

FDA Electronic Submissions Gateway (ESG) Update

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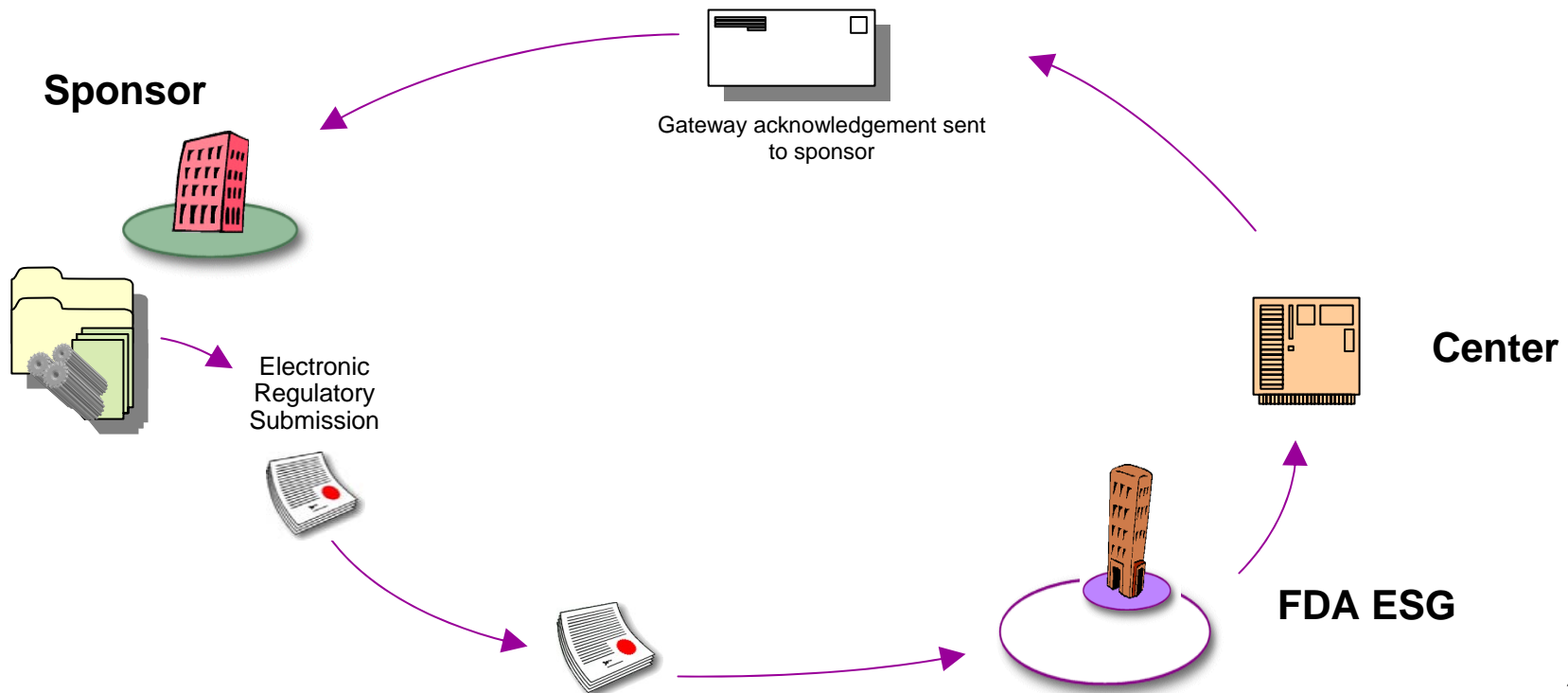
Talk Points

- **What is the Gateway**
- **Submission Options**
- **Gateway cost**
- **ROI for your investment**
- **Submission Statistics**
- **Digital Signatures**
- **Registration**
- **Most Frequent Errors**
- **ESG Issues**
- **AS1 support deadline**
- **Moving Forward**

What is the Gateway?

An Agency-wide solution and central transmission point for accepting secure electronic regulatory submissions over the Internet.

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 automatically routes them to the proper FDA Center or Office.



