Center for Biologics Evaluation and Research

Electronic Submission Program

Task No. TO21 — Contract No. 223-97-5513

Electronic Secure Messaging v2.0
Working Instructions for Industry

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1 INTRODUCTION

The Center for Biologics Evaluation and Research (CBER) regulates and oversees the safety and efficacy of the nation's blood supply, including plasma and other blood products, and biological and biotechnology products derived from living cells. CBER receives and reviews thousands of submissions from regulated industry and consumers. These submissions include Biologics License Applications (BLAs), Investigational New Drugs (INDs), 510(k)s, Pre-market Approvals (PMAs), New Drug Applications (NDAs), lot release protocols, and adverse event reports.

CBER's goals for the review of these submissions changed with the passing of the Prescription Drug User Fee Act (PDUFA) II and the Food and Drug Administration (FDA) Modernization Act (FDAMA). The acts mandate expedited review of license applications and INDs. To fulfill these mandates, the agency created the Electronic Submission Program (ESP) Program. Within CBER, the ERSR Electronic Document Room (EDR) and Electronic Secure Messaging (ESM) systems help to address some of the requirements of these mandates. ESM assists in fulfilling the ERSR goals enabling secure, electronic correspondence between CBER and its Industry partners.

1.1 OBJECTIVE

The purpose of this document is to provide Industry participants with instructions for sending IND/BLA amendments to CBER via secure mail. This document supports the Secure Messaging Pilot Industry Participation Document.

2 PRELIMINARY ACTIVITIES

The following section identifies the preliminary activities that Industry participants in the CBER ESM program must complete before sending an IND/BLA amendment via ESM to CBER. The use of either Tumbleweed Messaging Management Server (MMS) Virtual Private Network (VPN), or Secure Multipart Internet Mail Extensions (S/MIME) technology will be accepted.

Note: There is presently a size limitation of 50 megabytes for sending Regulatory amendments via secure mail.

2.1 REGISTER IND/BLA

The initial step is to register the IND or BLA for ESM with CBER. CBER can only accept amendments via ESM for fully electronic INDs or BLAs. First, contact Michael Fauntleroy (301-827-5132) regarding the filing of a non-repudiation of digital signatures agreement with CBER. This agreement covers any digital signature sent by a company to CBER. Once the agreement is on file, submit an ESM registration form to Dan Offringa (301-827-1385) or Joe Montgomery (301-827-1332). A form is required for each IND or BLA for which you wish to submit ESM amendments. For BLAs, registering an original application does not automatically register supplements to that application. Each BLA or supplement must be registered separately.

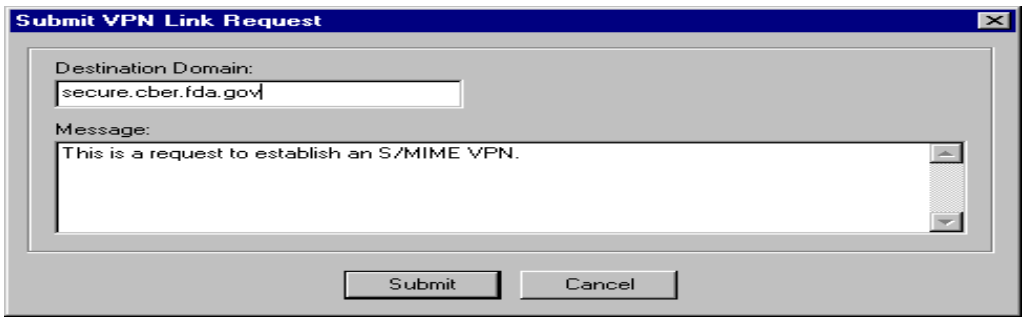
2.2 EXCHANGING CERTIFICATES (PUBLIC KEYS)

Prior to sending submissions via ESM, a certificate exchange of public keys must take place. The CBER MMS server employs Tumbleweed MMS VPN technology. The following describes how the certificate exchange is accomplished using either VPN to VPN or S/MIME to VPN technology.

2.2.1 Using VPN

In order to establish a VPN link connection with CBER using VPN technology, an email request must be made to the **secure.cber.fda.gov** email domain using Tumbleweed MMS. Figure 2.1.1-1 depicts submitting a VPN request using Tumbleweed MMS to the CBER MMS server.

