2006 5:43:26 PM	Details
<input type="checkbox"/>	1146864546398.814@lntap02.txt <i>New</i>	FDATST	422 bytes	May 5, 2006 5:39:27 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 5:37:29 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 5:29:09 PM	Details
<input type="checkbox"/>	1146856667604.848@lntap02.txt <i>New</i>	FDATST	421 bytes	May 5, 2006 3:26:26 PM	Details
<input type="checkbox"/>	1146856761585.868@lntap02.txt <i>New</i>	FDATST	181 bytes	May 5, 2006 3:26:26 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 3:19:22 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 3:17:48 PM	Details
<input type="checkbox"/>	1146854208038.944@lntap01.txt <i>New</i>	FDATST	422 bytes	May 5, 2006 2:42:40 PM	Details
<input type="checkbox"/>	1146854257350.964@lntap01.txt <i>New</i>	FDATST	422 bytes	May 5, 2006 2:42:40 PM	Details
<input type="checkbox"/>	1146854318576.984@lntap01.txt <i>New</i>	FDATST	181 bytes	May 5, 2006 2:42:40 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 2:38:39 PM	Details
<input type="checkbox"/>	Receipt for testsub.txt <i>New</i>	FDATST	3 KB	May 5, 2006 2:37:37 PM	Details

System Requirements

- **FDA ESG Web Interface users need the following:**
 - A high-speed internet connection
 - A web browser, either Internet Explorer 6 (or later) or Mozilla Firefox 1.0 (or later)
 - Hard disk space of at least three times the size of the submission
 - Sun's Java Runtime Edition JRE 1.4.2_08, for the browser plug-in files. See [System Requirements](#) on the FDA ESG webpage.
- **AS1 and AS2 Gateway-to-Gateway users need the following:**
 - A high-speed internet connection
 - An AS1 and/or AS2 compliant Gateway product
 - Hard disk space of at least three times the size of the submission.
 - Need to compress multi-file or directory submissions
- **Coordinate with infrastructure staff to ensure network will allow and can handle large submissions**

Sending large submissions

- **Need a minimum T3 line to reliably send submissions \geq 20 GB**
 - FDA is able to received and process a 25GB submission in 14 hours, this based on the sending party having a T3 line
 - Most original marketing applications are less than 10GB
 - 30 GB is the practical limit for sending a submission overnight and still have it received at the Center before the end of the next business day
 - Have successfully tested with submission up to 70 GB
- **FDA has received at least 4 submissions over 1GB in size - Largest submission was 4.6GB**
- **Business process / timing considerations**

Common Mistakes

- **Not using right private key for the public key sent to the FDA**
- **Turning off automatic Java update option**
 - In order to connect and upload/send files successfully to the FDA via the FDA ESG Web Interface, you must obtain and install Sun's JRE 1.4.2_08 plug-in files for the browser. JRE security policy files must also be updated.
 - The installed JRE will periodically prompt users to download the latest updates. The most recent versions of the JRE (JRE 1.4.2_09 and JRE 1.5) will not work with the FDA ESG web interface and must NOT be downloaded and installed.
- **Please read information on FDA ESG website**

Electronic Submissions Gateway

- **Important process information**
 - No paper required for gateway submissions
 - Accepted signature methods by FDA, at this time, for required FDA forms (e.g., 1571, 356h) and documents
 - Scanned signatures
 - Digital signatures
 - Flatten digital signatures, must include;
 - » the printed name of the signer
 - » the date and time when the signature was executed
 - » the reason for signature

10. SIGNATURE OF INVESTIGATOR	<p>Geroge.S.Rathbun</p> <p>For Demonstration Purposes Only</p> <p><small>1 Facsimile of Original Digital Signature</small></p> <p><small>Geroge.S.Rathbun CN=Geroge.S.Rathbun,OU=Test Use Only,DC=SafeSign,DC=org Date: Date: 2006-04-20 15:48:08 -0400 Reason: I attest to the accuracy and integrity of this document.</small></p>	11. DATE			
(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)					
<p>Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"><tr><td data-bbox="78 1082 405 1168">Food and Drug Administration CBER (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448</td><td data-bbox="654 1082 971 1168">Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852</td><td data-bbox="1220 1082 1715 1168">"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."</td></tr></table> <p>Please DO NOT RETURN this application to this address.</p>			Food and Drug Administration CBER (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."
Food and Drug Administration CBER (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."			

Current Activities / Next Steps

- **Change Control Board**
 - Add additional submission types
 - Enhancing the process

- **Testing release version 5.4.2**
 - Linking acknowledgements with submissions in the WebTrader interface
 - Expanded search options to manage trading partners
 - Disable automatic processing of XML submissions

Gateway Submission Numbers

	May	June	July	August	September (1 – 16)	Totals
AERS	9109	6188	5155	6408	2880	29,740
CDER	20	54	44	119	70	307
CBER	6	9	19	36	28	98
CDRH	153	312	272	198	38	973
Totals	9288	6563	5490	6761	3016	31,118

Electronic Submissions Gateway

- **Website:** <http://www.fda.gov/esg/>
 - Registration Information
 - System Requirements
 - User Guide
 - Tutorials
 - System Status
 - Help Desk
- **Email for Preparation / Registration / Policy :** esgprep@fda.gov
 - This account is for questions and help in setting up your Gateway test and production accounts. Please do not send email to individual email accounts.
- **FURLS Helpdesk**
 - 1 (800) 216-7331
 - www.cfsan.fda.gov/~furls/helpf2.html
 - 7:30 AM – 11:00 PM EST
 - This account is for production support.

