

FDA Electronic Submissions Gateway (ESG)

User Guide

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1. Introduction

The business of the Food and Drug Administration (FDA) is extremely information intensive. In recognition of this fact and of the potential benefits offered by information technology for information management, the FDA has undertaken a number of projects supporting the electronic submission of text and data from the industries it regulates.

One of these projects entails the establishment of an Agency-wide solution for accepting electronic regulatory submissions, referred to as the FDA Electronic Submissions Gateway (FDA ESG). The FDA ESG enables the submission of regulatory information for review. The overall purpose of the FDA ESG is to provide a centralized, agency-wide communications point for securely receiving electronic regulatory submissions. The new Agency Gateway will enable the FDA to process regulatory information through automated mechanisms while it enables:

- A single point of entry for receiving and processing all electronic submissions in a highly secure environment.
- Automating current electronic processes such as the electronic acknowledgment of submissions.
- Supporting the electronic Common Technical Document (eCTD).

The electronic submission process is defined as the receipt, acknowledgment, routing, and notification to a receiving Center of the receipt of an electronic submission. In this definition,

- "Receipt" means transfer of a submission from a sender's system to a temporary storage area in the FDA ESG.
- "Acknowledgment" to the sender that the submission was sent from the sender's system and received by the Gateway.
- "Routing" refers to delivering a submission to a Center-level storage area and initiating a load process to place a submission into a Center receiving system
- "Notification" of a submission's arrival is made to those individuals responsible for the Center's receiving system.
- Each of these terms denotes a step in the process of electronic submission delivery, and together, these steps comprise the whole scope of electronic submission delivery.

The FDA ESG is the central transmission point for sending information electronically to the FDA. Within that context, the FDA ESG is a conduit, or "highway", along which submissions

travel to reach their final destination. It does not open or review submissions; it merely routes them to the proper destination.

The FDA ESG uses a software application certified to comply with secure messaging standards. The screen graphics provided in the FDA ESG Web Interface sections of this User Guide are from the application.

1.1 Objective

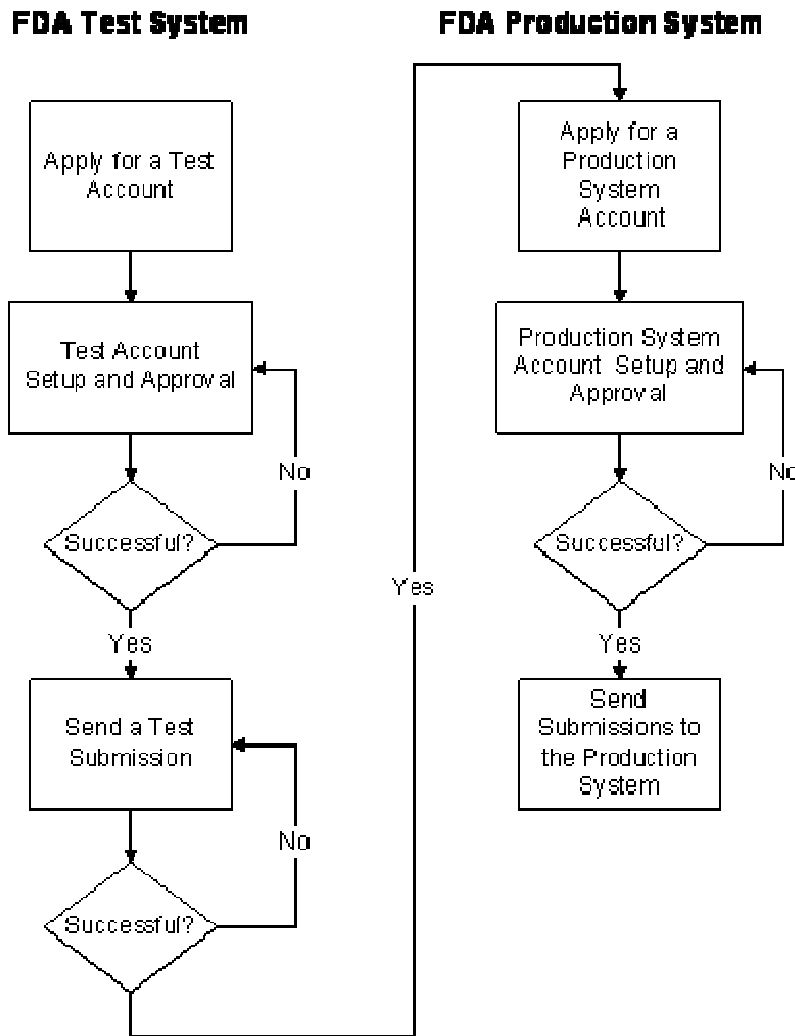
The objective of this User Guide is to provide industry participants with information and guidance on how to prepare and send documents through the FDA ESG. [See Table 2: Electronic Submissions Supported by the FDA ESG](#) for a list of submissions that the FDA ESG will accept. This document provides a high-level description of the electronic submission process via the FDA ESG.

2. Overview of the Registration Process

Registering to use the FDA ESG involves a sequence of steps that are to be conducted for all submitters and types of submissions. The first steps in the process are designed to ensure that the FDA ESG can successfully receive electronic submissions and that the electronic submissions are prepared according to published guidelines. The testing phase is done using the FDA ESG test system. Once the sender has passed the testing phase, an account will be set up allowing the submissions to be sent to the FDA ESG Production System.

The following diagram illustrates the steps in the process. The remaining sub-sections in Section 2 explain each of the steps in turn.

Figure 1: Overview of the Registration Process



2.1 Apply for a Test Account

Organizations that wish to submit electronically to the FDA must apply for an account to establish themselves as Transaction Partners. The term "Transaction Partner" refers to:

An external entity authorized by the FDA to submit electronic submissions. Authorization includes agreement to regulatory conditions, successful completion of a certification process, and FDA administrative inclusion as a Transaction Partner.

Application for a test account must be initially requested for the FDA ESG. This is done to enable Transaction Partners to send a test submission to the FDA ESG.

Applying for an account involves information-sharing activities between the Transaction Partner and the FDA to set up transmission, receipt, and identification parameters. This ensures the

correct identification of the Transaction Partner to the FDA. Digital certificate information is provided to the FDA as part of the application.

2.2 Test Account Setup and Approval

The account application is reviewed by the FDA ESG Administrator. The Administrator verifies that a letter of non-repudiation agreement is on file and that the digital certificate conforms to the X.509 version 3 standard and that all data fields in the Issuer and Subject fields are completed (see Appendix C., Digital Certificates for more information). The Administrator will also communicate with the Transaction Partner to confirm the application information. If these conditions are met, a test account is set up and connections to the FDA ESG test system are established before the submitting organization is approved as a Transaction Partner.

2.3 Send a Test Submission

By sending a test submission, the Transaction Partner ensures the following conditions are met:

- The test submission is received by the FDA ESG. A notification is sent by the FDA ESG confirming that the submission was successfully received.
- The submission is routed to the correct Center Holding Area.
- The submission is prepared according to regulatory guidelines. The Center sends an acknowledgement confirming that the submission was prepared correctly.

During the testing process, Transaction Partners who will be sending submissions larger than 1 GB in total size will be asked to send a 7.5 GB test submission. This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery. Send 7.5 GB test submissions to the "GW TEST" Center and select "SIZE TEST" as the submission type.

When testing connectivity, do not send the submission to the actual Center. Instead send all connectivity test submissions to the "GW TEST" Center with the submission type "CONNECTION TEST". Only guidance compliance test submissions should be sent to the FDA Center.

2.4 Apply for a Production System Account

Applying for a Production System Account in the FDA ESG follows the same process as applying for a test account. Reference [Section 2.1, Apply for a Test Account](#).

2.5 Production System Account Setup and Approval

The same process is followed to setup a Production System Account as for a Test Account. Reference [Section 2.2, Test Account Setup and Approval](#).

2.6 Send Submissions to the Production System

After completion of these steps, the Transaction Partner is enabled and approved to send submissions to the FDA ESG. The Production System Account allows the Transaction Partner to send any of the supported submission types to the FDA. **However, the FDA will only process those submission types for which the Transaction Partner has received prior approval.**

NOTE: It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.

3. Preparatory Activities

There are a number of preparatory activities that need to be completed before beginning the registration process. This section describes these preparatory activities and presents system and protocol issues for FDA ESG users to consider.

3.1 Submit Letter of Non-Repudiation Agreement

A letter of Non-Repudiation Agreement **must** be submitted to the FDA. Reference [Appendix H, Sample Letters of Non-Repudiation Agreement, for letter examples](#).

The non-repudiation agreement allows the FDA to receive electronically signed submissions in compliance with 21 Code of Federal Regulations (CFR) Part 11.100.

3.2 Obtain Digital Certificate

A digital certificate must be obtained.

Digital certificates ensure private and secure submission of electronic documents. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

Digital certificates can be obtained from either a public or private Certificate Authority (CA). It must be an X.509 version 3 certificate and all data fields in the Issuer and Subject fields must be completed. Reference [Appendix C., Digital Certificates](#) for more information on digital certificates.

3.3 Understand Submission Guidelines

Each FDA Center has specific guidelines that must be followed for successful submission. [Table 1: FDA Links to Submission Preparation Guidelines](#) below contains links to Center-specific preparation guidelines and contacts. [Table 2: Electronic Submissions Supported by the FDA ESG](#) lists electronic submissions supported by the FDA ESG. Important information on the use of digital/electronic signatures on FDA forms can be found in [Appendix J., Digital Signatures](#).

Center	Link
Center for Biologics Evaluation and Research (CBER)	http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm163685.htm
Center for Drug Evaluation and Research (CDER)	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm
Center for Devices and Radiological Health (CDRH)	http://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm
Adverse Event Reporting System (AERS)	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm
Center for Veterinary Medicine (CVM)	http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ElectronicSubmissions/default.htm
Office of the Commissioner (OC)	http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114043.htm
Center of Tobacco Products	http://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm

NOTE: Meeting the requirements for using the FDA ESG to route submissions does not mean that these submissions automatically meet FDA Center-specific submission requirements.

For each test submission type, a test submission must be validated by the Center before sending submissions to the Production System.

It is the responsibility of the Transaction Partner to consult the appropriate FDA Center for information on formats, deadlines, and other information or procedures for submissions.

The submission acronyms or names listed in Table 2 below are not to be used as attributes in the submission header. See Table G-1 in [Appendix G., AS2 Header Attributes](#), for a list of allowed attributes for the different submission types.

Center	Submissions
CBER	AERS – Adverse Event Reports

	<p>AERS Attachments</p> <p>BLA – Biologics License Application (eCTD and eBLA format)</p> <p>eCTD – Electronic Common Technical Document</p> <p>IDE – Investigational Device Exemption</p> <p>IND – Investigational New Drug Application (eCTD and eIND format)</p> <p>DMF – Drug Master File</p> <p>H1N1 Lot Release</p> <p>Promotional Materials</p> <p>Lot Distribution Data</p> <p>510K</p> <p>SDTM</p>
CDER	<p>AERS – Adverse Event Reports</p> <p>AERS Attachments</p> <p>ANDA – Abbreviated New Drug Application</p> <p>BLA – Biologics License Application (eCTD and eBLA format)</p> <p>eCTD – Electronic Common Technical Document</p> <p>NDA – New Drug Application (eCTD and eNDA format)</p> <p>IND – Investigational New Drug Application</p>
CDRH	<p>Adverse Events</p> <p>Electronic Submissions</p>
CVM	<p>Adverse Events Reports</p> <p>Electronic Submissions</p>
OC	<p>SPL - Structured Product Labeling (includes NDC Labeler Code Request, Establishment Registration and Drug Listing)</p>
Center of Tobacco	<p>Electronic Submission</p>

Products	
GW TEST*	CONNECTION TEST SIZE TEST

** These submission types are only supported in the Test environment and are intended solely for testing.*

3.4 Naming Conventions

A special consideration applies to the naming convention for files and directories. The following characters are not recommended for use when naming submission files and directories:

/ - forward slash
 \ - backslash
 : - colon
 ? - question mark
 " - quotation marks
 < - less than sign
 > - greater than sign
 | - vertical bar,
 space - If you need to use a space, use `_an_underscore_instead` or `SeparateWordsWithCapitalLetters`.

Note: Directories and sub-directories cannot begin with the "." (dot) character.

3.5 Determine Submission Method

There are three options for sending FDA ESG submissions:

1. FDA ESG Web Interface – 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.
2. Applicability Statement 2 (AS2) Gateway-to-Gateway – An electronic submission protocol that uses HTTP/HTTPS for communications.

Determining the best of these options for your organization will be influenced by the types of submissions to be transmitted, infrastructure capabilities, and business requirements.

One or more of these options can be selected to submit electronic documents to the FDA. However, a separate registration will be required for each option selected.

Considerations for each option are shown in Table 3 below.

Table 3: Considerations for Submission Protocol Choice

	FDA ESG Web Interface	AS2 Gateway-to-Gateway
Cost	None	High setup and support costs
Setup	Minimal	Need to install and configure Gateway
User-friendly web interface	Yes	No
Submission types supported	All, including AERS reports	All, including AERS reports
Long-term support by FDA	Yes	Yes
Preparation of multi-file submissions *	Occurs automatically	Multi-file submissions need to be archived and compressed using a tar and gzip utility prior to submission
Custom attributes for submission routing **	Automatically adds custom attributes to the AS2 header	Need to add custom attributes to the AS2 header
Routing IDs ***	N/A	Need to add routing IDs to the AS2 header
Integration to backend systems	No	Can be automated
Tracking of submission activity by Transaction Partner	Manual tracking	Can be automated
Automation of submission process	No	Yes

* See [Appendix B., Creating .tar Files and Compressing Files for Submission](#)

** See [Appendix G., AS2 Header Attributes](#)

*** See [Appendix K., AS2 Routing IDs](#)

A factor that determines how quickly a submission can be sent to the FDA ESG is the Transaction Partner's network connection to the Internet. Table 4 lists the maximum transmission rates for a variety of network connections and the optimal time it would take to send a 1 GB submission.

Table 4: Transmission Rates for Network Connections and Optimal Times for Transmission

Network Connection	Max. Transmission Rate (Mbps)	Time (min)
T1	1.54	83
T2	6.31	21
T3	44.7	3
OC1	51.8	2.5
OC3	155.4	0.8
T4	274.8	0.5
OC12	621.6	0.2

Mbps = Megabits per sec.

1 GB (Gigabyte) = 8,590 Megabits

Actual times will be greater than those listed in the table due to factors such as network configuration and the amount of traffic coming in and going out through the line. For example, submissions sent in the middle of the day typically take 1.5 – 2 times longer to send than those sent after business hours. Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG. These companies had T3 network connections or better. FDA recommends that submissions of this size be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

During the testing process, Transaction Partners who will be sending submissions larger than 1 GB in total size will be asked to send a 7.5 GB test submission. This test will allow Transaction Partners to identify and resolve network limitations that will impact the speed of delivery.

3.6 Connection Requirements

FDA ESG Web Interface users need the following:

- A high-speed internet connection.
- A web browser: Internet Explorer 6, 7, or 8 or Firefox 2.0.x.
- Hard disk space of at least three times the size of the submission. For instance, if the submission is 1MB in size, then at least 3MB of hard disk space is required.
- Sun's Java Runtime Edition (JRE) 1.5.0_18, for the browser plug-in files.

Reference [Appendix D., Java Runtime Edition Installation](#) for more information on obtaining and installing JRE.

Gateway functionality is optimized with JRE version 1.5.0_18 installed. It is recommended that the automatic Java update option on the computer be disabled to avoid the automatic installation of a different version of JRE. The steps to do this are as follows:

1. Select Control Panel from the Start menu.
2. Double click on the Java (or Java Plug-In) icon.
3. Click on the "Update" tab.
4. Uncheck the "Check for Updates Automatically" checkbox.
5. Click OK.

Gateway-to-Gateway users need the following:

- A high-speed internet connection,
- An AS2 compliant Gateway product,
- Hard disk space of at least three times the size of the submission.

3.7 Help and Information

There are resources that can be contacted if you need assistance with various aspects of the submission process. These are provided in the table below.

Table 5: Submission Process Aspects and Help and Information Contacts	
Submission Process Aspect	Contact
Preparation/Registration/Policy Questions	Email: esgprep@fda.hhs.gov
Technical Issues with Submissions after becoming a Production System Transaction Partner	Email: esgreg@gsni.com
Center-specific Submission Guidance	Reference Section 3.3, Understand Submission Guidelines .

4. FDA ESG Web Interface Electronic Submissions

The steps for the electronic submission process for FDA ESG Web Interface users are provided in the following sections.

4.1 Apply for a Test Account

Applying for an FDA ESG WebTrader Test account is a multi-step process. You should have the following information before beginning the process:

- Company and contact information
- Digital Certificate file location

You can obtain the FDA ESG Web Interface address and a temporary Login ID and password by emailing esgprep@fda.hhs.gov and indicating your intent to register for the FDA ESG.

The remainder of this section describes the FDA ESG Test Account Application process using screenshots from the FDA ESG Web Interface.

1. Using the address provided by the FDA, access the FDA ESG Web Interface.

The **Login** page is displayed. Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not continue. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.hhs.gov to request access to the test environment.

FDA U.S. Food and Drug Administration Department of Health and Human Services

FDA Electronic Submissions Gateway

User ID:
Password:
 I agree to the terms set forth in the System Notification below.
 Remember my user ID

[Login Help](#) [Web Trader Help](#)

Pop-up blocking software for your browser may interfere with this product. You may want to disable or uninstall such software.

YOU ARE ENTERING THE FDA ELECTRONIC SUBMISSIONS GATEWAY TEST ENVIRONMENT. THIS ENVIRONMENT IS TO BE USED FOR TEST SUBMISSIONS ONLY.

System Notification: This computer system, including all related equipment, networks and network devices (specifically including Internet access), is provided for authorized U.S. Government use. This computer system may be monitored for all lawful purposes, including ensuring that its use is authorized, for management of the system, to facilitate protection against unauthorized access, and to verify security procedures, survivability and operational security. Use of this computer system, authorized or unauthorized, constitutes consent to monitoring of this system. Unauthorized use may subject you to criminal prosecution, and/or administrative disciplinary action including having access privileges revoked. Under 18 U.S.C. 1001, anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subject to criminal penalties.