Electronic Submissions Gateway – Submission Options

- **FDA ESG Web Interface (WebTrader)**

- The FDA ESG Web Interface sends submissions via Hyper Text Transfer Protocol Secure (HTTPS) through a web browser according to Applicability Statement 2 (AS2) standards.
- Low cost option
- Uses applet

- **Gateway to Gateway (AS2)**

- **Applicability Statement 2 (AS2) Gateway-to-Gateway**
 - An electronic submission protocol that uses HTTP/HTTPS for communications.
- Attribute/Header and routing ID information will be used to route submission
- Requires an AS2 compliant gateway software

Gateway Cost

- **The FDA does not charge for the use of ESG**
- **The only costs incurred should relate to following;**
 - **The purchase of an x.509 version 3 class I PKI certificate with a duration of 1-3 years, which typically costs from \$20-\$30**
 - **The desired network infrastructure improvement costs (ESG was tested using various internet connection bandwidth from T1 to an OC3 line)**
 - **The ESG WebTrader applet does not require installation of any software other than JAVA, which is available for free**
 - **Cost of desktop support**

Multiple WebTrader Accounts

- **A company can have multiple WebTrader accounts**
 - FDA recommends that companies should have multiple WebTrader accounts if they submit large numbers of submissions
 - The naming convention for multiple accounts from the same company is: Company name followed by the user initials
 - E.g. Sun PhRMA - SRP
- **Testing of multiple accounts**
 - Each account must send a guidance compliant test submission
 - Only one load test is required if the accounts requested are located in same physical location or on the same physical network as previous accounts established for the company

FDA Electronic Submission Gateway - ROI

Below are a few of the benefits realized following the implementation of the FDA ESG:

- **Improves costs, resource requirements, and time efficiencies for both Sponsors and the Agency**
- **Facilitated moving product teams to a fully electronic submission process**
- **Obviated need to burn CDs/DVDs or create tapes**
- **Reduced hardware/software, costs, and resources associated with media creation**
- **Eliminated QC of submission associated with creating media**
- **Eliminated courier and FedEx fees associated with Regulatory submissions**
- **Eliminated paper output**
- **Reduced costs associated to processing, tracking, and archiving paper**

FDA Electronic Submission Gateway – ROI (cont.)

- **Reduced costs associated with maintenance of 3 DocuTech printers**
- **Eliminated need for DocuTech printers (within 1st year of implementation)**
- **Facilitated redeployment and reduction of resources required to process paper or media-based submissions**
- **Provided a more efficient and secure transfer of electronic submissions**
- **Enabled implementation of SAFE Digital Signatures which facilitated additional benefits/gains**
- **Facilitates earlier receipt of the submission by the Agency and access to the submission by the Reviewer**

FDA Electronic Submission Gateway – ROI (cont.)

Comparative Costs Projections Based on 1500 submissions

Operating Costs

Item	<u>Traditional Media</u>			<u>ESG</u>		
	Unit Cost	Quantity	Total Cost	Unit Cost	Quantity	Total Cost
Shipping	\$8.25	1500	\$12,375.00	N/A		
Credentials (digital certificates)	N/A			\$20.00	20	\$400.00
Resources:						
Hours	\$63.89	1500	\$95,835.00	\$63.89	104	\$6,644.00
Quarter Hours	N/A			\$15.97	1500	\$23,955.00
Materials:						
CDROM	\$0.15	1490	\$223.00	N/A		
DLT	\$50.00	10	\$500.00	N/A		
Binders (Cover Letters)	\$1.50	1500	\$2,250.00	N/A		
Total Cost			\$111,183.00			\$30,999.00

ESG Registration Statistics

	Production		Pre-Production
	May 2006	Today	Today
# of Accounts			
AS1	24	28	43
AS2	2	26	62
WebTrader	19	308	427
Total	45	362	532
# of Companies			
AS1	20	25	33
AS2	2	23	41
WebTrader	15	94	149
Total	29	109	177

Gateway Submission Statistics by Month

	<u>2006</u>								Totals
	May	June	July	Aug	Sept	Oct	Nov	Dec	
AERS	9,109	6,188	5,155	6,408	5,621	6,393	7,759	8,523	55,156
CDER	20	54	44	119	207	283	411	501	1,639
CBER	6	9	19	36	56	49	61	58	294
CDRH	153	312	272	198	95	237	172	136	1,575
CVM									
Totals	9,288	6,563	5,490	6,761	5,979	6,962	8,403	9,218	58,664