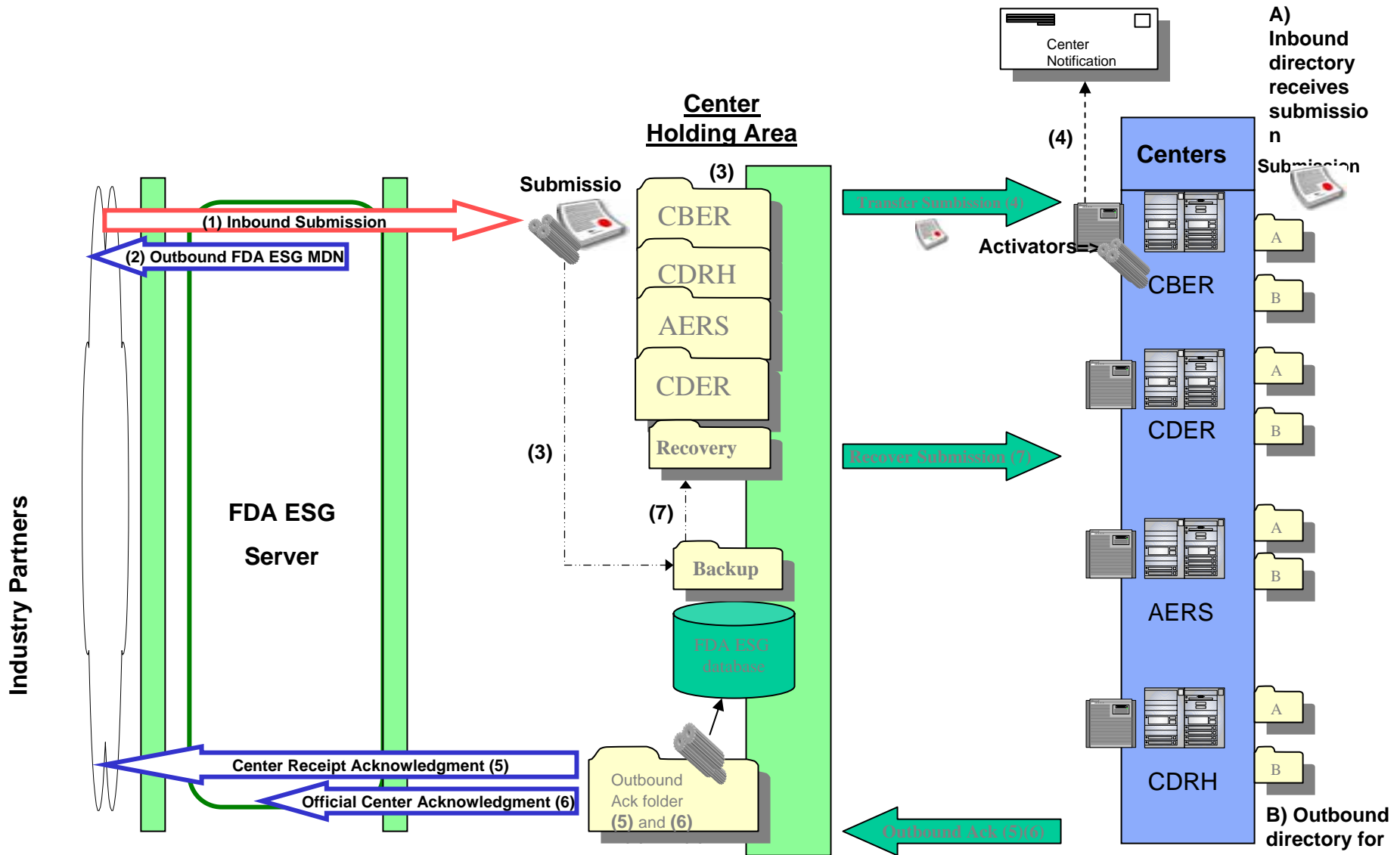
Appendix

Additional FDA ESG Process Details

Processing of an Inbound Submission

1. **FDA ESG receives an inbound submission.**
2. **FDA ESG sends a Message Delivery Notification (MDN) to the submitter (Message 1).**
 - Receipt of an MDN confirms that the submission was successfully received by the FDA ESG.
3. **The inbound submission is processed, submission is unpackaged and deposited in the Center Holding Area.**
 - A copy of the submission is stored for 7 days in the Backup directory.
4. **The submission is automatically transferred to the Center.**
 - The official receipt timestamp is applied to the submission.
 - An email is sent notifying the Center that a submission has arrived.
5. **A Center Receipt Acknowledgement is automatically generated and sent to the submitter via the FDA ESG (Message 2).**
 - This Acknowledgement contains the official receipt timestamp.
6. **The Center validates and processes the submission.**
 - Depending on the submission, an Official Center Acknowledgement may be sent (Message 3).
 - If errors occur during validation and loading, they will be noted in the Official Center Acknowledgement.
7. **If necessary, the Backup copy of the submission may be recovered by the Center.**

Processing of an Inbound Submission



Multi-file or directory submission

- **FDA ESG Web Interface Submissions**

- The FDA ESG Web Interface utilizes the tar and gzip functionality for file system consolidation when submitting files.
- Because this process is done automatically during the signing of the file, no intervention is required.

- **Gateway-to-Gateway (B2B) Submissions**

- Partners are required to both tar and gzip (compress) multi-file submissions.
- For best optimization when processing and transmitting large submission files, first "tar" the files and then compress them using gzip.
- To fulfill this requirement
 - The current AS2 solution will/should have a tar and zip utility prescribed. There are Operating System-specific utilities available for performing the tar operation.
 - If the application does not have tar/gzip capabilities, a utility must be acquired. Please refer to the User Guide on the FDA ESG website for recommended utilities.