Figure 2.2.1-1-VPN Request



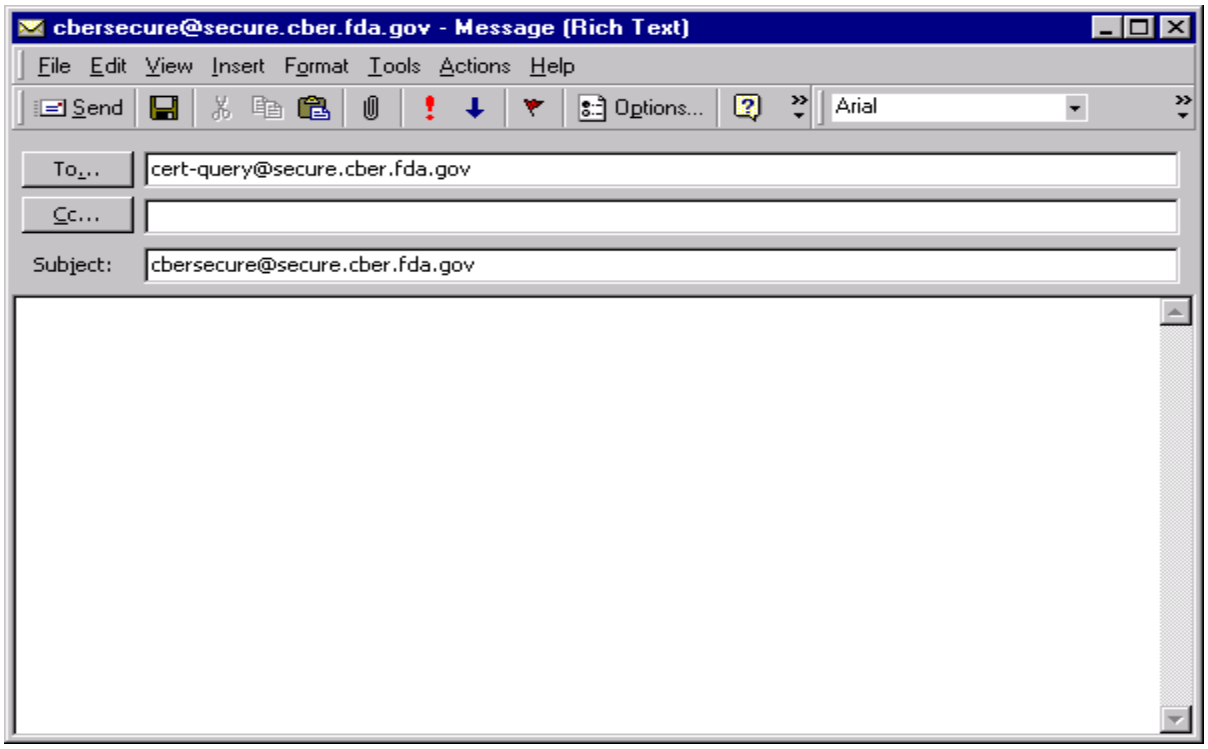
2.2.2 Using S/MIME

The following identifies the steps required to establish an S/MIME connection with the CBER MMS server:

1. **Generate certificate –** For email encryption**,** generate or obtain certificate from a Certificate Authority (CA) (e.g. Verisign, Entrust, or Baltimore).

2. **Send message –** In the **To:** field of the email message header, type cert-query@secure.cber.fda.gov. In the **Subject:** field of the message header, type the following - cbersecure@secure.cber.fda.gov. The message body should not contain any content. Figure 2.1.2-1 depicts a sample S/MIME request to the CBER MMS server.

Figure 2.2.2-1- Sample S/MIME Request



2.3 CREATING ADOBE CERTIFICATE

All IND/BLA amendment submissions received via ESM must be accompanied by an Adobe Acrobat (v.4.05 or greater) **Self-Sign Security** electronic signature on the Form FDA 1571(es) and Form FDA 356H(es). ***Note:*** Form FDA 1571(es)/Form FDA 356H(es) will refer to both the standard forms and electronic forms.

2.3.1 Generate Certificate Using Adobe Acrobat v.5.0

The following steps identify how to generate a certificate using Adobe Acrobat v.5.0:

1. Launch Adobe Acrobat.
2. From the '**Tools'** menu bar, select **Self-Sign Security** followed by **Log In** from the drop down list.
3. From the Self-Sign Security-Log In screen, select '(**New User Profile**)'.
4. Enter the required User Attribute information and choose a password.
5. Press the **OK** button.
6. Press the **Save** button.
7. From the '**Tools'** menu bar, select **Self-Sign Security** followed by '(**User Settings**)'.
8. From the '**Self-Sign Security**' Screen, select '(**User Information**)'.
9. Click the **E-Mail** button.
10. Type the following email address in the **To:** field of the message header - csm@secure.cber.fda.gov
11. Press the **E-Mail** button.
12. After sending the message, contact ESM Administrator Dan Offringa (301-827-1385) or Joe Montgomery (301-827-1332).
13. Verify with ESM Administrator that the Adobe certificate fingerprint is valid.

2.3.2 Generate Certificate Using Adobe Acrobat v.4.0

The following steps identify how to generate a certificate using Adobe Acrobat v.4.0:

1. Launch Adobe Acrobat.
2. From the '**Tools'** menu bar, select **Self-Sign Security** followed by **Log In** from the drop down list.
3. From the Self-Sign Security-Log In screen, select '(**New User Profile**)'.
4. Enter the required User Attribute information and choose a password.
5. Press the **OK** button.
6. Press the **Save** button.