	<u>2007</u>												Total
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	
AERS	9,576	9,948	12,158	14,696	12,917	15,177	12,546	12,906	14,925	14,810	13,568	16,335	159,562
CDER	457	600	650	785	1,009	950	880	1,132	930	1,212	1,258	1,312	11,175
CBER	68	58	85	102	101	106	119	193	149	179	181	163	1,504
CDRH	176	108	127	102	75	138	80	205	267	118	70	61	1,527
CVM							45	58	35	55	46	49	288
Totals	10,277	10,714	13,020	15,685	14,102	16,371	13,670	14,494	16,306	16,374	15,123	17,920	174,056

Submission Statistics: Top 10 AS2 Companies

Pfizer	22,383
Abbott Laboratories	8,514
Eli Lilly	8,433
Genentech, Inc.	5,591
Wyeth	2,621
Astrazeneca	2,274
Purdue Pharma	1,225
Quality Associates Inc**	997
Ranbaxy/OHM Laboratories	668
Merck	313

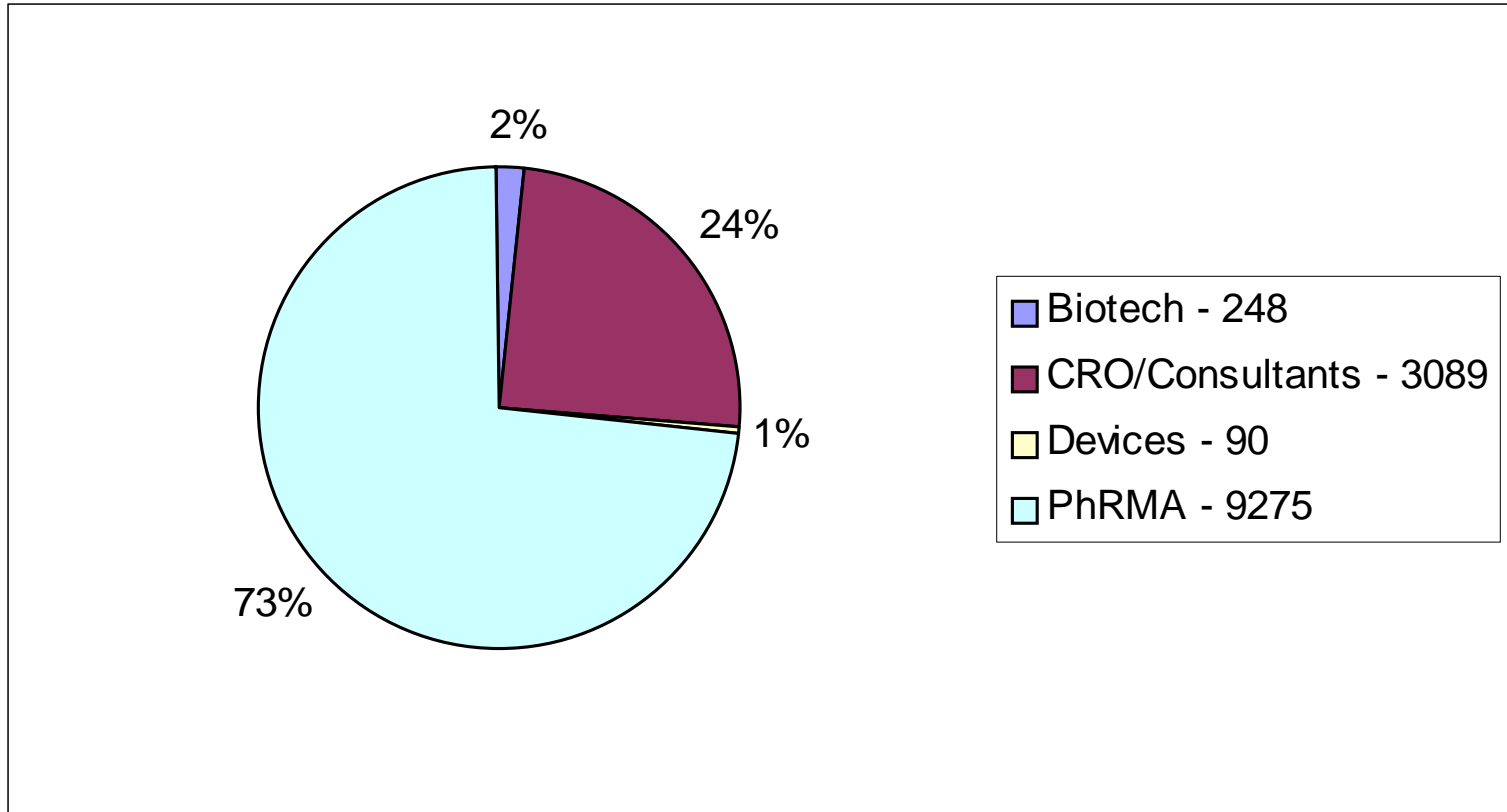
*Numbers include AERS and multi-file submissions