Licensed to: [FDA](#)

2. Enter the **User ID** and **Password** provided by the FDA and click the **Login** button.

The **WebTrader registration wizard** is displayed. This wizard will guide you through the remainder of the application process.

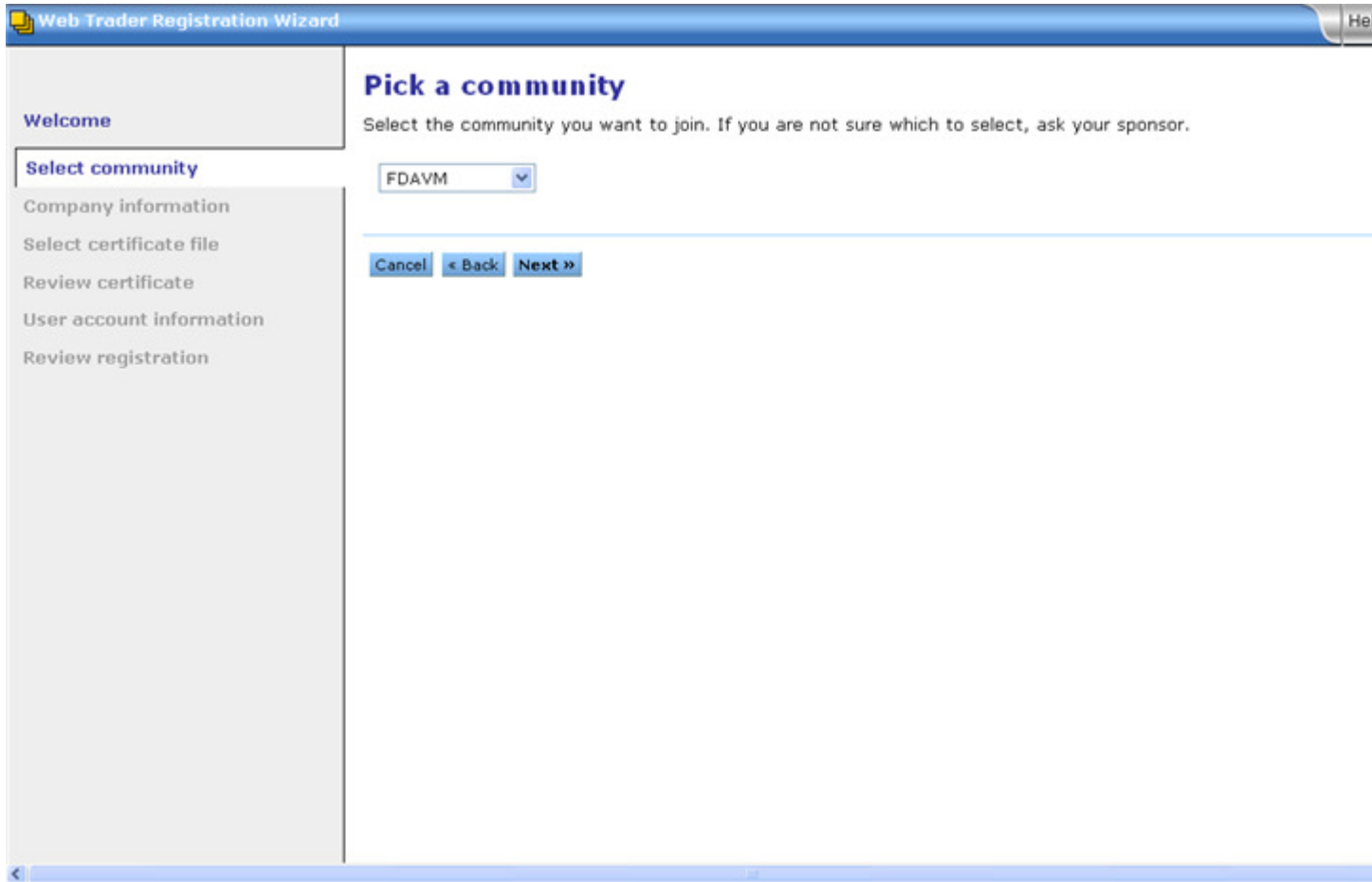


4. Click the **Next** button.

The **Pick a Community** page is displayed

The community represents where submissions will be sent for logging, verification, and ultimately routing to the appropriate FDA Center. The only community will be "FDA VM."

Reference [Appendix E., Glossary of Terms](#), for more information about the community.



6. Click the **Next** button.

The **Enter company information** page is displayed.

This page records your company's name for identification purposes.

NOTE: If you already have an account, whether it is AS2 or WebTrader, you must enter a unique string (different from the one used when registering for their first account) in the Company name field. This is to ensure that this account is treated as a separate identity in the database.

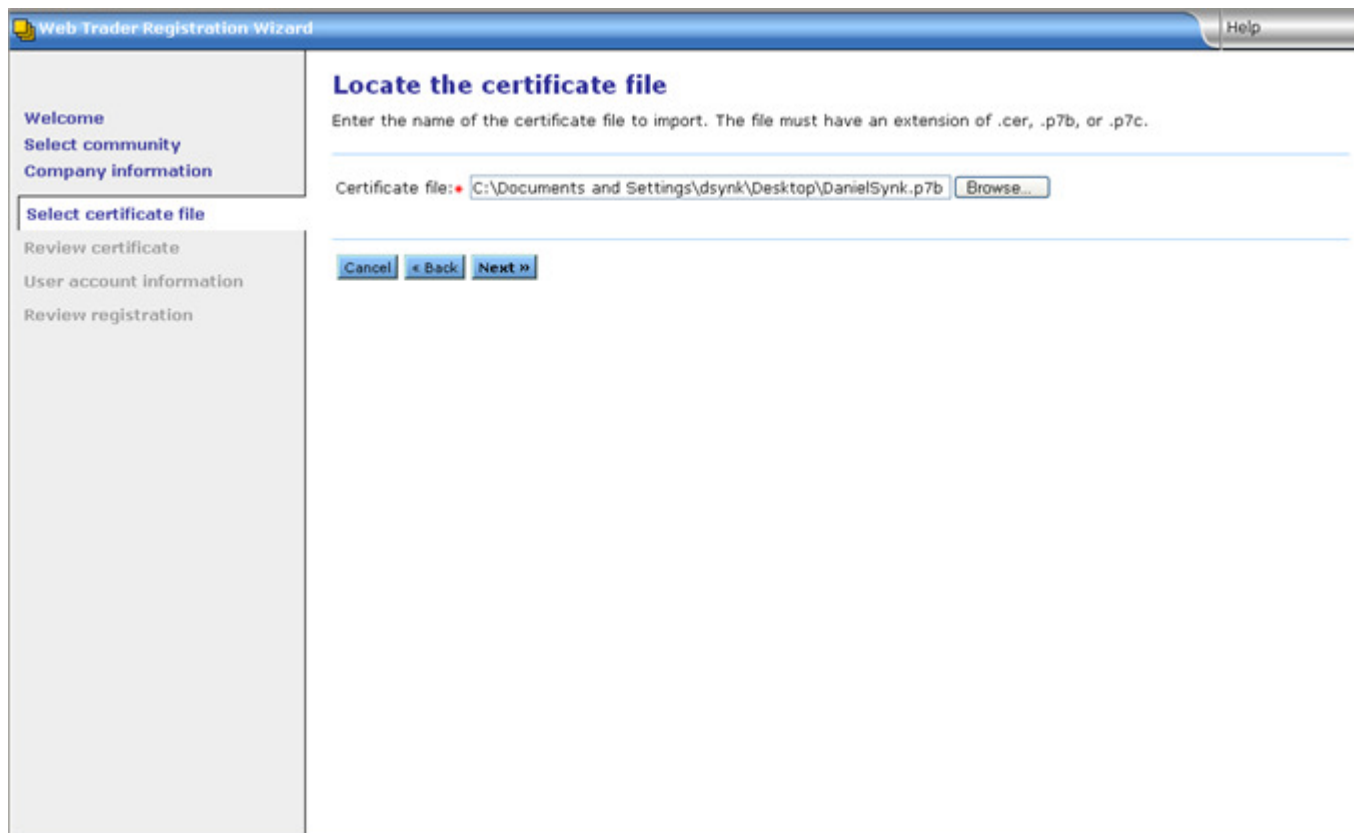
The screenshot shows a web browser window titled "Web Trader Registration Wizard" with a "Help" button in the top right corner. On the left side, there is a vertical navigation menu with the following items: "Welcome", "Select community", "Company information" (which is highlighted), "Select certificate file", "Review certificate", "User account information", and "Review registration". The main content area is titled "Enter company information" and contains a text input field labeled "Company name:" with the text "Arena Drug Company" entered. Below the input field are three buttons: "Cancel", "< Back", and "Next >".

8. Click the **Next** button.

The **Locate the certificate file** page is displayed.

This page is used to specify the location of the certificate file. Each submission must be accompanied by a certificate. The digital certificate must be an X.509 version 3 certificate.

Reference [Appendix C., Digital Certificates](#) for more information about digital certificates.



NOTE: There are situations when a valid certificate is not accepted by the registration module and an error message is returned. If this occurs, zip the certificate file and email it to the FDA ESG administrator at esgprep@fda.hhs.gov. Once received, FDA will assess the certificate and send a response.

10. Provide the desired digital certificate file in the **Certificate file** field by entering the name of the certificate or browsing for one on your hard drive by clicking on the **Browse...** button.

The **View certificate details** page is displayed.

This page is used to review the certificate information and to assign a name to the certificate. Carefully review the "Issuer" and "Subject" fields to be sure that all data fields are completed (i.e., for each data element such as "CN", there is a value that follows the equals sign).

Web Trader Registration Wizard Help

Welcome
[Select community](#)
[Company information](#)
[Select certificate file](#)

Review certificate
[User account information](#)
[Review registration](#)

View certificate details

Review the certificate details below. Click the next button if this certificate is correct or click the back button to select a different certificate.

Certificate details

Field	Value
Version	3
Issuer	emailAddress=dsynk@gnsi.com, CN=Daniel Synk, OU=Daniel Synk, O=GNSI, L=Rockville, ST=Maryland, C=US
Serial number	92c10060478e0366
Subject	emailAddress=dsynk@gnsi.com, CN=Daniel Synk, OU=Daniel Synk, O=GNSI, L=Rockville, ST=Maryland, C=US

Certificate path
Daniel Synk

[« Back](#) [Next »](#)

12. Click **Next**.

The **Enter user account information** page is displayed.

This page is used to specify the user ID, password, and contact information selected by the Transaction Partner. After registration is complete, this user ID and password will be used by the Transaction Partner to log on to the FDA ESG Web Interface.

Web Trader Registration Wizard Help

Welcome
Select community
Company information
Select certificate file
Review certificate

User account information
Review registration

Enter user account information

Enter user account information. After registering you will use this information to log into WebTrader.

User ID:

Name:

Password:

Verify password:

E-mail address:

Phone number:

Alternate contact

Name:

E-mail address:

Phone number:

Note:

14. Enter a new login User ID and Password. Remember this User ID and Password – it will be used for subsequent Logins.

15. Click **Next**.

The **Registration summary** page is displayed.

This final page provides an account summary.

The screenshot shows the 'Web Trader Registration Wizard' interface. The title bar includes 'Web Trader Registration Wizard' and a 'Help' button. On the left, a navigation pane lists steps: 'Welcome', 'Select community', 'Company information', 'Select certificate file', 'Review certificate', 'Login information', and 'Review registration' (which is highlighted). The main content area is titled 'Registration summary' and contains the following text: 'Review the information below. Click the finish button to submit this registration or click the back button to make changes.' and '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.' Below this is the 'Company information' section with details: 'Company name: Arena Drug Company', 'Sponsor: FDATST', 'User ID: drugco50', and 'Certificate: emailAddress=spalle@gnsi.com, CN=Srini Palle, OU=Srini Palle WebTrader, O=GNSI, L=Rockville, ST=Maryland, C=US'. The 'Primary contact' section lists: 'Contact name: Annie Rice', 'Phone number: 103-777-0968', and 'E-mail address: arice@adc.com'. The 'Alternate contact' section lists: 'Contact name: Jerry rose', 'Phone number: jrose@gnsi.com', and 'E-mail address: 103-777-0968'. At the bottom, there is a checkbox labeled 'I hereby certify that the information provided herein is true and that I am authorized to register with the FDA.' and three buttons: 'Cancel', 'Back', and 'Finish'.

17. Check box to certify the accuracy of your information.

18. Click the **Finish** button to return to the **Login** page, or close the browser window.

4.2 Test Account Setup and Approval

After successful Test Account setup, the FDA sends an email to the email address provided for the contact, indicating approval as a Transaction Partner and authorization to send a test submission. Typically, the approval notification is sent on the next business day.

The test submission cannot be sent until this notification has been received.

Java Runtime Edition (JRE) must be installed to send a submission. [Reference Appendix D., Java Runtime Edition Installation](#) for the installation procedures.

Once you have fulfilled these criteria, proceed to Section 4.3 for instructions on sending a test submission.

4.3 Send a Test Submission

After Test Account Setup and Transaction Partner approval, a test submission must be sent to ensure that the submission "conduit" is working properly from end to end. To do this, follow the steps below.

Confirm that the correct version of the JRE is installed before you begin. Reference [Appendix D., Java Runtime Edition Installation](#) for the version information and installation procedures.

1. Using the address provided by the FDA, access the FDA ESG Web Interface application.

The **Login** page is displayed.

FDA U.S. Food and Drug Administration

FDA Electronic Submissions Gateway

User ID:

Password:

I agree to the terms set forth in the System Notification below.

Remember my user ID

Login

Pop-up blocking software for your browser may interfere with this product. You may want to disable or uninstall such software.

YOU ARE ENTERING THE FDA ELECTRONIC SUBMISSIONS GATEWAY TEST ENVIRONMENT. THIS ENVIRONMENT IS TO BE USED FOR TEST SUBMISSIONS ONLY.

System Notification: This computer system, including all related equipment, networks and network devices (specifically including Internet access), is provided for authorized U.S. Government use. This computer system may be monitored for all lawful purposes, including ensuring that its use is authorized, for management of the system, to facilitate protection against unauthorized access, and to verify security procedures, survivability and operational security. Use of this computer system, authorized or unauthorized, constitutes consent to monitoring of this system. Unauthorized use may subject you to criminal prosecution, and/or administrative disciplinary action including having access privileges revoked. Under [18 U.S.C. 1001](#), anyone who makes a materially false, fictitious, or fraudulent statement to the U.S. Government is subject to criminal penalties.

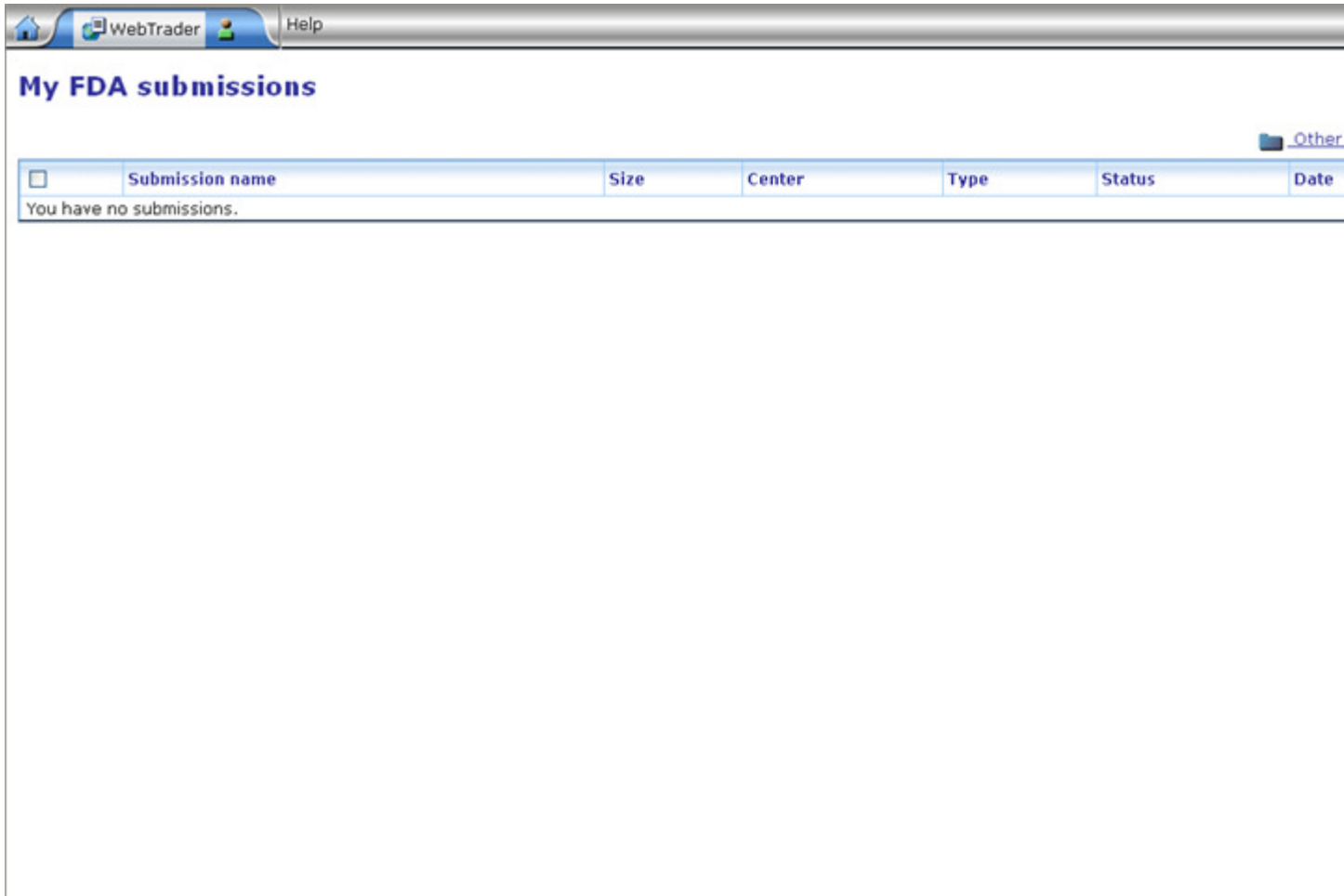
Licensed to: [FDA](#)

Note the test environment warning on the **Login** page. If the **Login** page does not have this warning, do not send a test submission. Exit the browser and contact the FDA ESG Administrator at esgprep@fda.hhs.gov to request access to the test environment.