**CDRH submissions only

Submission Statistics: Top 10 WebTrader Companies

Amgen	1541
Wyeth	1328
GSK	920
Merck	816
AstraZeneca	758
J&J	660
Pfizer	660
Novo Nordisk	485
Centocor	431
Novartis	403

Submission Statistics by Industry



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 (see example):
 - the printed name of the signer
 - the date and time when the signature was executed
 - the reason for signature
- **Please utilize the pdf self sign signature on the FDA fillable forms.**
- **The Agency does not check electronic/digital signatures unless there is a directed inspection involving the submission transmission.**

Digital Signatures (cont.)

- **Industry should maintain the self sign certs associated with the self sign signature just in case there is a directed inspection.**
- **The Agency cannot hold electronic signatures to greater level of rigor than paper signatures. The Agency does not check every signature on a paper based document/submission.**
- **The x.509 version 3 class I certificate employed by the ESG allows the Agency to attribute the origin of the submission.**
- **The Agency has to be able to determine the origin of a submission. The Agency's General Counsel (GC) articulated this as the standard we had to meet in implementing fully electronic submission transmission.**
- **The PKI cert (x.509 version 3 class I certificate) accomplishes this through the use of a public/private key exchange.**

Digital Signatures (cont.)

- **Use 1571 and 356h electronically fillable forms with your electronic submission transmissions to CDER and CBER via the ESG**
 - 1571 (<http://www.fda.gov/opacom/morechoices/fdaforms/1571es.pdf>)
 - 356h (<http://www.fda.gov/opacom/morechoices/fdaforms/356Hes.pdf>)
 - **If these forms are not included in your electronic submission transmissions, CBER and CDER will not be able to leverage their automated loading processes. The absence of these forms reduces the Centers automated loading process to a manual process. The affect - a large increase in the time required by the Centers to make submissions available to our review community.**
 - **356h and 1571 Form Field sizes**
 - The important fields from the Agency perspective are the application number and submission type for documents transmitted for regulatory review via the ESG.
 - The current forms fields have the maximum number of characters allowed.
 - If the form field is not large enough, please abbreviate the text in the field.
 - FDA contractors or administrative reviewers read the submission 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.
 - Increasing the form field size or otherwise altering the forms would require OMB approval

Digital Signatures (cont.)

FAQs

Question: It appears if PDF signature not used, will FDA accept the submission?

Answer: Yes, FDA does not validate the signature during the submission process. Signature validation issues would be addressed as part of an inspection.

Question: Sponsors are concerned that some fields cannot handle the full text.

Answer: Important fields are the application number and submission type.

Question: Use of non-public key Elec/Dig signatures results in an error message during eCTD validation steps associated with a "secured" pdf file being present within the eCTD (in violation of an ICH eCTD "rule").

Answer: FDA understands that this would/has occurred and would not/has not "turned-back" submissions based upon this. 'It is a by-product of a regional requirement they have for facilitating/enabling expedited processing of the eCTDs.'

Electronic Submissions Gateway Process - Before You Register

- **Submit a Letter of Non-Repudiation Agreement**
 - A letter of Non-Repudiation Agreement must be submitted to the FDA. The non-repudiation agreement allows the FDA to receive electronically signed submissions in compliance with 21 Code of Federal Regulations (CFR) Part 11.100.
 - Send letter to Office of Regional Operations, (ORO)
 - Send copy to ESG Project Manager
 - Sample letters are on the FDA ESG website
- **Obtain a Digital Certificate**
 - The FDA ESG uses digital certificates to secure the transaction and communications.
 - A digital certificate is an electronic document which conforms to the International Telecommunications Union's X.509 specification.
 - FDA accepts X.509 .v3 certificates
 - Certificate must be valid for 1-3 years
 - Use the public key when registering
 - Public key has the extension of .p7b or .cer
 - Use the private key to sign the submissions
 - Private key has the extension of .p12 or .pfx
 - ESG website has information on how to obtain a digital certificate
- **Determine Submission Method**
 - Web-based (WebTrader)
 - Gateway-to-Gateway (B2B) submissions using industry standards for the transport protocol (AS2)
 - A separate registration will be required for each option selected

Electronic Submissions Gateway Process - Before You Register (Cont.)

- **Understand Submission Guidelines**

- Each FDA Center has specific guidelines that should be followed for preparing electronic submissions.
- Center-Specific Submission Preparation Guidelines on the ESG website provides links to center specific guidelines.

- **Submission Types**

- Each FDA Center will accept only certain specific types of submissions.
- See Submission Types by Center on the ESG website for accepted submission types by each center

ESG Account Registration and Setup Process for WebTrader/AS2

1. **Send an email request to esgprep@fda.gov , include the submission method you intend to use, contact persons name and company name in the email.**
2. **FDA will email back the registration information**
3. **Register online using the information provided**
4. **FDA will review the registration and activate the account**
5. **FDA will send an approval notification and guidelines for test preparation**
 - **FDA will send trading profile information and certificate if it is an AS2 registration**
6. **Complete the guidelines and send test submission**

Most Frequently Occurring Errors – WebTrader Registrations

- **Correct JRE (java runtime environment) or JCE (java cryptography extension) are not installed**
- **Firewall rules are not set to allow communications over port 3080**
 - **Firewall port 3080 must be open for the WebTrader applet to send submissions to the FDA**
 - **WebTrader User Interface communications are done through port 443**
- **Certificate fails on import**
 - **Send the certificate to esgreg@gnsi.com**

Most Frequently Occurring Errors – AS2 Registrations

- **Firewall rules are not set properly to allow connections with FDA ESG**
- **A private URL is provided during registering**
- **Custom attributes are not included in the message header**
- **Firewall rules are not set to allow communications over port 4080**
 - **All Gateway-to-Gateway communications ESG are done using port 4080**

Issues

- **If your certificate is not accepted by the FDA registration module or if you have to replace an existing certificate**
 - Enclose the .cer or .p7b file in a ZIP file and send as an email attachment to esgreg@gnsi.com
 - OR change the .cer or .p7b extension to .txt and send as an email attachment to esgreg@gnsi.com (please specify the original extension of the file)

Issues (cont.)

- **WebTrader My FDA submissions fails to display in Firefox browser.**
 - This is a high frequency issue
- **WebTrader My FDA submissions slow to display in Internet Explorer.**
 - This is a medium frequency issue
- **Custom folders are not available**
- **The popup for receipt/ACK displays off-screen**
- **Sorting unavailable in WebTrader interface**
- **WebTrader receipt/ACK links broken if account name contains special characters**
- **Fixed in the next release (v5.5.2)**
 - **Deleting record in WebTrader results in page not found**
 - **WebTrader wrongly shows a red bar when sending a large submission (>2GB)**

AS1 Support deadline

- **The FDA ESG support for AS1 ends March 1, 2008. All AS1 users must migrate to AS2 or WebTrader accounts before this date**
- **Of the 25 AS1 companies**
 - **16 companies have production AS2 accounts**
 - **1 company has been approved for production AS2 account but not registered**
 - **1 company registered but not sent test submissions**
 - **4 companies are testing**
 - **3 companies have not registered for a test AS2 account yet**

Moving Forward...

- **Upgrade Axway Interchange (5.5.2) for added functionality and improved performance**
- **Add CFSAN to production**
- **Set up ESG service in support of Janus with NCI, USDA, and VAERS**
- **Validate custom attribute alternative to partners using non-Axway AS2 gateways for routing of submissions**
 - **5.4.2 supports routing IDs for Axway AS2 gateways**

ESG resources and contact information

- **Website:** <http://www.fda.gov/esg/>
 - Registration Information
 - System Requirements
 - User Guide and Tutorials
 - Digital Signatures and Certificates
 - System Status and Help Desk
 - Links to submission guidelines
- **Email for preparation/Registration/Policy:** esgprep@fda.gov
 - This email is for question and help in setting up test and production accounts
- **Email for technical issues:** esgreg@gnsi.com
 - This email is for system and submission related issues
- **FDA project manager: Michael Fauntleroy**
 - **Email:** michael.fauntleroy@fda.hhs.gov
 - **Phone:** 301-827-5132
 - **Address:** Office of the Director (HFM-25)
Center for Biologics Evaluation and Research
Food and Drug Administration
11400 Rockville Pike, Room 4119
Rockville, MD 20857