3. Enter the **User ID** and **Password** that was set up in the registration wizard. Reference Step in Section 4.1, Apply for a Test Account.

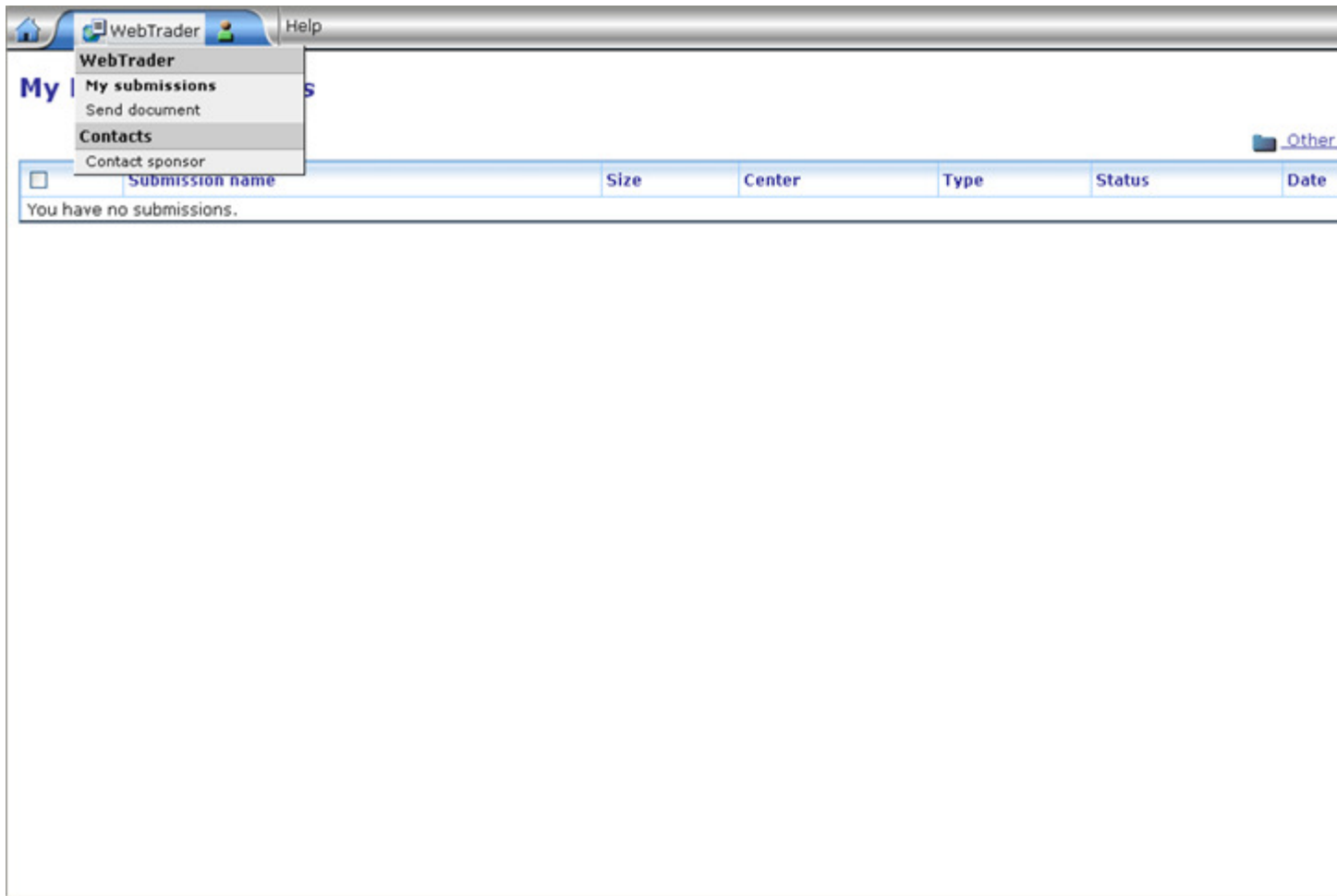
4. Click the **Login** button.

After a successful login, the **My FDA submissions** page is displayed. This page lists all messages received from the FDA ESG.



5. Click the **WebTrader** icon.

The **WebTrader** drop-down menu is displayed.



7. Select the **Send document** menu item.

The **Send document** page is displayed.

WebTrader Help

Send document

Select who will receive the document

Gateway: FDAVM

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 to the submission will be relative from the provided directory path unless an alternate root directory is entered.

Path:

Root directory:

Submission type:

Select a signing certificate

Current file: C:\Documents and Settings\dsynk\My Documents\Desktop docs\Desktop Items\DanielSynk.pfx

New file:
MyCertificate.p12 or MyPrivateKey.pfx

8. Select an FDA Center from the **Center** drop-down box. The Centers that can be selected at present are CBER, CDER, CDRH, CFSAN, CVM, Center for Tobacco Products, GWTEST, and OOPD. Upon choosing a Center, the **Submission type** drop-down box will be populated with the correct submission types for that Center.

9. Single File Submissions: Click the **Browse** button associated with the **Path** textbox to select the test submission.

10. Multi-File Submissions: Click the **Browse** button associated with the **Root Directory** textbox to select the directory that contains all the files in the test submission. Make sure that the name of any file or sub-directory does not start with "." (dot). **Note:**the **Path** field is still required for multi-file submissions. Make sure you have entered a path as well as a root directory.

11. Select a test submission type from the **Submission type** drop-down box. **About submission types:**

- **Connectivity tests** ensure that your connection to the ESG is up and running. They should be sent to the "Testing" Center.

- **Load tests** ensure that you are able to send large submissions through the ESG; you should perform a load test if you are planning on sending submissions larger than 100MB. Load tests should be sent to the "Testing Center." See Section 4.4, Sending Large Submissions.
- **Guidance-compliant submission tests** are reviewed by your Center so they can clear you for a production account. Guidance-compliant submissions should be sent to your Center.

12. Select a signing certificate by clicking the associated **Browse** button and selecting the signing certificate. All submissions require a certificate to digitally sign and encrypt the submission.

Note that connectivity tests should only be sent to TESTING, not actual centers.

The completed **Send document** page should be populated similar to the page below.

The screenshot shows a web browser window with the title 'WebTrader' and a 'Help' button. The main content area is titled 'Send document'. Below the title, there are several sections:

- Select who will receive the document:** Gateway: FDAVM, Center: GWTEST (dropdown menu).
- 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 submitted will be relative from the provided directory path unless an alternate root directory is entered.
 - Path: C:/Documents and Settings/dsynk/My Documents/testSubm (with a 'Browse...' button)
 - Root directory: C:/Documents and Settings/dsynk/My Documents (with a 'Browse...' button)
 - Submission type: Connectivity Test (dropdown menu)
- Select a signing certificate:** Current file: C:\Documents and Settings\dsynk\My Documents\Desktop docs\Desktop Items\DanielSynk.pfx. New file: C:\Documents and Settings\dsynk\My Documents\Desktop (with a 'Browse...' button). Below the 'New file' field, it says 'MyCertificate.p12 or MyPrivateKey.pfx'.

At the bottom left of the form area, there is a blue 'Send' button.

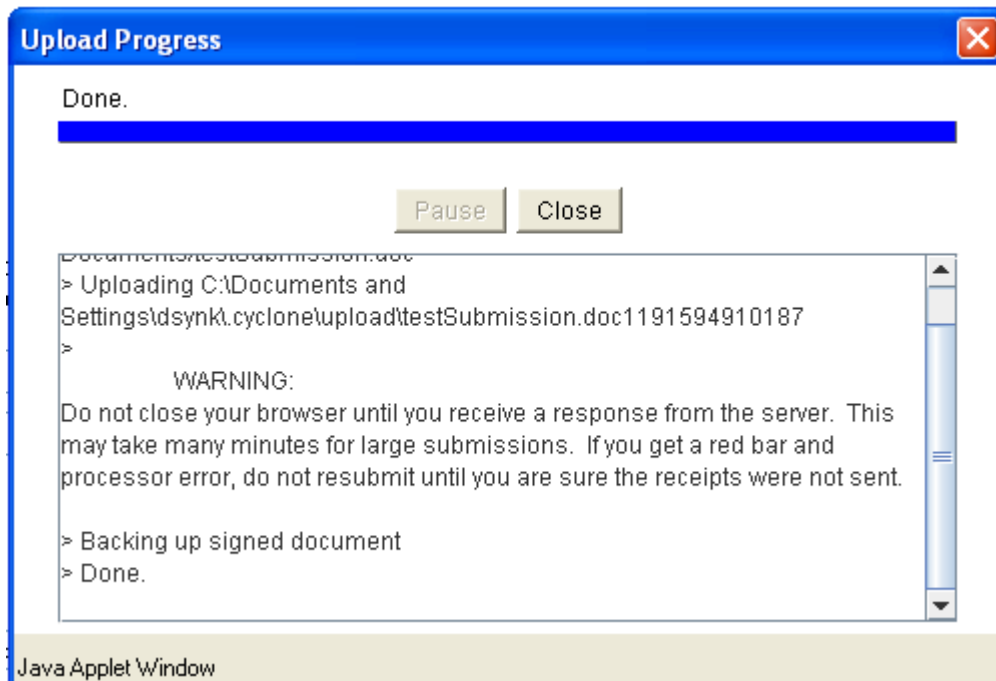
14. Click the **Send** button on the **Send document** page.

The **Enter password** dialog box is displayed on top of the **Send document** page.



16. Enter the certificate password and click **OK** in this dialog box.

The **Upload Progress** dialog box is displayed on the **Send document** page:

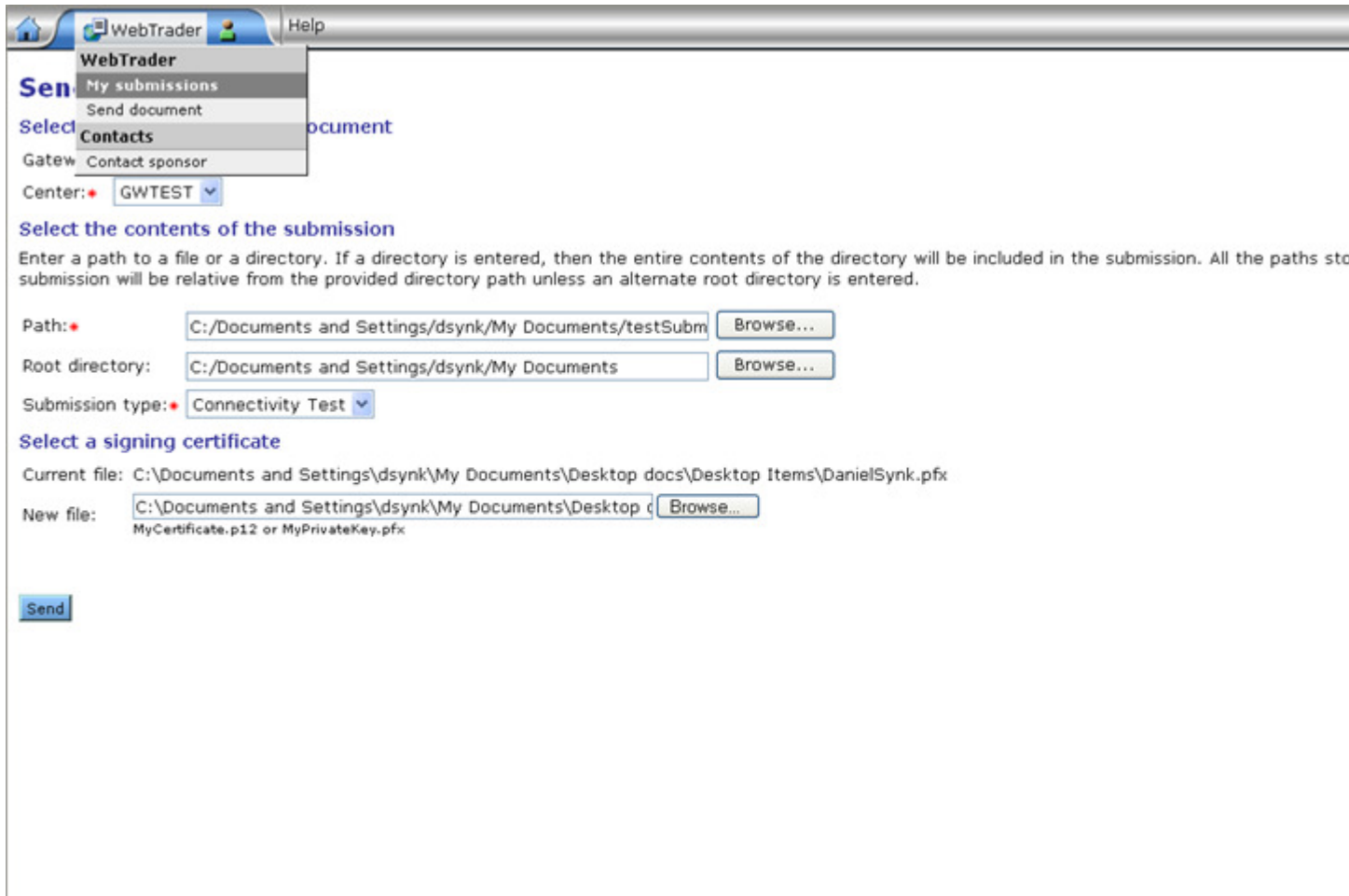


18. When the upload is complete (indicated by the display of **Done**), click the **Close** button in the **Upload Progress** dialog box.

At this point, the test submission is sent. The FDA ESG logs the submission and verifies submission destination and type. When the submission is successfully received at the FDA, a receipt email will be listed on the **My FDA Submissions** page.

20. To access the receipt, click on the **WebTrader** icon to access the Inbox.

The **WebTrader** drop-down menu is displayed.



22. Select the **My Submissions** menu item.

The **My FDA submissions** page is displayed.

WebTrader Help

My FDA submissions

Other

<input type="checkbox"/>	Submission name	Size	Center	Type	Status	Date
<input type="checkbox"/>	testSubmission.doc	25.8 KB	GWTEST	ConnectTest	<ul style="list-style-type: none"> • Backup found • Receipt • Acknowledgement New 	Oct 05, 2007 10:35:10 AM

[Delete backups](#) | [Delete records](#)

The receipt for the test submission should be displayed here. This first receipt confirms that the submission was received by the FDA ESG. Click on the **Details** link to access the receipt contents.

If there are any errors in the submission, the receipt will not appear on the My FDA submissions page but will be sent to the Documents in Inbox page. The receipt will contain information about why the submission failed.

The FDA ESG will then route the test submission to the Center Holding Area. When the Center system successfully receives the submission, a second acknowledgement will be sent confirming that the Center has received the submission. The Center will then validate the test submission.

Contact the FDA ESG testing representative at esgprep@fda.hhs.gov if the receipt for the test submission or the Center Acknowledgements is not received.

The next step is to apply for an FDA ESG Production System Account. This process is described in the following section.

4.4 Apply for a Production System Account

The steps for applying for an FDA ESG Production System Account are the same as those described in [Section 4.1, Apply for a Test Account](#).

However, there is a difference in the Login page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown below:



The screenshot shows the FDA Electronic Submissions Gateway login page. At the top, there is a blue header with the FDA logo on the left, the text "U.S. Food and Drug Administration" in the center, and the Department of Health and Human Services logo on the right. Below the header, the page title "FDA Electronic Submissions Gateway" is centered. The main content area contains a login form with the following elements: a "User ID" text box, a "Password" text box, a checkbox labeled "Remember my user ID", and a "Login" button. Below the form, it says "Licensed to: FDA". At the bottom of the page, there is a warning: "Pop-up blocking software for your browser may interfere with this product. You may want to disable or uninstall such software."

If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.hhs.gov and obtain the correct address for the FDA ESG Login page.

4.5 Production System Account Setup and Approval

After successfully completing the Production System Account setup, the FDA sends an email to the email address provided for the primary contact, indicating approval as a Transaction Partner and authorization to send submissions to the FDA ESG. Typically, the approval notification is sent on the next business day.

Submissions cannot be sent to the FDA ESG until this notification has been received.

4.6 Send Submissions to the Production System

The steps to send a Submission to the FDA ESG are the same as those in [Section 4.3, Send a Test Submission](#).

However, there is a difference in the Login page. The **Login** page *should not* have the test environment warning that it has when sending a test submission; it should look like the **Login** page shown in Section 4.5, Apply for a Production System Account.

If the **Login** page does have the warning, do not send a submission. Exit the browser, contact the FDA ESG Administrator at esgprep@fda.hhs.gov, and obtain the correct address for the FDA ESG Login page.

4.7 Sending Large (> 7.5 GB) Submissions

The FDA ESG is able to receive and process regulatory submissions up to 100 GB in size. The major consideration in determining how quickly large submissions are transmitted to the FDA ESG is the bandwidth available to the Transaction Partner between their company and the FDA ESG. FDA has the following recommendations concerning the transmission of large regulatory submissions.

During the testing phase, send a 7.5 GB test submission. This test will allow Transaction Partners to evaluate bandwidth availability and to adjust their network configuration as necessary. This test submission should be sent to the "Testing" Center with "7.5 GB Submission" as the submission type.

Send a 7.5 GB test submission that is representative of an actual submission. The web interface archives and compresses the submission into a single file prior to transmission. Submissions that consist of text files will compress to a greater extent than PDF files, will transmit faster, and thus give an inaccurate assessment of the time it takes for submissions to be sent and processed by the FDA ESG.

Send submissions greater than 7.5 GB in size overnight. Pilot testing with selected Industry Transaction Partners has shown that it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG. These companies had T3 network connections or better. FDA recommends that large submissions be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

Sending large submissions may result in the FDA ESG web interface erroneously reporting that the transmission was not successful, even though the FDA ESG has successfully received the transmission. This is a known bug and FDA has asked Axway to provide an update to the web interface that fixes this error.

When the FDA ESG has received a complete submission, a backup copy is made before the Java applet receives a reply from the server confirming the submission is complete. For large

submissions (> 7.5 GB), this can take many minutes. Since there is no network activity for such a long time, the session timeouts and the Java applet never receives the response. The FDA ESG has received the submission successfully, but the Java applet returns an error and indicates that the submission needs to be resumed. Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request. Since this is a large submission, it will take several hours before the first acknowledgement is received.

If you receive this error and it has clearly occurred at the end of the transmission, do not resend the submission right away. Wait for several hours (or longer depending on the size of the submissions) and see if the MDN is sent before attempting to resend the submission.

4.8 Tracking Submissions

Once a submission has been sent using the FDA ESG Web Interface, the Transaction Partner can track the submission to ensure that it was received by the FDA ESG and the Center.

4.8.1 The Submission Process

When a submission is sent using the FDA ESG Web Interface, it goes through the following steps:

The submission is transmitted using the FDA ESG Web Interface to the Gateway. When the FDA ESG receives this submission, it sends a receipt known as a Message Delivery Notification (MDN) to the Inbox of the account from which the submission was received.

The submission is delivered from the FDA ESG to a central holding area for all the Centers.

The submission is then delivered from the holding area to the appropriate Center. When a Center receives a submission, it sends an acknowledgement to the Inbox of the account from which the submission was sent.

4.8.2 Message Delivery Notifications (MDNs) and Acknowledgements

When a submission is sent using the FDA ESG web interface, the following two messages are delivered to the Inbox of the account from which the submission was sent.

A receipt from the FDA ESG, also known as an MDN. This message denotes that the submission has been delivered to the FDA ESG. The name of the receipt message includes the file name of the submission that was sent. If a directory of files was submitted, the file name of the submission will be the name of the directory followed by the extension ".tar.gz". The MDN message contains the message ID of the submission and a date stamp for when the submission was received by the FDA ESG. These items may be used to track a submission.

An acknowledgement from the Center to which the submission was sent. This file is named with a unique alphanumeric string known as the Core ID. The Core ID is also used by the FDA ESG to track a submission.

A sample Inbox looks similar to this, once submissions have been sent:

My FDA submissions [Other documents](#)

<input type="checkbox"/>	Submission name	Size	Center	Type	Status	Date
<input type="checkbox"/>	testSubmission.doc	25.8 KB	GWTEST	ConnectTest	<ul style="list-style-type: none">• Backup found• Receipt• Acknowledgement <i>New</i>	Aug 23, 2007 05:17:15 PM

[Delete backups](#) | [Delete records](#)

4.8.3 Message IDs and Core IDs

Among other information, the MDN contains a Message ID and a time stamp denoting the time the submission was received. The Message ID is a unique alphanumeric string that identifies each submission. This Message ID can also be used to track a submission and to correlate a submission to its Center acknowledgement.

A sample MDN looks similar to the file shown below. The Message ID and date stamp in this MDN are highlighted.

Message-ID: <1140124426654.2852@11nap01>
Date: Thu, 16 Feb 2006 21:13:46 GMT
From: esgprep@fda.gov
Subject: AcmeDrugCompany; ZZFDA
Mime-Version: 1.0
Content-Type: multipart/signed; micalg=sha1; protocol="application/pkcs7-signature"; boundary="-----_Part_65_16583928.1140124426654"
X-Cyclone-From: ZZFDA
X-Cyclone-To: AcmeDrugCompany
Content-Length: 1952

-----_Part_65_16583928.1140124426654
Content-Type: multipart/report; report-type=disposition-notification;
boundary="-----_Part_64_17446017.1140124426654"

-----_Part_64_17446017.1140124426654
Content-Type: text/plain; charset=us-ascii

This MDN (Message Disposition Notification) was automatically built on Thu, 16 Feb 2006 21:13:46 GMT in response to a message with id <12689343.1140124473009.JavaMail.sacharya@pvenkat> received from ZZFDA on Thu, 16 Feb 2006 21:13:46 GMT.

Unless stated otherwise, the message to which this MDN applies was successfully processed.

-----_Part_64_17446017.1140124426654
Content-Type: message/disposition-notification

Original-Message-ID: <12689343.1140124473009.JavaMail.sacharya@pvenkat>
Disposition: automatic-action/MDN-sent-automatically; processed
Received-Content-MIC: Jkm19bjOa6J8JBn/pv87oYIBnTA=, sha1

When a Center receives a submission, it associates the submission's Message ID with a Core ID. This Core ID can be used along with the Message ID generated as part of the MDN to track a submission on the FDA ESG. A sample acknowledgement message with the Core ID highlighted is shown below:

MessageId: <12689343.1140124473009.JavaMail.sacharya@pvenkat>

CoreId: 1140124426155.2844@11nap01

DateTime Receipt Generated: 02-16-2006, 16:17:11

The date and time stamp contained in this message conveys when CBER received your submission from the Electronic Submission Gateway. If your submission was received at CBER after 4:30 PM EST, the official receipt date for the submission is the next government business day.

4.8.4 Accessing MDNs and Acknowledgements

To access an MDN after sending a submission,

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.
2. From the WebTrader menu, select the "Check inbox" option. The receipts that are displayed specify the name of the submission file as part of their name.
3. Click the Details link next to the name of the required receipt to see its details.

To access an acknowledgement after sending a submission,

1. Log on to the ESG using the user name and password for the account from which you sent the submissions.
2. From the WebTrader menu, select the "Check inbox" option. The messages with ".ack" or ".txt" extensions are the acknowledgements from Centers for submissions. The message name before the extension denotes the Core ID generated by the Center for the submission.
3. Click on the name of the required acknowledgement to see its details.

5. AS2 Gateway-to-Gateway Electronic Submissions

The steps below represent the current understanding of the AS2 Gateway-to-Gateway submission process. Further refinement and clarification of these steps will be provided in future revisions of the user guide.

5.1 Apply for a Test Account

An online application form is provided for Transaction Partners to register for AS2 test accounts. The registration URL and a temporary Login ID and password can be obtained from the FDA ESG Administrator by sending an email to esgprep@fda.hhs.gov indicating intent to register for the FDA ESG.

The following information is required to complete the AS2 application form:

- Contact information - The name and contact information of a person whom the FDA may contact for questions or additional information. Enter the following information:
 - Company name
 - Primary Contact name
 - Primary Contact phone
 - Primary Contact email
 - Alternate contact name
 - Alternate phone
 - Alternate email
- o **NOTE:** Partners who have either an FDA ESG Webtrader or AS2 account already, must enter a unique string (different from the one used when registering for the FDA ESG Webtrader or AS2 account) in the Company name field. This is to ensure that this account is treated as a separate identity in the database.
- The URL from where test submissions will be sent and where acknowledgements and notifications will be received from the FDA.
- The digital certificate used to digitally sign and encrypt the test submission.
- The organization's ID number. This could be, but does not have to be the Data Universal Numbering System (DUNS) number.
- Firewall security information:
- Secure Socket Layer (SSL) Information – user name and password (if one is needed for SSL)
- Proxy Information – if a proxy server is used.

5.2 Test Account Setup and Approval

After submitting the application information as described above, the FDA ESG Administrator will communicate with the Primary Contact to validate the information provided, to setup the test account, and to test the AS2 Gateway-to-Gateway connection. At that time, the FDA ESG Administrator will also obtain security and proxy information from the Transaction Partner.

The FDA ESG Administrator will provide the following information so that the Transaction Partner can set up an account for the FDA ESG within their own Gateway. This FDA ESG account will enable the receipt of messages from the FDA ESG.

- The FDA ESG Administrator's contact information
- The URL to which the Transaction Partner will send test submissions
- The FDA digital certificate for test submissions
- The FDA ID number

At this point the Gateway-to-Gateway connection will be tested to ensure that secure messages from the Transaction Partner to the FDA ESG and from the FDA ESG to the Transaction Partner's AS2 Gateway are successfully received.

NOTE: The FDA ESG uses SSL over port 4080 for all AS2 inbound and outbound transactions.

5.3 Send a Test Submission

1. Contact the appropriate Center testing representative or appropriate programmatic representative for safety reporting to schedule a specific test date and time. [Reference Section 3.3, Understand Submission Guidelines](#), in the FDA Electronic Submissions Gateway User Guide for information on how to prepare an electronic submission and Center contact information.
2. For multi-file submission, the entire submission must reside in a single directory. This directory must then be converted to a single .tar.gz file. Reference [Appendix B., Creating tar Files and Compressing Files for Submission](#), for instructions on creating this compressed file. Take special note of the naming conventions for files and directories to ensure delivery of a complete submission.
3. There are two ways to set up routing controls dictating where a document is sent:
 - a. Add the custom header attributes to the header of the message to indicate the type of submission (e.g., an IND) and destination (e.g., CBER). Reference [Appendix G., AS2 Header Attributes](#), for information on header attributes content and format. OR
 - b. Use a unique routing ID to identify the types of submissions and destination. The selection of the routing ID can be automated in the Cyclone/Axway products through the back-end integration pick-up as described in [Appendix K., AS2 Routing IDs](#).
4. At the scheduled date and time, send the test submission to the FDA. The FDA ESG will send a Mail Delivery Notification (MDN) indicating that the test submission was received successfully. The FDA ESG will then route the test submission to the Center Holding Area. The Center will validate the test submission. For all submissions, an Acknowledgement will be sent documenting the official date and time of receipt by FDA, and in some cases the Center/programmatic area business rules describing the establishment of that date and time. The Centers/programmatic area has the option to send an Acknowledgement (via AS2) indicating whether the submission was valid or invalid.
5. Contact the FDA ESG System Administrator at esgreg@gsi.com if either the MDN or the Center Acknowledgement is not received.

Once a test submission has been successfully received and validated, the Transaction Partner is approved to apply for and setup a Production System Account. This account will be used to send submissions to the FDA.

5.4 Apply for a Production System Account

The steps for applying for a Production System AS2 Gateway Account are the same as those described in Section 2.1, Apply for a Test Account in the FDA Electronic Submissions Gateway User Guide.

Be sure to indicate on the application form that this application is for a Production System Account.

5.5 Production System Account Setup and Approval

The steps for setup and approval of a Production System AS2 Gateway Account are the same as those described in [Section 2.1, Apply for a Test Account](#) in the FDA Electronic Submissions Gateway User Guide. Upon completion of this step, the Transaction Partner is now ready to send submissions to the FDA ESG.

5.6 Send Submissions to the Production System

For each submission sent to the FDA ESG, at least two messages will be sent, and up to three messages will be sent back to the Transaction Partner.

1. The Transaction Partner will receive the MDN from the FDA ESG indicating that the submission was received successfully.
2. For all submissions, an Acknowledgement will be sent documenting the official date and time of receipt by FDA, and in some cases the Center/programmatic area business rules describing the establishment of that date and time.
3. Indication of submission validity or invalidity (at Center/programmatic area option).

5.7 Sending Large (> 7.5 GB) Submissions

NOTE: This section primarily applies to Transaction Partners sending regulatory submissions to CBER and CDER and does not apply to Transaction Partners sending Safety Reports.

The FDA ESG is able to receive and process regulatory submissions up to 100 GB in size. The major consideration in determining how quickly large submissions are transmitted to the FDA ESG is the bandwidth available to the Transaction Partner between their company and the FDA ESG. Transaction Partners who will be sending regulatory submissions larger than 1 GB in size, FDA has the following recommendations.

- During the testing phase, send a 7.5 GB test submission. This test will allow Transaction Partners to evaluate bandwidth availability, transmission time, and to adjust their network configuration as necessary. During pilot testing of the FDA ESG, industry testers found that bandwidth availability and network configuration had a major impact on the time to transmit submissions larger than 5 GB. This submission should be sent to "GW TEST" Centers with "SIZE TEST" as the submission type.
- Send a 7.5 GB test submission that is representative of an actual submission (PDF files and SAS transport files). The web interface archives and compresses the submission into a single file prior to transmission. Submissions that consist of text files will compress to a greater extent than PDF files, will transmit faster, and thus give an inaccurate assessment of the time it takes for submissions to be sent and

processed by the FDA ESG. FDA **strongly** encourages Transaction Partners to send test submissions comprised of PDF files and SAS transport files.

- Send submissions greater than 7.5 GB in size overnight. Pilot testing with selected Industry Transaction Partners has shown that, depending on available bandwidth, it takes approximately 24 hrs for submissions 15 GB to 25 GB in total size to be transmitted and processed by the FDA ESG. These companies had T3 network connections or better. FDA recommends that large submissions be sent overnight, starting at 4:30 PM EST, in order for the submission to be received by the target Center before the end of the next business day.

Sending large submissions may result in the FDA ESG erroneously reporting that the transmission was not successful, even though the FDA ESG has successfully received the transmission. This is a known bug and FDA has asked Cyclone Commerce to provide an update that fixes this error.

When the FDA ESG has received a complete submission, a backup copy is made before a reply from the FDA ESG is sent confirming the submission is complete. For large submissions (> 7.5 GB), this can take many minutes. Since there is no network activity for such a long time, the session timeouts and a response is not received. The FDA ESG has received the submission successfully, but an error is generated indicating that the submission needs to be resumed. Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request. Since this is a large submission, it will take several hours before the first acknowledgement is received.

If you receive this error and it has clearly occurred at the end of the transmission, do not resend the submission right away. Wait for several hours (or longer depending on the size of the submissions) and see if the MDN is sent before attempting to resend the submission.

5.8 Common AS2 Errors

Here are some of the most common causes of failed AS2 submissions:

- Your firewall rules are not set to allow connections with the FDA over port 4080. The FDA requires that all communications with the ESG occur with HTTPS over port 4080.
- You provide a private URL during registration. (A private URL is one located inside of your company's firewall.)
- The submissions's message header does not contain custom attributes.

We recommend two strategies to avoid these errors:

- Work with your IT infrastructure team throughout the registration process. Make sure they are aware of specific security settings that need to be enabled for successful AS2 registration and transmission.

- Create a local environment that simulates the FDA to test your submissions before you actually connect to the FDA. Trading partners who test locally have a much higher rate of success than those who don't.

Contact esgreg@gnsi.com if you have any problems with your registration or submissions.

6. References/Resources

The following table provides some additional references and resources related to electronic submissions and the FDA ESG.

Table 6: Additional References

Document	Web Link
CBER Annual Report	http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm122930.htm
Electronic Regulatory Submissions and Review	http://www.fda.gov/Drugs/DevelopmentApprovalProcesses/FormsSubmissionRequirements/ElectronicSubmissions/UCM085361
Electronic Submissions through the FDA ESTRIGATEWAY Frequently Asked Questions (FAQ)	http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114807.htm
FDA AERS Electronic Submissions Web Site	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm
Guidance for Industry Part 11, Electronic Records; Electronic Signatures - Scope and Application	http://www.fda.gov/cder/guidance/5667fnl.htm
Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs and ANDAs	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf
Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Postmarketing Expedited Safety Reports	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369.pdf
Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format - Investigational New Drug Applications (INDs)	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM150028.pdf
Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations	http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm124751.pdf

Guidance for Industry: Providing Regulatory Submissions to Office of Food Additive Safety in Electronic Format -- General Considerations	http://vm.cfsan.fda.gov/~dms/opaeguid.html
ICH Home Page	http://www.ich.org/
PDUFA Main Page on FDA Site	http://www.fda.gov/oc/pdufa/default.htm
PhRMA Home Page	http://www.phrma.org/

Appendix A. Troubleshooting the FDA ESG Web Interface

Problem: Started sending wrong submission

Solution: When the upload progress window appears, press **Cancel** and this will cease the uploading of that submission.

Problem: Computer froze/crashed while sending the file.

Solution: If the submission had begun transmitting (i.e., signing was already completed) to the FDA ESG when the computer froze or crashed, log back into the FDA ESG web interface. The file you were attempting to send will be on the top left hand side. Your options are to resume sending or deleting the submission. Check to make sure there is ample disk space. It is recommended that you have disc space of at least three times the size of the transmission.

Problem: Received a disk space error.

Solution: Make sure there is ample disk space to backup the submission. It is recommended that you have disk space of at least three times the size of the transmission. Note that every time a submission is sent to the FDA ESG, a back up copy of the packaged (encrypted, tarred, and gzipped) submission file is stored on the local PC. This backup file is stored under:

C:\Documents and Settings\<<your identity>\cyclone\backup.

These backup copies can be deleted by first logging in to the FDA ESG web interface. Then go to: WebTrader Recent Folder Sent.

Select the desired entries for deletion. This will remove entries from the Sent view and will also remove the backup files from the backup directory on the local PC.

Problem: Received a signing encryption error

Solution: Verify the correct public key certificate was uploaded during the registration process by contacting the FDA ESG Administrator at esgprep@fda.hhs.gov and comparing the md5 fingerprints within the certificate.

Problem: Received a private key error

Solution: This error occurs when there is a mismatch between the public and private key for a certificate. Check to ensure the correct private key for the public certificate sent to the FDA ESG is in place. Obtain the correct private key and resend the document.

Problem: A FIPS error was received while sending a submission

Solution: Make sure the correct JRE version or security policies are properly installed. Reinstall the JRE using instructions provided with that package. Reference [Appendix D., Java Runtime Edition Installation](#), for more information.

Problem: The following error was received when trying to import a digital certificate using the FDA ESG Web interface:

"Invalid certificate file

An error has occurred while importing the certificate file. Most likely you selected the wrong file type."

Solution: 1) Check the file extension. The file extension must be ".p7b" or ".cer". Files with these extensions represent the public key part of the certificate. Only the public key part of the certificate can be imported. Reference [Appendix C., Digital Certificate](#), for more information. 2) Make sure the local PC has been configured to recognize and use the digital certificate. Reference the operating system instructions on the local PC for more information.

Problem: When using the FDA ESG Web interface, an error message was received at the very end of a submission saying there was no response from the server and that the submission failed.

Solution: When the FDA ESG has received a complete submission, a backup copy is made before the Java applet receives a reply from the server confirming the submission is complete. For large submissions (> 7.5 GB), this can take many minutes. Since there is no network activity for such a long time, the session timeouts and the Java applet never receives the response. The FDA ESG has received the submission successfully, but the Java applet returns an error and indicates that the submission needs to be resumed. Receipt of the first acknowledgement (MDN) confirms that the submission was successfully received by the FDA ESG and that it is okay to cancel the resume request. Since this is a large submission, it will take several hours before the first acknowledgement is received.

FDA has asked Cyclone Commerce to provide an update to the web interface that fixes this error.