Thank-you

Supplemental Information - Purchasing Certificates

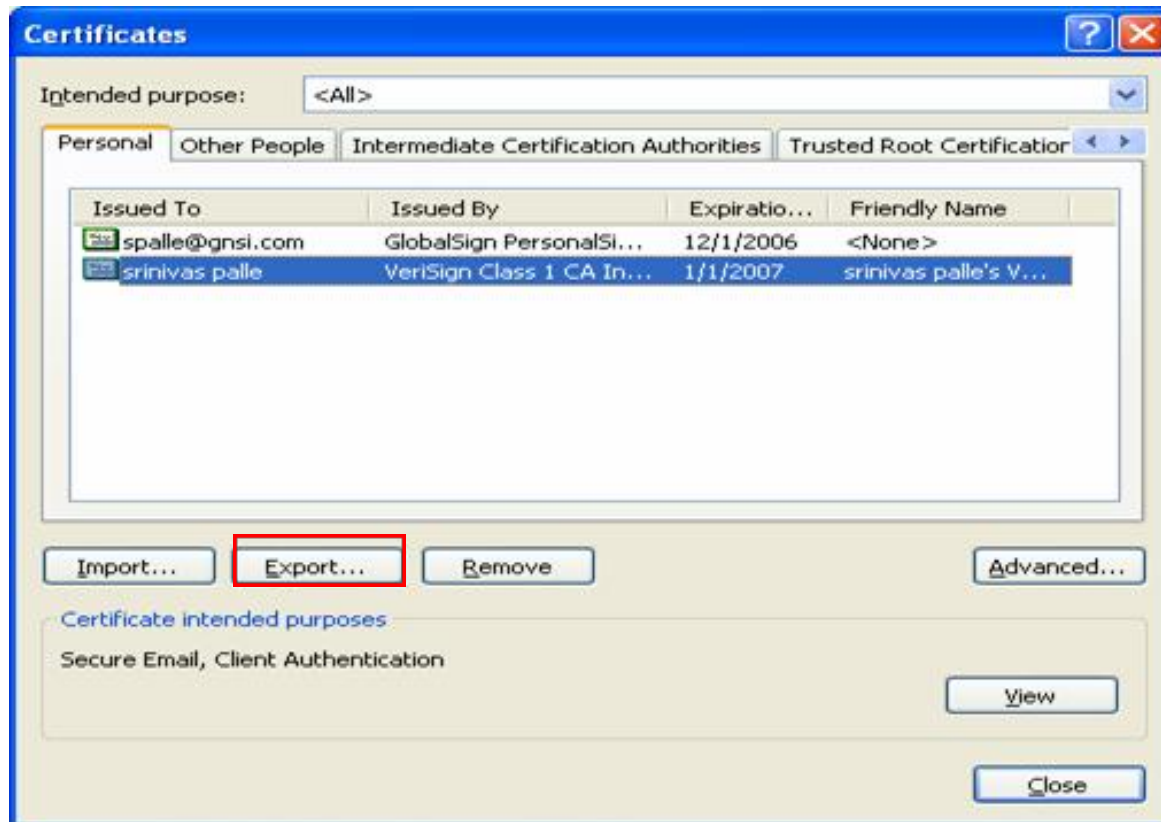
- If you are trying to use an outsourced certificate, the following are the companies that sell the X.509 certificates (Displayed in alphabetical order). Click on the link to go to website where you can purchase the certificate.
 - **Geotrust:**
http://www.geotrust.com/products/client_certificates/my_credentials.asp
 - **GlobalSign:**
http://www.globalsign.net/digital_certificate/personalsign/index.cfm If you select this, buy PersonalSign2 Pro™ Certificate with one year validity
 - **Verisign:** <http://www.verisign.com/products-services/security-services/pki/pki-application/email-digital-id/index.html>

Supplemental Information - Installing Certificates

After you make the choice from the above list follow the on screen instructions to complete the purchase. 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. AS1/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.

Supplemental Information – Exporting public key (cont.)

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



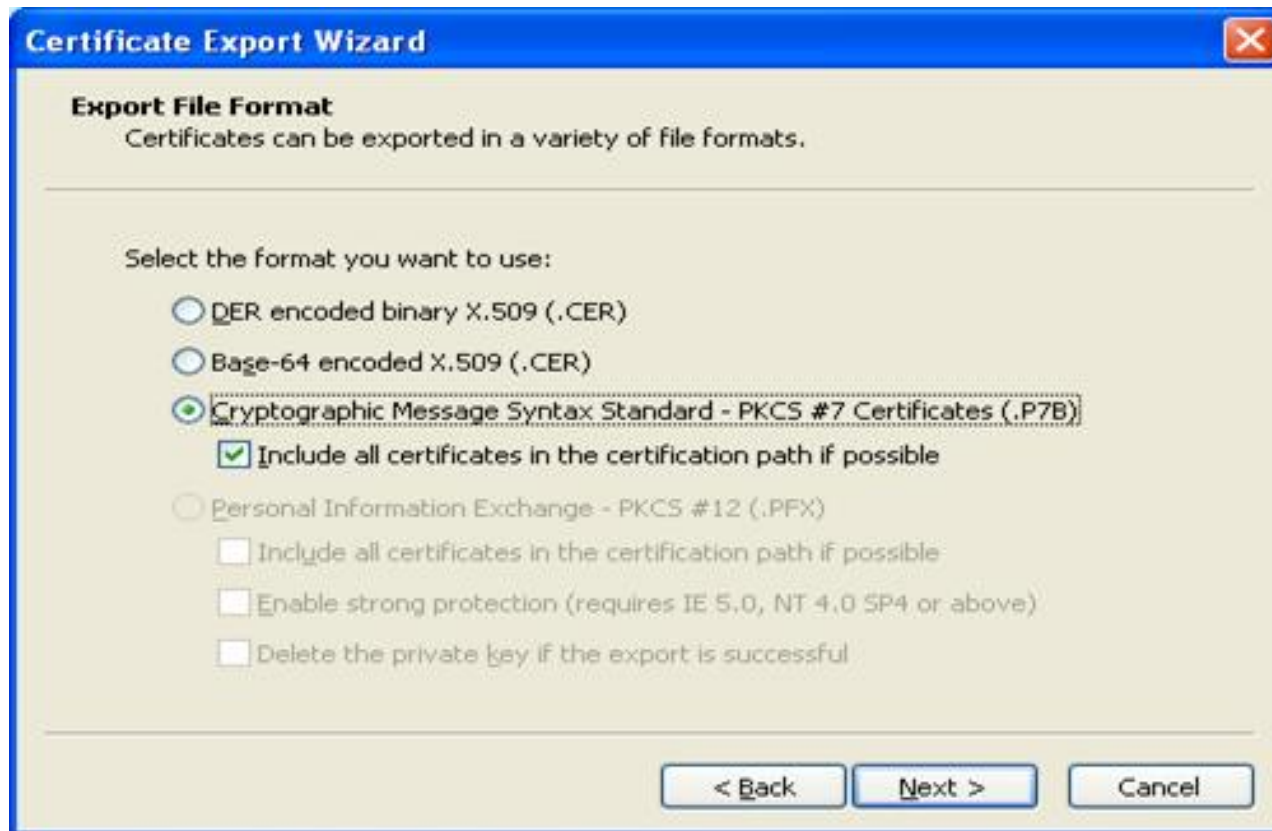
Supplemental Information – Exporting public key (cont.)

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



Supplemental Information – Exporting public key (cont.)

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



Supplemental Information – Exporting public key (cont.)