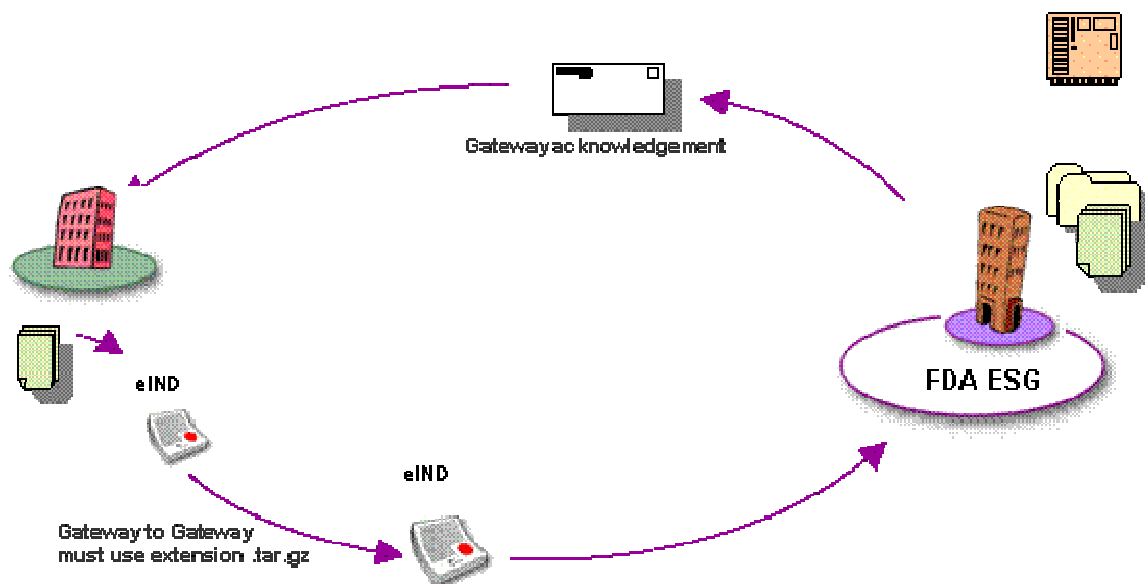
Appendix B. Creating tar Files and Compressing Files for Submission

Creating tar files for FDA ESG Web Interface Submissions

During the file upload process, the FDA ESG Web Interface utilizes the tar functionality for file system consolidation when submitting files. The process occurs during the electronic "signing" of the submission. Before the file is transmitted, it is tarred and gzipped, encrypted, signed, and mime-wrapped (or packaged) before transmitting to the FDA ESG.

.tar.gz files should not contain files or sub-directories that have a "." (dot) at the beginning of its name.

The figure below illustrates this process.



Upon receiving the file, signature is verified; file is unzipped/untarred, unwrapped/decrypted

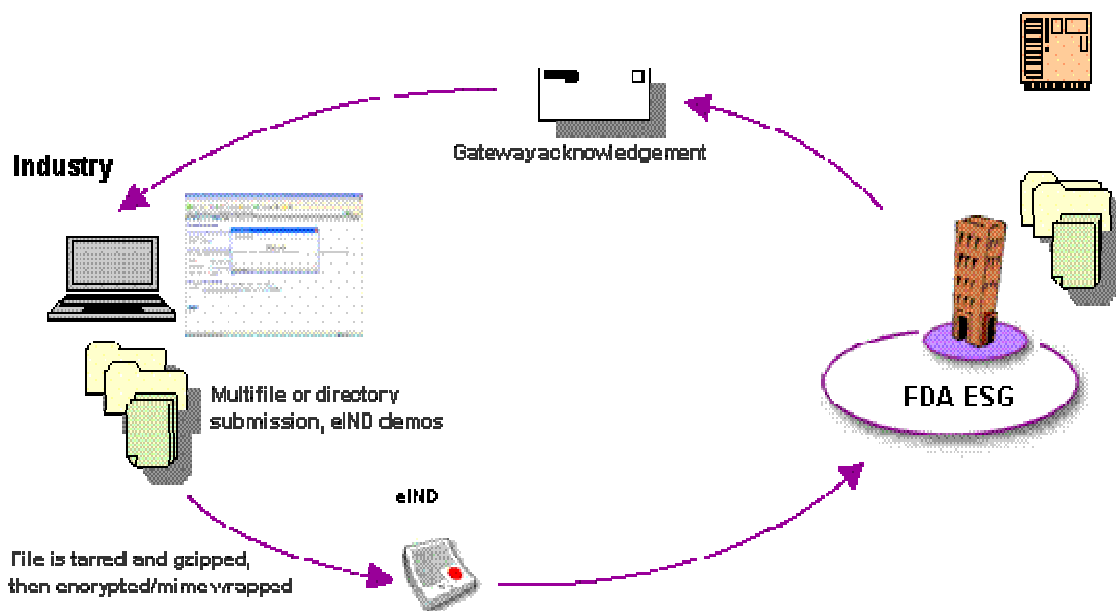
Because this process is done automatically during the signing of the file, no intervention is required from the user to ensure the file is tarred and gzipped.

Creating tar files for Gateway-to-Gateway Submissions

Partners are required to both tar and gzip (compress) multifile submissions. (gzip is the original UNIX ZIP format and is used as a compression utility to reduce the size of the archive file.)

For best optimization when processing and transmitting large submission files, first "tar" the files and then compress them using gzip. Valid files acquire a .tar.gz extension resulting from the process of tarring the directory (containing multiple files) and gzipping the created tar archive.

The figure below illustrates this process.



Upon receiving the file, signature is verified; file is unzipped/untarred, unwrapped/decrypted, delivered to Center Holding Area

To fulfill this requirement, the current AS2 solution 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. Listed below are recommended utilities that support tar and gzip manually (external from application) or automatically (to be integrated with application).

To create tar files: GNU Tar Utility at <http://www.gnu.org/software/tar/tar.html>

To gzip files: gzip Utility at <http://www.gzip.org/>

Apache Ant Java package should be integrated into the application when creating .tar.gz files automatically through the application.

Appendix C. Digital Certificates

A digital certificate is an electronic document which conforms to the International Telecommunications Union's X.509 specification. It is a document which typically contains the owner's name and public key, the expiration date of the public key, the serial number of the certificate, and the name and digital signature of the organization which issued the certificate. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

Encrypting and digitally signing documents using certificates provides the following assurances about document transmissions:

- Only the addressee (and no unauthorized users) can read the message. Encryption provides this assurance.
- The message cannot be tampered with. That is, data cannot be changed, added, or deleted without the sender's knowledge. A document's digital signature provides this assurance.
- Parties sending documents are genuinely who they claim to be. Likewise, when those parties receive documents signed by the sender, they can be confident about the source of the documents. A document's digital signature provides this assurance.
- The parties who send documents cannot readily claim they did not send them. This is referred to as non-repudiation of origin. A document's digital signature provides this assurance.
- Parties who are sent documents cannot readily claim they did not receive them. This is referred to as non-repudiation of receipt. The signed document acknowledgment provides this assurance.

Using the certification

The public key in the FDA's certificate is used to encrypt a document for transmission. The FDA ESG uses the public key to verify the digital signature of a document received from a specified source.

Before encrypted and signed documents (sent submissions) are exchanged with the FDA ESG, there must be a certificate exchange to obtain the other's certificate and public key. Each party obtains a certificate with a public-private key pair, either by generating a self-signed certificate

or by obtaining a certificate from a Certificate Authority. The private half of the key pair always remains on the party's computer. The public half is provided to the FDA ESG during the registration process and includes the certificate and public key, or the certificate alone.

Certificates not accepted by the registration module

There are situations when a valid certificate is not accepted by the registration module and is identified as invalid. If this occurs, zip the certificate file and email it to the FDA ESG administrator at esgprep@fda.hhs.gov. Once received, FDA will assess the certificate and send a response.

Certificates not accepted by the FDA ESG

The FDA ESG cannot accept certificates with blank data elements in the Issuer or Subject fields. These certificates will cause the FDA ESG to fail due to a defect in the Gateway software. The certificates provided should be valid for at least one year and no more than three years. Note, this requirement applies to both Pre-production (Test) and Production ESG systems.

NOTE: DO NOT SUBMIT CERTIFICATES WITH BLANK DATA FIELDS IN THE ISSUER AND SUBJECT FIELDS

Where to obtain a certificate

The FDA ESG supports Public Key Infrastructure (PKI) to securely trade submissions over the Internet. PKI is a system of components that use digital certificates and public key cryptography to secure transactions and communications.

PKI uses certificates issued by certificate authorities (CAs) to provide authentication, confidentiality, integrity and non-repudiation of data.

Options

There are two PKI options supported – in-house and outsourced. The option chosen can depend on a number of factors, such as cost, human and system resources, and the degree or sophistication of security desired. PKI establishes digital identities that can be trusted. The CA is the party in a PKI that is responsible for certifying identities. In addition to generating a certificate, this entails verifying the identity of a subscriber according to established policies and procedures. This is the case for in-house and outsourced PKIs.

In an organization that generates and uses its own self-signed certificates, the trading parties must verify the certificates and establish a direct trust. Once established that an identity or issuer of an identity can be trusted, the trust anchor's certificate is stored in a local trust list. The FDA ESG has a local trust list for storing and managing established trust relationships. The application maintains a list of common public CA certificates similar to those kept in web browsers. Although convenient, this predetermination of trust might not complement every

organization's security policy. The decision of who to trust rests with the individual organization.

In-House

An in-house PKI makes it possible to achieve complete control of security policies and procedures. It also carries the burden of management and cost to set up and maintain the system.

FDA recommends using certificates with 3 years validity.

Outsourced

Third-party certificate authorities can be leveraged to purchase X.509 certificates for general use. The CA manages the security policies and details such as certificate revocation. The level of outsourcing can range from purchasing a public key certificate that is valid for 1 year to 3 years from a commercial CA, to outsourcing all of the PKI services that an organization requires.

If you plan to use an outsourced certificate, the following are just a few of the many companies that sell the X.509 certificates (Displayed in alphabetical order). FDA recommends using certificates with three years validity. Please note that some vendors do not offer a three year certificate on their website, but you may call them directly to purchase a three year certificate. Telephone contact information is available on each vendor's website.

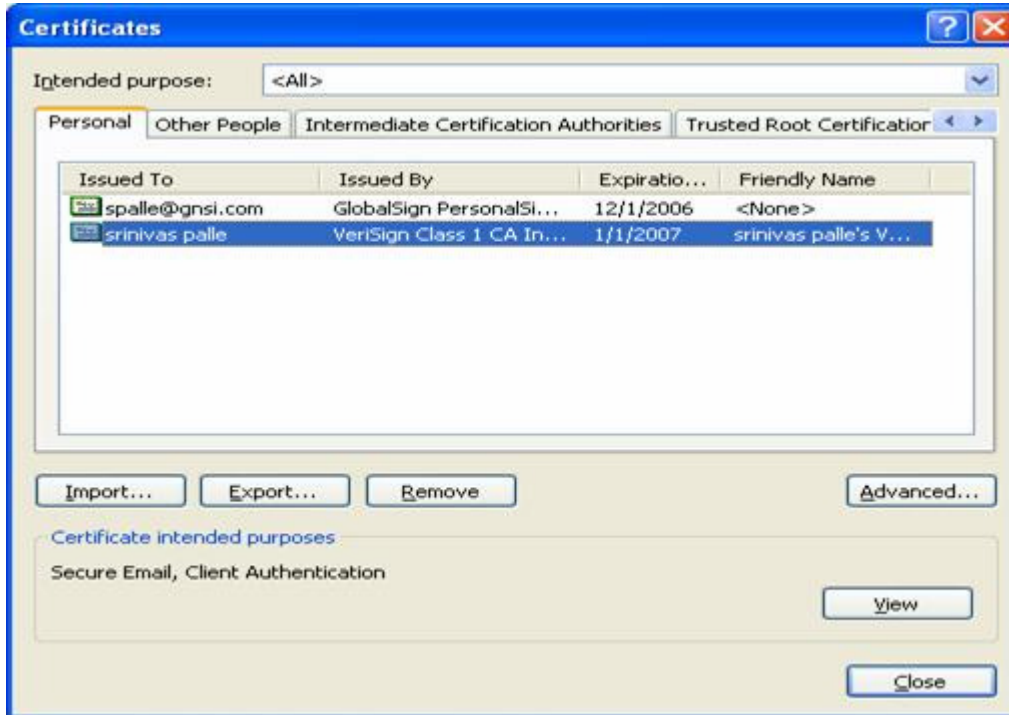
FDA recommends using certificates with 3 years validity.

- Comodo: <https://secure.instantssl.com/products/frontpage?area=SecureEmailCertificate>
- GeoTrust: <http://www.geotrust.com/signing-products/secure-email/index.html>
- GlobalSign: http://www.globalsign.com/digital_certificate/personalsign/index.htm#2
- TrustCenter: http://www.trustcenter.de/en/products/tc_personal_id.htm
- Verisign: <http://www.verisign.com/authentication/individual-authentication/digital-id/index.html>

Note: References to commercial products are for illustrative purposes only and does not constitute an official FDA endorsement.

CA will send you an email with PIN number and a link to a website where you can import/install the certificate. Accept all defaults and say "yes" to all pop-ups, your certificate will be installed in your browser. Note, if you are using WebTrader, you do not have to install the certificate on the same machine that you will be using. Once the certificate is installed in the browser you can export the public and private keys out and use them where ever you want. AS2 users will need to install the certificates in their system. Configuring the certificates may defer from sponsor to sponsor depending on what gateway software being used.

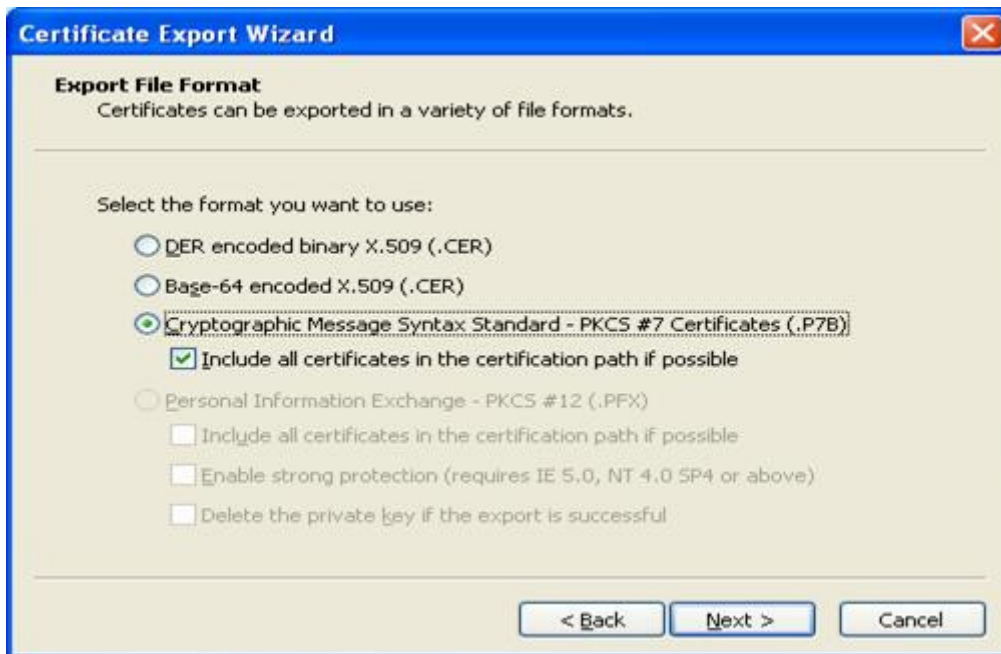
1. From Internet Explorer go to Tools Internet Options Content tab Certificates
2. Select your certificate in the **Personal** tab.
3. Click on the **Export** button to create public and private keys, which can be used for the Gateway.



4. To export public key (.cer or .p7b) select **Next** on the next screen
5. Select **No, do not export the private key** option and click on the **Next** button.



6. Select the options as shown on the screen below. Click on the **Next** button. Or if you want to export the certificate with .P7B extension/format or to export .CER extension/format follow the next step.



7. Select **Cryptographic Message syntax Standard – PKCS #7 Certificates (.P7B)**, check **Include all certificate in the certification path if possible**.



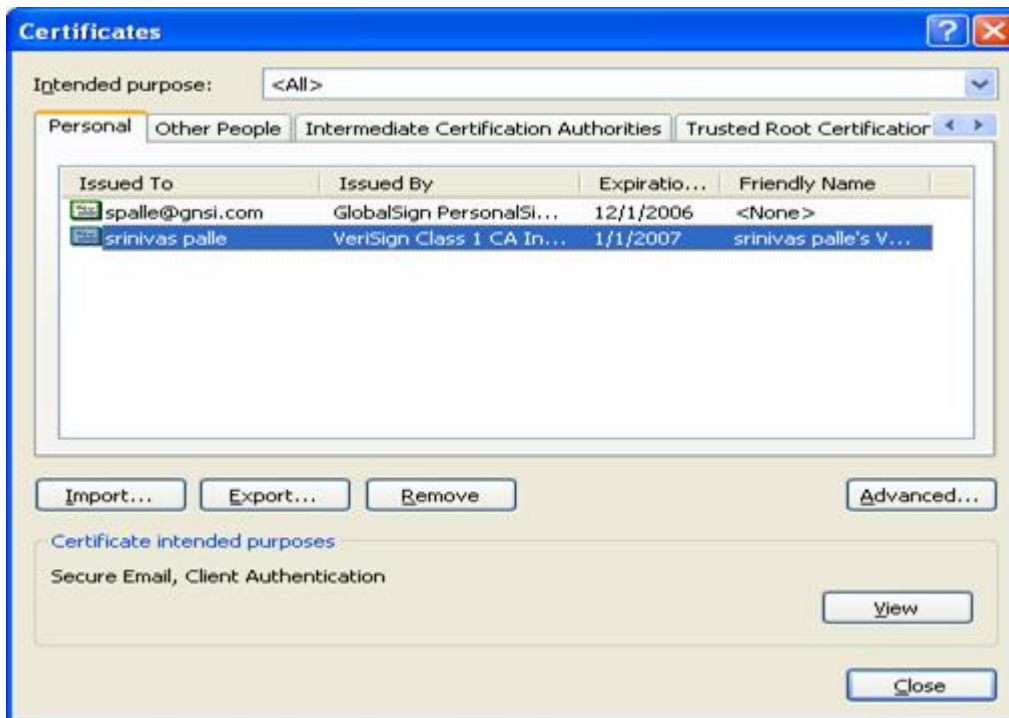
8. Select **DER encoded binary X.509 (.CER)** and click on the **Next** button.

9. Give a file name and select the location where you want to save the file. Click on the **Next** button. Then click on **Finish**.

Your public key is ready. This is the key that you should use when registering.

To export private key (.PFX or .P12)

1. Select the certificate and click on **Export**, Click on **next** on the next screen



2. Select **Yes, export the private key** and click on the **Next** button.



3. Select the options as shown below and click on the **Next** button.



4. Create a password for your private key. Confirm the password and click on the **Next** button. If you forget the password you can export the private key again and create a password.



The image shows a Windows-style dialog box titled "Certificate Export Wizard". The window has a blue title bar with a close button (red X) in the top right corner. The main content area is light beige and contains the following text and controls:

- Password**
- To maintain security, you must protect the private key by using a password.
-
- Type and confirm a password.
- P**assword: [password field containing seven asterisks]
- C**onfirm password: [password field containing seven asterisks]
-
- At the bottom right, there are three buttons: "< Back", "Next >", and "Cancel".

5. Create a file name and select the location where you want to save the file and click on the **Next** button. On the next screen, click on **Finish** and then click on **OK**.



Appendix D. Java Runtime Edition Installation

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 1.5.0_18 plug-in files for the browser. JRE security policy files must also be updated.

These two components can be retrieved from the following Java Sun site:

Install Client-side JRE 1.5.0_18

Click the following link to access the SUN JRE download page.

NOTE: If your security settings prohibit PDF files from opening hyperlinks or you do not see the download page, copy and paste the entire address into your browser bar.

https://cds.sun.com/is-bin/INTERSHOP.enfinity/WFS/CDS-CDS_Developer-Site/en_US/-/USD/ViewProductDetail-Start?ProductRef=jre-1.5.0_18-oth-JPR@CDS-CDS_Developer



Java SE Runtime Environment 5.0 Update 15 First Customer Ship



Provide Information, then Continue to Download

Select Platform and Language for your download:

Platform:

Language:

I agree to the Java Runtime Environment 5.0 Update 15 License Agreement

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6. Select "Windows" from the platform menu. Check the **I agree to the Java Runtime Environment 5.0 Update 15 License agreement** check box. Click continue.

7. Click the link under Windows Offline Installation. Save the file to your disk.

Download Information and Files

Get the latest Java Runtime Environment to use Sun Download Manager

Internet Explorer Users: Check the top of this page for a "Java(TM) Web Start ActiveX Control" message in the information bar. If it appears, click it to finish detecting your Java version.

We were unable to detect a recent version of Java Runtime Environment (JRE) on your system. With the latest JRE, you can automatically download, install, and run Sun Download Manager (SDM) directly from this page. We highly recommend SDM to easily manage your downloads (pause, resume, restart, verify, and more). Visit java.com for the latest JRE.

Required Files

File Description and Name	Size
Windows Offline Installation 📄 jre-1_5_0_15-windows-i586-p.exe	16.11 MB

Optional Files

File Description and Name	Size
Windows Online Installation (typical download size is ~7.1MB) 📄 jre-1_5_0_15-windows-i586-p-iftw.exe	0.24 MB

Notes:

- For download problems or questions, please see the [Download Center FAQ](#).
- If you logged in first, you can complete this download any time in the next 30 days. Just visit your [Download History](#).
- For Customer Service, contact [Download Center Customer Service](#).

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Related Resources


- [Java.sun.com](#)
- [Solaris Developer Center](#)
- [JavaFX](#)
- [Web Developer Resource Center](#)
- [Developer Services](#)
- [JavaOne Online](#)
- [Sun Student Developer Program](#)
- [SunSolve](#)
- [Sun Microsystems Press](#)
- [Sun Partner Advantage Program for ISVs](#)

8. Run the installer that you just downloaded. Accept all the defaults in the install wizard.
9. When the installation is complete, reboot your computer, if requested. Proceed to the next step.

Install the Unlimited Strength Java Cryptography Extension (JCE) files

1. Go to the JCE download page:

https://cds.sun.com/is-bin/INTERSHOP.enfinity/WFS/CDS-CDS_Developer-Site/en_US/-/USD/ViewProductDetail-Start?ProductRef=jce_policy-1.5.0-oth-JPR@CDS-CDS_Developer




Downloads

SDN Home > Download Center >

Java(TM) Cryptography Extension (JCE) Unlimited Strength Jurisdiction Policy Files 5.0

Provide Information, then Continue to Download

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- Click on the link under Required Files to download the ZIP file containing local_policy.jar and US_export_policy.jar. These files will replace the existing files located in C:\Program Files\Java\jre1.5.0_18\lib\security.



Downloads

SDN Home > Download Center >

Download Java SE Runtime Environment 5.0 Update 15 First Customer Ship for Windows, Multi-language

Download Information and Files

Get the latest Java Runtime Environment to use Sun Download Manager

Internet Explorer Users: Check the top of this page for a "Java(TM) Web Start ActiveX Control" message in the information bar. If it appears, click it to finish detecting your Java version.

We were unable to detect a recent version of Java Runtime Environment (JRE) on your system. With the latest JRE, you can automatically download, install, and run Sun Download Manager (SDM) directly from this page. We highly recommend SDM to easily manage your downloads (pause, resume, restart, verify, and more). Visit java.com for the latest JRE.

Required Files

File Description and Name	Size
Windows Offline Installation  jre-1_5_0_15-windows-i586-p.exe	16.11 MB

Optional Files

File Description and Name	Size
Windows Online Installation (typical download size is ~7.1MB)  jre-1_5_0_15-windows-i586-p-iftw.exe	0.24 MB

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Getting Started?

- » New to Java Center
- » New to Solaris Center
- » Sun Studio

Download Resources

- » FAQs
- » Download History
- » Sun Download Manager
- » Download Center Customer Service

Related Resources

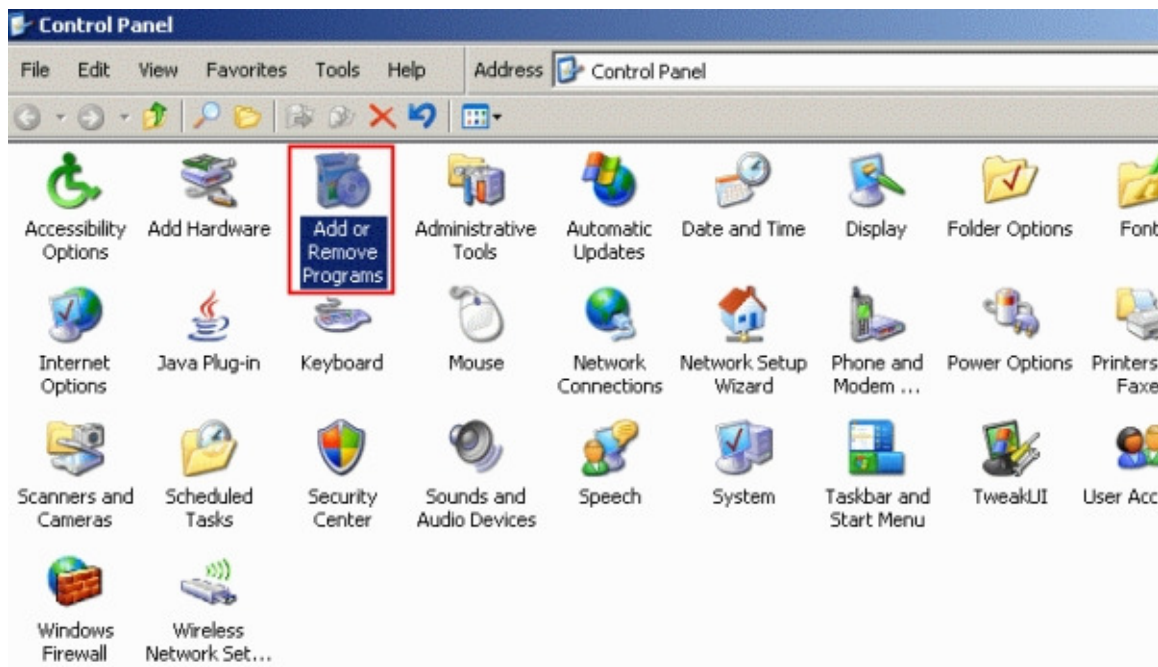
- » [Java.sun.com](http://java.sun.com)
- » Solaris Developer Center
- » JavaFX
- » Web Developer Resource Center
- » Developer Services
- » JavaOne Online

3. Backup your old local_policy.jar and US_export_policy.jar files before replacing them. You can either rename them (for example, local_policy_old.jar) or put them in a different directory (for example, C:\Program Files\Java\jre1.5.0_18\lib\security\archive).
4. Once you have backed up your old files, open the ZIP file that you downloaded. Extract the new files into C:\Program Files\Java\jre1.5.0_18\lib\security. **Make sure that you extract the new files directly into C:\Program Files\Java\jre1.5.0_18\lib\security and not into a subdirectory.**

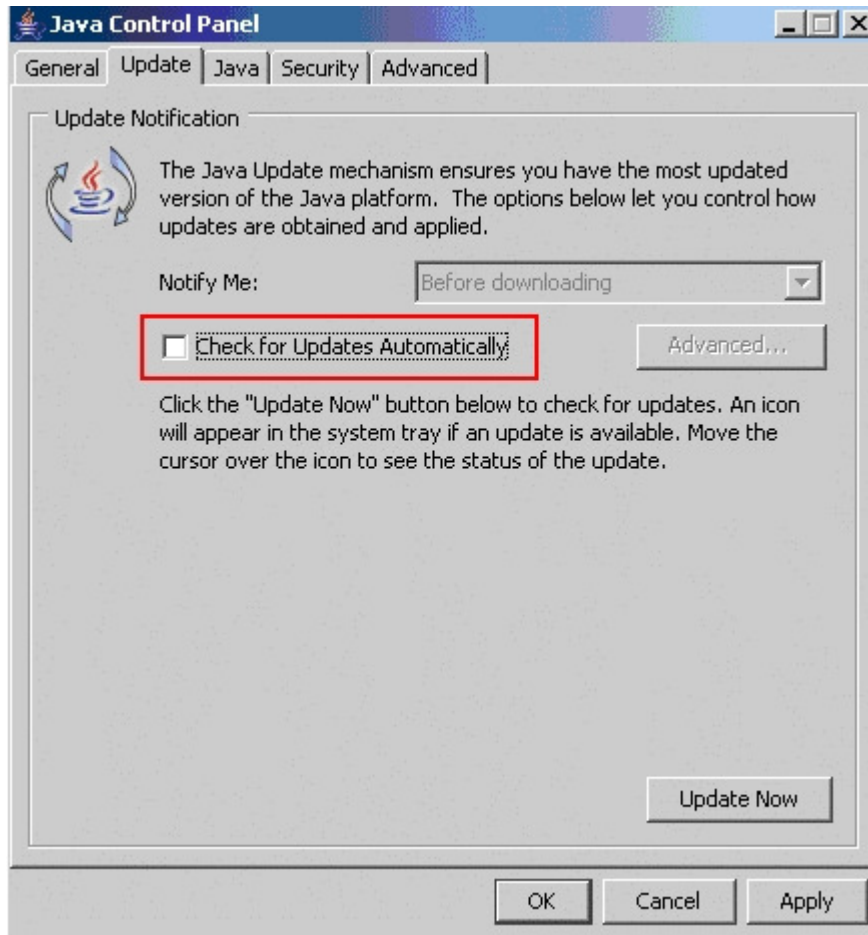
Turning Off Automatic Updates for Java

The installed JRE will periodically prompt users to download the latest updates. Versions of JRE other than 1.5.0_18 will not work with WebTrader. 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. Automatic checking for updates can be disabled on the Windows operating system as follows:

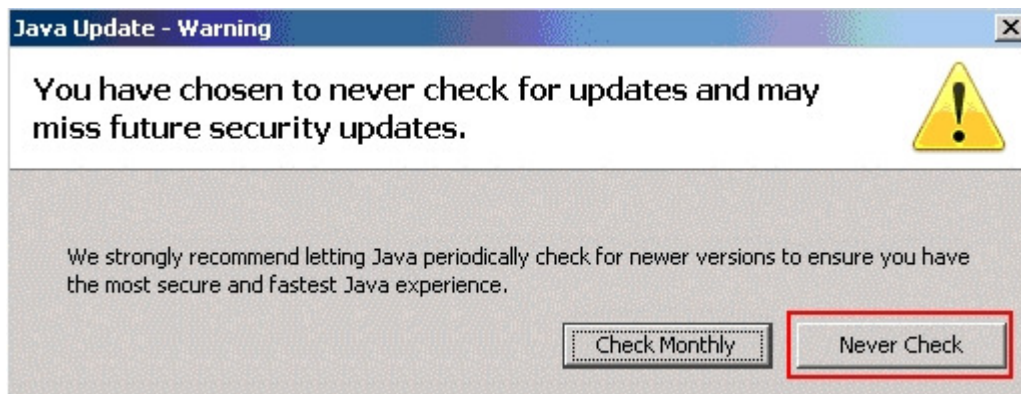
1. Select "Control Panel" from the "Start" menu.
2. Double-click on the "Java" icon in the "Control Panel" window to launch the JRE control panel.



3. Click on the "Update" tab. There will be a checkbox labeled "Check for Updates Automatically". Make sure the checkbox is not checked and then "Apply" the change.



4. With the box unchecked, a warning box will popup: Click the Never Check button to make sure that the Java Runtime Environment will not automatically be updated. If the JRE is automatically updated, WebTrader will stop working.

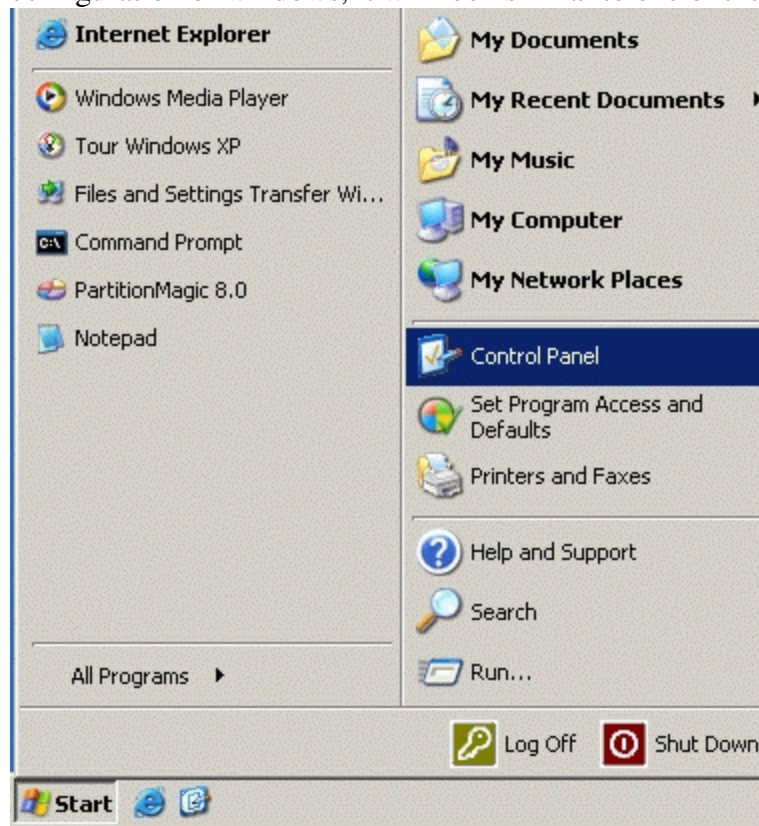




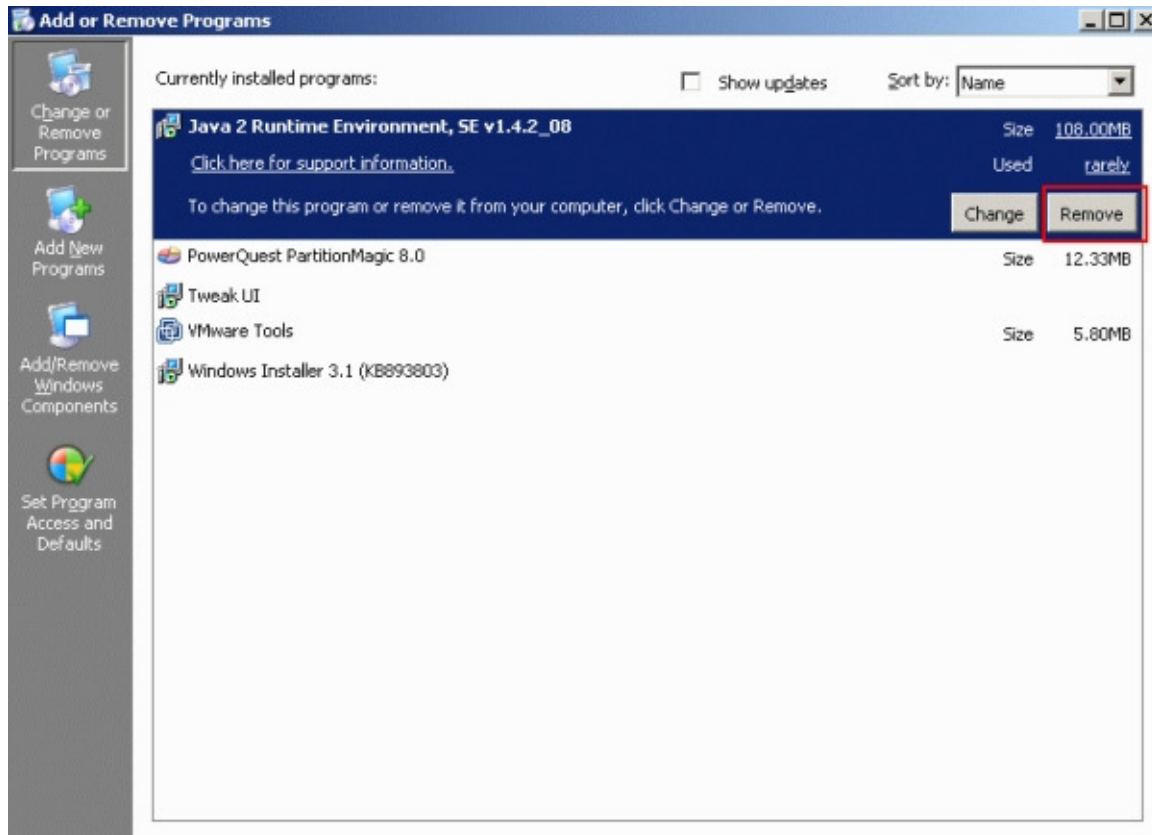
Updating to JRE 1.5.0_18

WebTraders who are currently running JRE 1.4.2_07 or 1.4.2_08 must update the JRE to 1.5.0_18. To update to JRE 1.5.0_18 we recommend uninstalling the older/current version of JRE and a clean install of JRE 1.5.0_18. Follow the below steps to uninstall the current JRE version. Once the current JRE version is uninstalled follow the 3 above steps Install Client-side JRE 1.5.0_18, Install the Unlimited Strength Java Cryptography Extension (JCE) files and Turning Off Automatic Updates for JAVA in that order.