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



Supplemental Information – Exporting public key

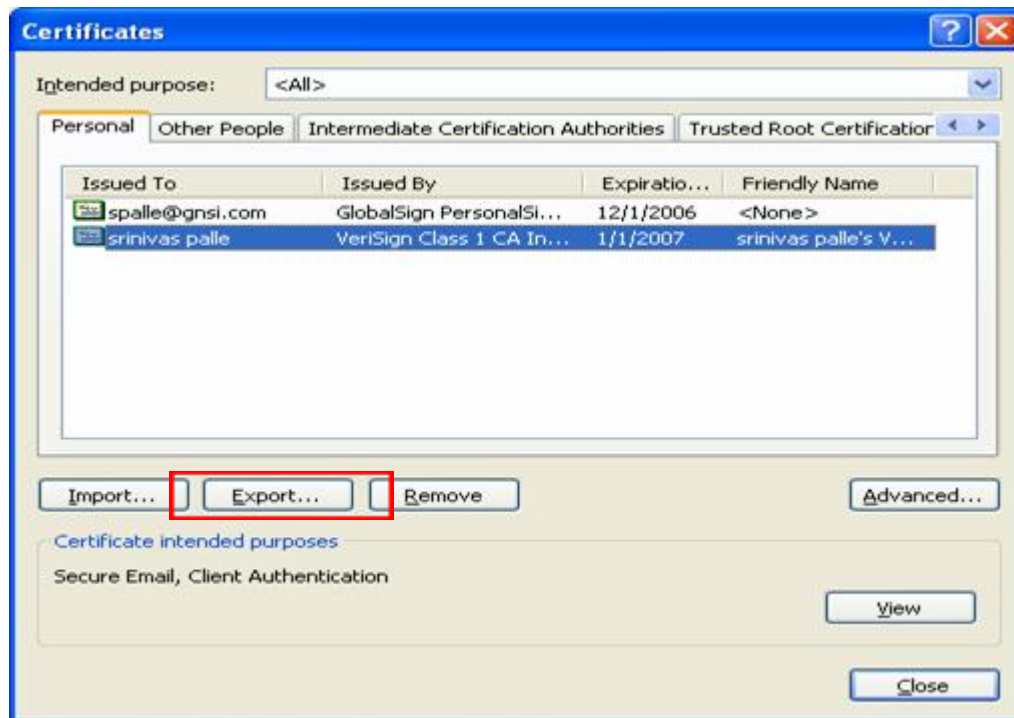
(cont.)

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.**

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

Supplemental Information – Exporting private key

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



Supplemental Information – Exporting private key (cont.)

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



Supplemental Information – Exporting private key (cont.)

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



Supplemental Information – Exporting private key (cont.)

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 (X) in the top right corner. The main content area is light beige and contains the following text:

Password
To maintain security, you must protect the private key by using a password.

Type and confirm a password.

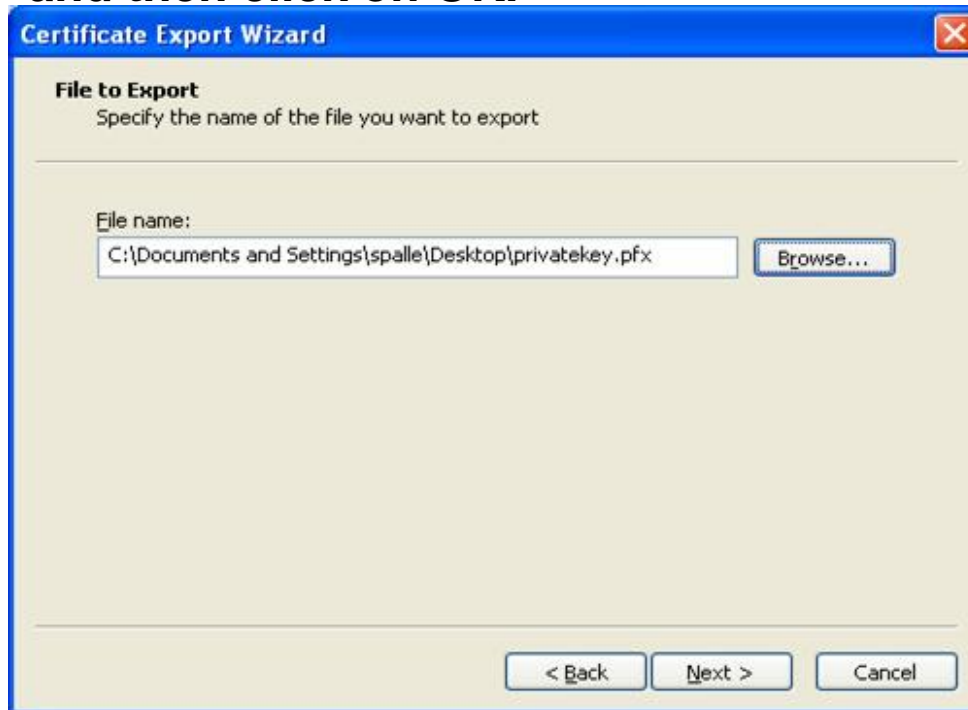
Password:

Confirm password:

At the bottom of the dialog, there are three buttons: "< Back", "Next >", and "Cancel".

Supplemental Information – Exporting private key (cont.)

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.**



This is the key that you will use to sign the submissions