1. Use Add or Remove Programs to uninstall the currently installed JRE version.
 - a. Select Add or Remove Programs from control panel. Depending on the configuration of windows, it will look similar to one of the following screenshots.

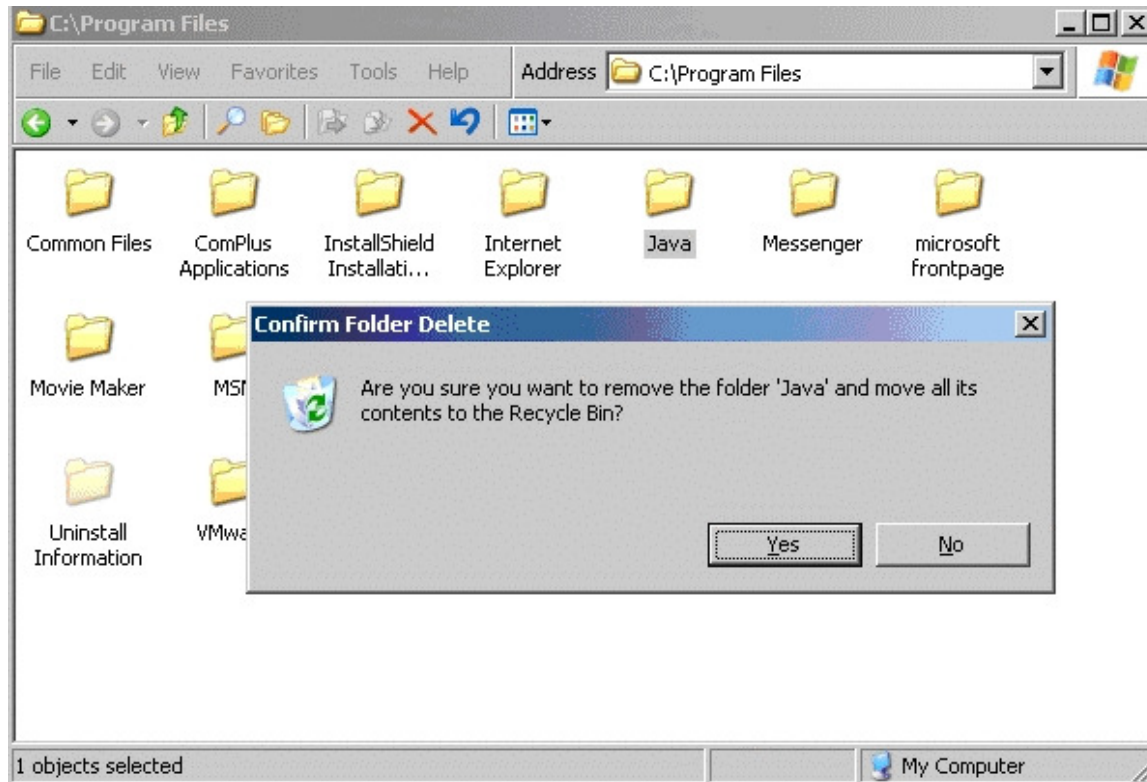


- b. From the Add or Remove Programs dialog box, click on the **Remove** button beside the Java 2 Runtime Environment entry. There might be more than one. Make sure **every** version is removed. If asked to reboot after one or more of the removal programs finishes, do so, then continue using the Add or Remove Programs box to remove **every** version of the Java 2 Runtime Environment:

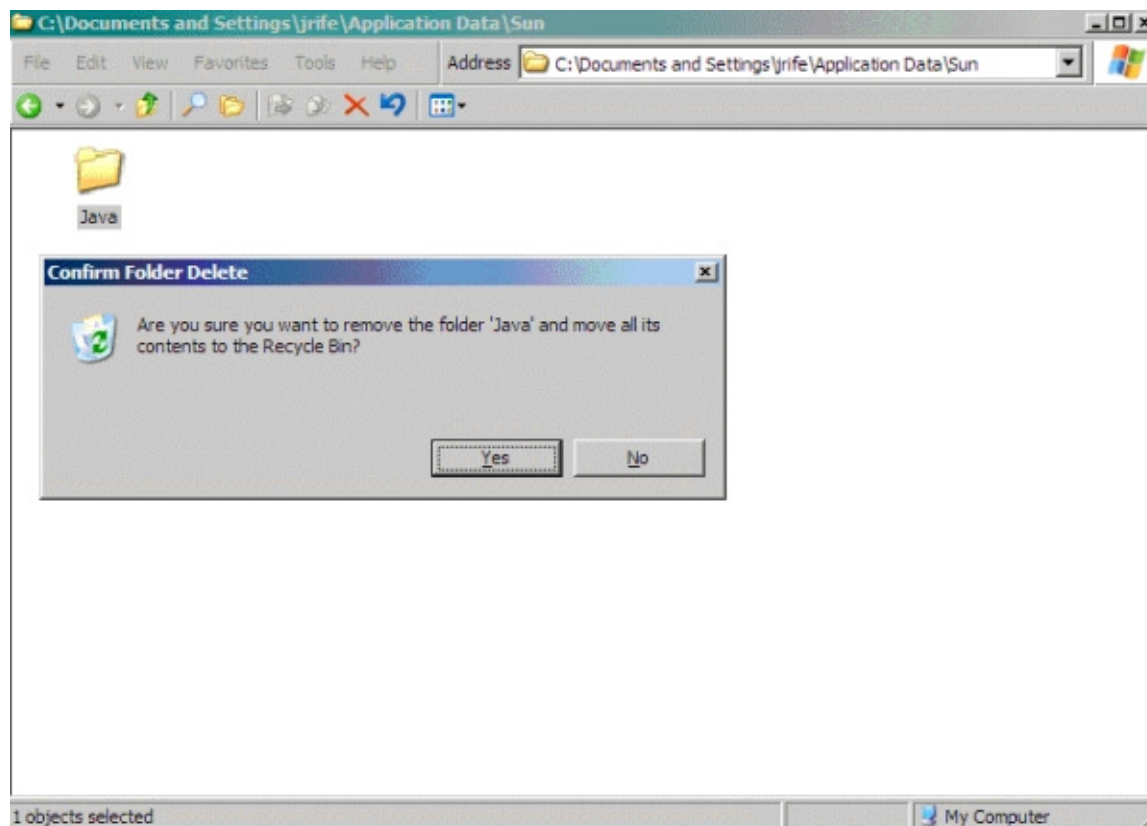


2. Manually delete files

- a. The JRE uninstall program does not delete all files that are part of the Java Runtime Environment because some were created automatically when Java runs programs. These are safe to delete, and will also help ensure compatibility with the FDA ESG WebTrader software.
- b. To delete all the previous version files, using Explorer, in the C:\Program Files\ directory highlight the Java folder and press the delete key. Click on the **Yes** button to confirm deletion.



- c. Again, using Explorer, delete the Java folder in C:\Documents and Settings\[your username]\Application Data\Sun\ directory. Highlight the Java folder and press the delete key. Click on the **Yes** button to confirm deletion.



Appendix E. Glossary of Terms

Table E-1: Glossary of Terms

Term	Definition
AS2	Applicability Statement 2. An electronic submission protocol that uses HTTP/HTTPS for communications.
Certificate Authentication	Verification of the identity of a person or process. Authentication confirms that a message truly came from the source that sent it.
Certificate Authority (CA)	An organization that issues digital certificates containing the applicant's public key and other identification information.
Certificate Confidentiality	Assurance that a message has been disclosed only to the parties authorized to share the information.
Certificate Integrity	Assurance that the information has not been altered in any way and is precisely true to the source.
Community	An entity that contains all the necessary components for submission: a component that receives and routes submissions (the FDA ESG), and its external (e.g., a member of the regulated industry) and internal

	(e.g., FDA Center) Transaction Partners.
Digital Certificate	An attachment to an electronic message that allows the recipient to authenticate the identity of the sender via third party verification from an independent certificate authority. Digital certificates are used to identify encryption and decryption codes between message senders and recipients.
Non-repudiation	<p>A means to provide proof of the integrity and origin of data, both in a non-forgeable relationship that can be verified by any third party at any time, or, an authentication that, with high assurance can be asserted to be genuine.</p> <p>The sender of data is provided with proof of delivery and the recipient is assured of the sender's identity, so that neither can later deny having processed the data.</p>
Private Key	<p>In secure communication, an algorithmic pattern used to encrypt messages that only the corresponding public key can decrypt. The private key is also used to decrypt messages that were encrypted by the corresponding public key. The private key is kept on the user's system and is protected by a password.</p> <p>The private key is normally known only to the key owner. Messages are encrypted using the public key (see below) and decrypted using the private key. For digital signatures, however, a document is signed with a private key and authenticated with the corresponding public key.</p>
Public Key	<p>The public key of a public-private key encryption. This key is used to confirm electronic signatures on incoming messages or to encrypt a message so that only the holder of the private key can decrypt the file or message.</p> <p>A public key is held in a digital certificate. Public keys are usually published in a directory. Any public key can encrypt information; however, data encrypted with a specific public key can only be decrypted by the corresponding private key, which the key owner keeps secret.</p>
Transaction Partner	The entity sending submissions/communicating with the receiving and routing component (the FDA ESG) of the community.

Appendix F. Acronyms

A list of acronyms relevant to the FDA ESG is provided below:

Acronym	Phrase
AERS	Adverse Event Reporting System
AS2	Applicability Statement 2
CA	Certificate Authority
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
DUNS	Data Universal Numbering System
eANDA	Electronic Abbreviated New Drug Application
eBLA	Electronic Biological License Applications
eCTD	Electronic Common Technical Document
eDMF	Electronic Drug Master File
eIDE	Electronic Investigational Device Exemption
eIND	Electronic Investigational New Drug Application
eNDA	Electronic New Drug Application
EDR	Electronic Document Room
FDA	Food and Drug Administration
FDA ESG	FDA Electronic Submissions Gateway
HTTP	Hyper Text Transfer Protocol
HTTPS	Hyper Text Transfer Protocol Secure
IND	Investigational New Drug
JCE	Java Cryptography Extension
JRE	Java Runtime Edition
MDN	Message Delivery Notification
OCIO	Office of Chief Information
PDUFA	Prescription Drug User Fee Act
PKI	Public Key Infrastructure

RAM	Random Access Memory
SSL	Secure Socket Layer

Appendix G. AS2 Header Attributes

In addition to tarring/gzipping the actual documents, AS2 submissions must include the following attributes in their AS2 headers. The additional information is comprised of:

- FDA submissions Type
- FdaSubmissionType: Abbreviated New Drug (add submission type information)
- Center Name-
- FdaCenter: CDER (add Center information)

The Mime Headers are to be located in the outermost MIME wrapper and will appear as follows:

X-Cyclone-Metadata-FdaSubmissionType: Abbreviated New Drug
X-Cyclone-Metadata-FdaCenter: CDER

The following example represents how the standard AS2 mime header should appear after appending the Center and SubmissionType attributes and upon and presented at the FDA ESG.

Message-ID: 1115406057162.328983@WIN2K3-ESX6
Date: Fri, 06 May 2005 19:00:57 GMT
From: esx6
Mime-Version: 1.0
Content-Type: application/pkcs7-mime; smime-type=enveloped-data;
name=smime.p7m
Content-Transfer-Encoding: binary
Content-Disposition: attachment; filename=smime.p7m
Disposition-Notification-To: esx6
Disposition-Notification-Options: signed-receipt-protocol=optional,
pkcs7-signature; signed-receipt-micalg=optional, sha1
AS2-Version: 1.1
AS2-To: db-as2
AS2-From: esx6-as2
X-Cyclone-Metadata-FdaSubmissionType: EANDA
X-Cyclone-Metadata-FdaCenter: CDER
Content-Length: 3607

This information must be included in the outermost portion of the outermost MIME wrapper.

The table below indicates the allowable attribute values for each FDA Center destination:

Table G-1: Allowable Center Attribute Values

Center Destination	Allowed Attribute Values
CBER	<p>AERS</p> <p>AERS_Attachments</p> <p>EBLA</p> <p>ECTD</p> <p>EIDE</p> <p>EIND</p> <p>eDMF</p> <p>H1N1_Lot_Release</p> <p>Promotional_Material</p> <p>Lot_Distribution_Data</p> <p>510K</p> <p>SDTM</p>
CDER	<p>AERS</p> <p>AERS_Attachments</p> <p>EANDA</p> <p>EBLA</p> <p>ECTD</p> <p>ENDA</p> <p>EIND</p>
CDRH	<p>Adverse_Events</p> <p>Electronic_Submissions</p>
CFSAN	<p>BNFs</p>

	Color_Master_File Food_Contact_Notification Food_Master_File GRAS Notice New_Protein_Consultation Petitions PNC Threshold_of_Regulation
CVM	Adverse_Events_Reports Electronic_Submissions
OOPD	Orphan-drug_Designation_Requests HUD_Designation_Requests
GWTEST	ConnectTest SizeTest
OC	SPL
CTP	Electronic Submission

Appendix H. Sample Letters of Non-Repudiation Agreement

A letter of Non-Repudiation Agreement for digital signatures must be submitted to the FDA prior to registering as a transaction partner for the FDA ESG. The letter must be submitted in paper form (preferably on company letterhead) and signed with a traditional handwritten signature. The letter must be sent to:

Office of Regional Operations (HFC-100)
5600 Fishers Lane
Rockville, MD 20857.

A copy must be sent to:

Michael Fauntleroy
Office of the Director (HFM-26)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Room 4119
Rockville, MD 20852.

The following two letters are provided as samples for a Letter of Non-Repudiation Agreement. The information in square brackets [] will be provided by the submitter.

SAMPLE LETTER #1

[Company Letterhead]

[Today's Date]

Office of Regional Operations (HFC-100)
5600 Fishers Lane
Rockville, MD 20857

Re: Electronic Signatures

Dear Sir or Madam:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that [Company Name], [Company Address], intends that electronic signatures executed by our employees, [List of employee names] are the legally binding equivalent of traditional hand-written signatures.

Sincerely yours,

[Hand-written signature]

[Name of Company Representative]

[Company Representative Title]

[Employee Name #1]: _____ [Hand-written signature of employee #1]

[Employee Name #2]: _____ [Hand-written signature of employee #2]

[Employee Name #3]: _____ [Hand-written signature of employee #3]

[etc]

SAMPLE LETTER #2

[Company Letterhead]

[Today's Date]

Office of Regional Operations (HFC-100)
5600 Fishers Lane
Rockville, MD 20857

Re: Electronic Signature Certificate Statement

To Whom It May Concern:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, this is to certify that [Company Name], intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional hand-written signatures.

Sincerely yours,

[Hand-written signature]

[Name of Company Representative]

[Company Representative Title]

Appendix I. EDIFACT Message Structure

Required message structure (EDIFACT)

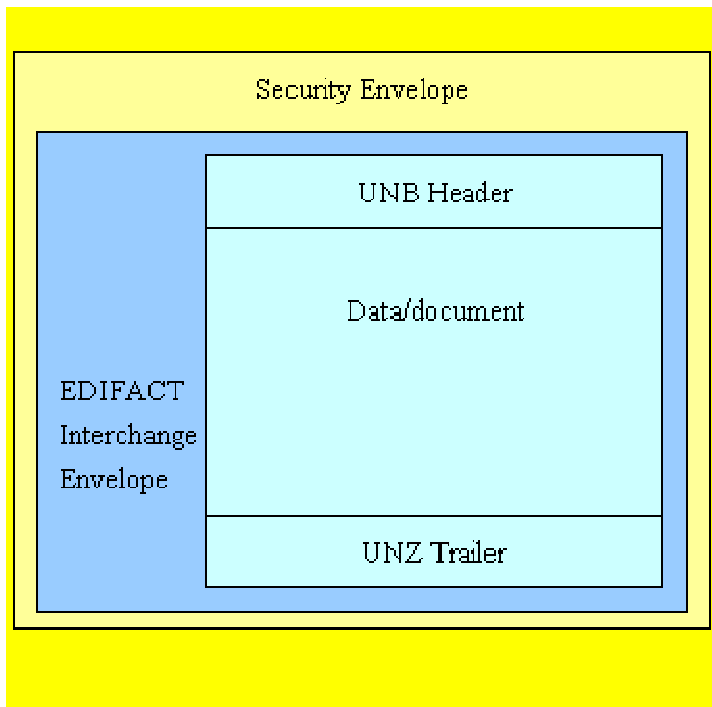
S/MIME SMTP E-mail Header

Example:

UNB+UNOB:1+016968919:01+FDA:
ZZ+060310:0127+37' → **Header**

SGML document → **SGML
Document**

'UNZ+1+37' → **Trailer**



EDIFACT UNB Header Information		
Description	Code	Comments
Identification of the start of the UNB header	UNB	The code for the start of the UNB header should be UNB in upper case letters
Version of the standard of the UNB header	UNOB:1	The current version code should be UNOB in upper case letters
Interchange sender identification code and sender code qualifier	xxxxxxx:01 (for AS2 submissions this should match the routing ID)	xxxxxxx should be the number assigned to your company by Dun and Bradstreet Information Services. (For industry sending to the FDA, the sender code qualifier is 01.)
Interchange recipient	FDA:zz	xxxx should be the code for the receiving center (CDER, CBER, CDRH, CVM, CFSAN)
Date and time of preparation	yymmdd:hhmm	For now, a two-digit designation should be used for the year

Interchange control reference	Up to 14 alphanumeric characters	You should assign a unique reference number for each interchange. Otherwise the system will not recognize the transmission as new
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UNZ Trailer Information		
Description	Code	Comments
Identification of the start of the trailer	UNZ	The code for the start of the trailer is UNZ in upper case letters
Interchange control count	Up to 6 numerical characters	Counts either the number of messages or the number of functional groups within the interchange. Usually, this is 1
Interchange control reference	Up to 14 alphanumeric characters	This should be the same as the interchange control reference in the UNB header

EDI headers and trailers are made up of a series of data elements separated by plus (+) signs. A colon should separate segments of the individual data elements. An apostrophe should be used to terminate the header, body of the message, and the trailer.

Appendix J. Digital Signatures

FDA does not require submission of a paper copy for electronic submissions submitted using the FDA ESG.

FDA forms (e.g., 1571, 356h) and documents require a signature. Accepted signature methods by FDA are:

- Scanned signatures
- Digital signatures
- Flattened digital signatures. A flattened digital signature must include:
 - the printed name of the signer
 - the date and time when the signature was executed
 - the reason for signature

Please use the Adobe Acrobat Self-Sign plug-in to insert your signature on fillable FDA forms.

The FDA cannot hold digital signatures to a higher standard than paper signatures. The FDA will not check the signature on an electronic or paper-based submission unless there is a directed

inspection involving that submission. Please maintain the security certificates associated with your digital signatures in case of a directed inspection.

The FDAAs General Counsel (GC) has said that the FDA must be able to determine the origin of a submission in order to implement fully electronic submissions. The PKI (x.509 version 3 class I) certificate employed by the ESG allows the FDA to determine the origin of the submission through the use of a public/private key exchange.

Please use the 1571

(<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf>) and 356h (<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf>) fillable PDF forms with your electronic submissions to CDER and CBER via the ESG.

- If you do not include these forms with your electronic submissions, CBER and CDER will not be able to leverage their automated loading processes, reducing the process to a manual one. This results in a large increase in the time required by the Centers to make submissions available to our review community.
- **356h and 1571 Form Field Sizes**
 - For documents sent through the ESG for regulatory review, the most important form fields from the FDAAs perspective are the application number and the submission type.
 - The current form fields have the maximum number of characters allowed. If a form field is not large enough, please abbreviate the text in the field. Increasing the size of a form field or otherwise altering a form would require OMB approval.
 - FDA contractors or administrative reviewers read a submissionns cover letter and selected text to determine the nature and content of the submission. FDA-generated data and information is utilized in FDA submission tracking databases.

Consult with an FDA Center representative to determine which signature method is required for each type of submission.

Example of a flattened digital signature:

10. SIGNATURE OF INVESTIGATOR Geroge.S.Rathbun For Demonstration Purposes Only <small>Facsimile of Original Digital Signature</small>	<small>Geroge.S.Rathbun Cn=Geroge.S.Rathbun,CU=Test Use Only,DC=SafeSign,DC=org Date: Date: 2008-04-20 15:46:08 -0400 Reason: I attest to the accuracy and integrity of this document.</small>	11. DATE
(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)		
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:		
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."
Please DO NOT RETURN this application to this address.		

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Frequently Asked Questions about Digital Signatures

1. **Q.** A question mark (?) appears if I don't use PDF Self-Sign to create a signature. Will the FDA accept such a submission?

A. Yes. The FDA will not validate a signature during the submission process unless there is a directed inspection of the submission.

2. **Q.** What if I can't fit my full text into a form field?

A. The most important form fields are the application number field and the submission type field.

3. **Q.** Because I used a non-public key digital signature, I received an error message during the eCTD validation steps regarding a "secured" PDF file being present within the eCTD. Will my submission still be accepted?

A. The FDA understands that this can occur and will not reject submissions based on this.

Appendix K. AS2 Routing IDs

NOTE: The Pre-production System (v5.5.2) now supports the use of AS2 Routing IDs for all gateway systems.

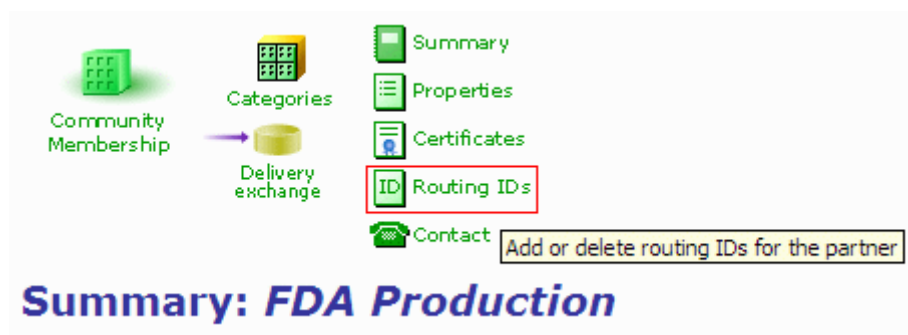
As an alternative to using the [AS2 Header Attributes \(Appendix G\)](#) process for sending submissions to the FDA ESG, you can use unique routing IDs for your submissions to indicate the type of submission and the intended Center. This Appendix describes how to automate the selection of the routing ID in **Cyclone/Axway products** through the **incoming** back-end integration pickup. **If you are not using a Cyclone/Axway product, refer to your gateway software's documentation for help configuring routing IDs.**

The routing IDs for each submission type are listed at the end of the appendix.

Before routing IDs can be selected, they must be added to your partner profile.

1. In your FDA partner profile, click on the "Routing IDs" link.

Figure 1: Partner Profile



2. Use the "Add" button at the bottom of the page to add extra routing IDs to the FDA partner.

Note: "ZZFDA" (production) or "ZZFDATST" (test) *must* be the first routing ID listed. Otherwise, the submission will not be processed correctly by the FDA.

Figure 2: Change Routing IDs Pages

Only file system integration pickups have the ability to automatically select a routing ID. If you are not currently using file system integration pickups to interface with the back-end server, you must create a file system integration pickup must be created. Refer to your gateway software's documentation for more information on this procedure.

3. After you create a file system integration pickup, create a directory structure on the disk that matches the routing ID's path and configure the integration pickup to automatically select a routing ID based on directory names.
4. In this example, the path to the integration pickup is **C:\bin\cyclone\common\data\out**, as shown in [Figure 3: File System Settings, Directory Name](#). This path should match the directory structure you created in step 3.

Figure 3: File System Settings, Directory Name

Change this integration pickup exchange

Transport: *File system*

Test results: Success

Enable this integration pickup

File system settings | From address | To address | **Message attributes** | EDI Splitter | Inline processing | Advanced

Enter the directory path. This must be a directory on the trading engine server's file system. If the directory does not exist the trading engine in a multiple computer cluster, make sure the directory is shared.

Directory name:

(Example: C:\temp or /usr/temp)

Click on the **Message attributes** tab. This will access the following screen:

Figure 4: Message Attributes, Adding

Message attribute directory mapping

Select message attributes that correspond to the names of subdirectories. Each item in the selected attributes list represents another subdirectory level. For example, add "From routing ID" and "To routing ID" to the selected attributes list in that order. Then, place a payload in a subdirectory named "ABC/DEF". The payload will be assigned a "From routing ID" attribute set to "ABC" and a "To routing ID" set to "DEF".

Available attributes

- Business protocol
- Content MIME type
- Document type
- FdaCenter
- FdaSubmissionType
- Integration ID
- To routing ID**
- From routing ID

Selected attributes

Buttons: Add >>, << Remove, Move up, Move down

Create a new message attribute

Fixed message attributes

Assign fixed values to message attributes

Name	Metadata name	Value
There are no message attributes defined		

Add a message attribute

Attribute name:

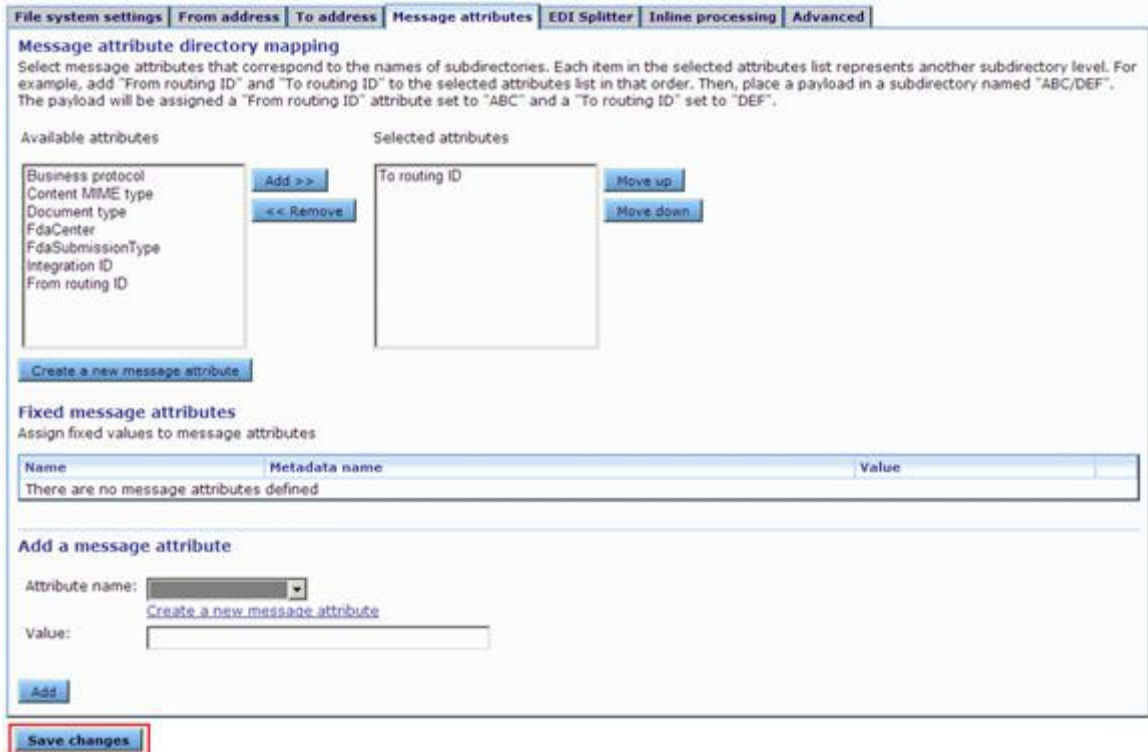
Value:

Add

Your list of **Available attributes** may differ from those shown. The only attribute here that must be on your list is **To routing ID** which is highlighted here.

5. Click on **To routing ID** in the list of attributes. Then click on the **Add** button. After the screen refreshes, **To routing ID** should be listed under **Selected attributes**:

Figure 5: Message Attributes, Added



6. Click on the **Save changes** button to commit the changes to the integration pickup.
7. Next, create the appropriate directories in the file system to match the FDA Routing IDs to which submissions are to be sent.

Figure 6: Available Routing

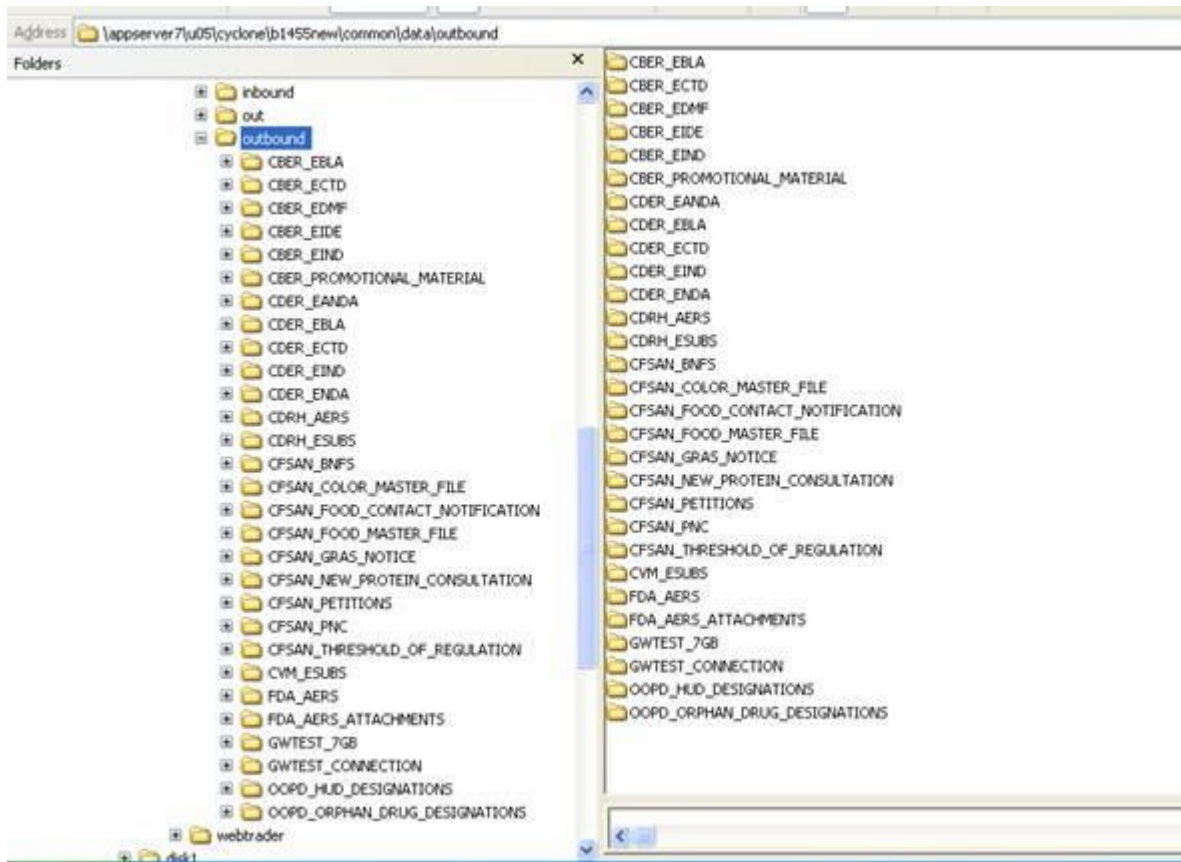


Figure 6: Available Routing shows a sample directory and subdirectories that correspond to some of the available routing IDs. A complete list of routing IDs for the FDA ESG are in Figure 7: Submission Types Supported by the FDA ESG.

8. Create subdirectories beneath the base integration pickup directory as shown, then drop the documents that you wish to submit into the appropriate directory. For example, to send an AERS report, place the document in the "FDA_AERS" directory.
9. For multi-document submissions, the original directory structure must be converted to a single file by using "tar" and then "gzip", and the resulting file **must** have an extension of **.tar.gz** for the FDA ESG to correctly recognize it as a multi-document submission. You **must** perform the tar and gzip procedure before dropping the file into the appropriate directory, since the Cyclone/Axway software does not know how to tar and gzip on its own.

Note: FDA_AERS and FDA_AERS_ATTACHMENTS submissions cannot be sent as multi-document submissions under any circumstances.

Figure 7: Submission Types Supported by the FDA ESG

Center Destination	Submission Types	Routing ID	Test	Production
CBER	AERS	FDA_AERS	Yes	Yes
	AERS_Attachments	FDA_AERS_ATTACHMENTS	Yes	Yes
	EBLA	CBER_EBLA	Yes	Yes
	ECTD	CBER_ECTD	Yes	Yes
	EIDE	CBER_EIDE	Yes	Yes
	EIND	CBER_EIND	Yes	Yes
	eDMF	CBER_EDMF	Yes	Yes
	Promotional_Material	CBER_PROMOTIONAL_MATERIAL	Yes	Yes
	Lot_Distribution_Data	CBER_LOT_DISTRIBUTION_DATA	Yes	Yes
	H1N1_Lot_Release	CBER_H1N1_Lot_Release	Yes	Yes
	510K	CBER_510K	Yes	Yes
	SDTM	CBER_SDTM	Yes	No
CDER	AERS	FDA_AERS	Yes	Yes
	AERS Attachments	FDA_AERS_ATTACHMENTS	Yes	Yes
	EANDA	CDER_EANDA	Yes	Yes
	EBLA	CDER_EBLA	Yes	Yes
	ECTD	CDER_ECTD	Yes	Yes
	ENDA	CDER_ENDA	Yes	Yes
	EIND	CDER_EIND	Yes	Yes
CDRH	Adverse_Events	CDRH_AERS	Yes	Yes
	Electronic_Submissions	CDRH_ESUBS	Yes	Yes

CFSAN**	Food_Master_File	CFSAN_FOOD_MASTER_FILE	Yes	No
	Color_Master_File	CFSAN_COLOR_MASTER_FILE	Yes	No
	Food_Contact_Notification	CFSAN_FOOD_CONTACT_NOTIFICATION	Yes	No
	New_Protein_Consultation	CFSAN_NEW_PROTEIN_CONSULTATION	Yes	No
	Threshold_of_Regulation	CFSAN_THRESHOLD_OF_REGULATION	Yes	No
	GRAS_Notice	CFSAN_GRAS_NOTICE	Yes	No
	BNFs	CFSAN_BNFS	Yes	No
	PNC	CFSAN_PNC	Yes	No
	Petitions	CFSAN_PETITIONS	Yes	No
CTP	Electronic Submission	CTP_ESUB	Yes	Yes
CVM	Electronic_Submissions	CVM_ESUBS	Yes	Yes
	Adverse Events Reports	CVM_AERS	Yes	No
OCPP	SPL	OC_REGLIST_SPL	Yes	Yes
OOPD	HUD_Designation_Requests	OOPD_HUD_DESIGNATIONS	Yes	No
	Orphan_drug_Designation_Requests	OOPD_ORPHAN_DRUG_DESIGNATIONS	Yes	No
GWTEST**	ConnectTest	GWTEST_CONNECTION	Yes	No
	SizeTest	GWTEST_7GB	Yes	No

* This center is a pilot program that is only being deployed in Pre-Production. Only authorized users should submit to the OCPP.

** These submission types are only supported in the Test environment and are intended solely for testing.