7. Open a Portable Digital Format (PDF) document and digitally sign the pdf file using the certificate.
8. Open your email browser, create a new message and attach the electronically signed pdf document.
9. Type the following email address in the **To:** field of the message header - csm@secure.cber.fda.gov.
10. After sending the message, contact ESM Administrator Dan Offringa (301-827-1385) or Joe Montgomery (301-827-1332).

3 SENDING THE SECURE MESSAGE

The following steps must be completed before a submission is ready to be submitted to CBER. Amendments submitted via ESM will be automatically processed by CBER. Therefore, it is very important that these instructions and the CBER Guidance regarding IND/BLA structure are followed when submitting amendments via ESM. Any deviations may prevent the amendment from being accepted by CBER.

3.1 OUTLINE OF STEPS

The following identifies the steps needed to create and send an IND/BLA amendment submission via ESM:

1. Create IND/BLA amendment submission structure. All files/folders **except** the Form FDA 1571(es)/Form FDA 356H(es) and the roadmap.pdf file must reside inside the zipped file.
2. Electronically sign the Form FDA 1571(es)/ Form FDA 356H(es). The form can be obtained from Michael Fauntleroy.
3. Create an email message to send to CBER.
4. Type the cover page information attributes in the body of the email message (See Section 3.2.10). Note this is only required if not using electronic Form FDA 1571es/Form FDA 356Hes.
5. Attach the Zip file, the electronically signed Form FDA 1571(es)/Form FDA 356H(es) and roadmap.pdf file to the email message.
6. Encrypt and send the email message to the cbersecure@secure.cber.fda.gov mailbox.

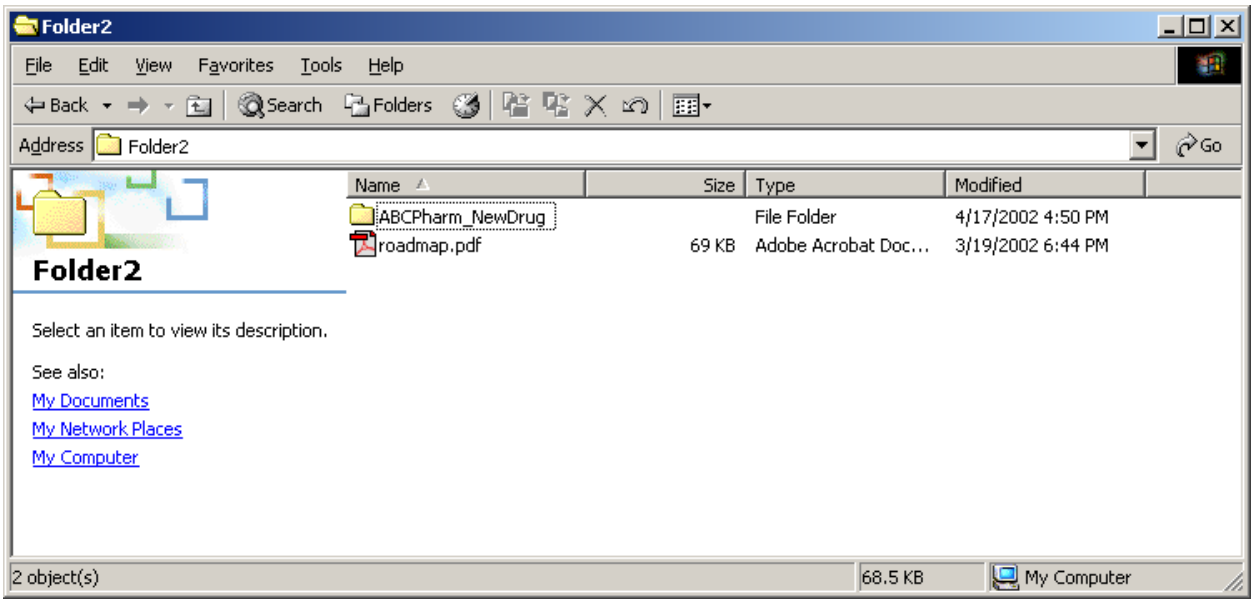
3.2 DESCRIPTION OF STEPS

The following section describes the steps for preparing and sending an IND/BLA amendment submission via ESM:

3.2.1 IND Amendment Structure

All IND amendment files and folders except the roadmap.pdf should be contained in the main IND folder (i.e., ABCPharm_NewDrug). The main IND folder should have the same name as the main IND folder that exists in CBER so that it is recognized as part of the original submission. The roadmap.pdf must reside at the same level as the main IND folder. Figure 3.2.1-1 provides an example of how the amendment folder should be structured.

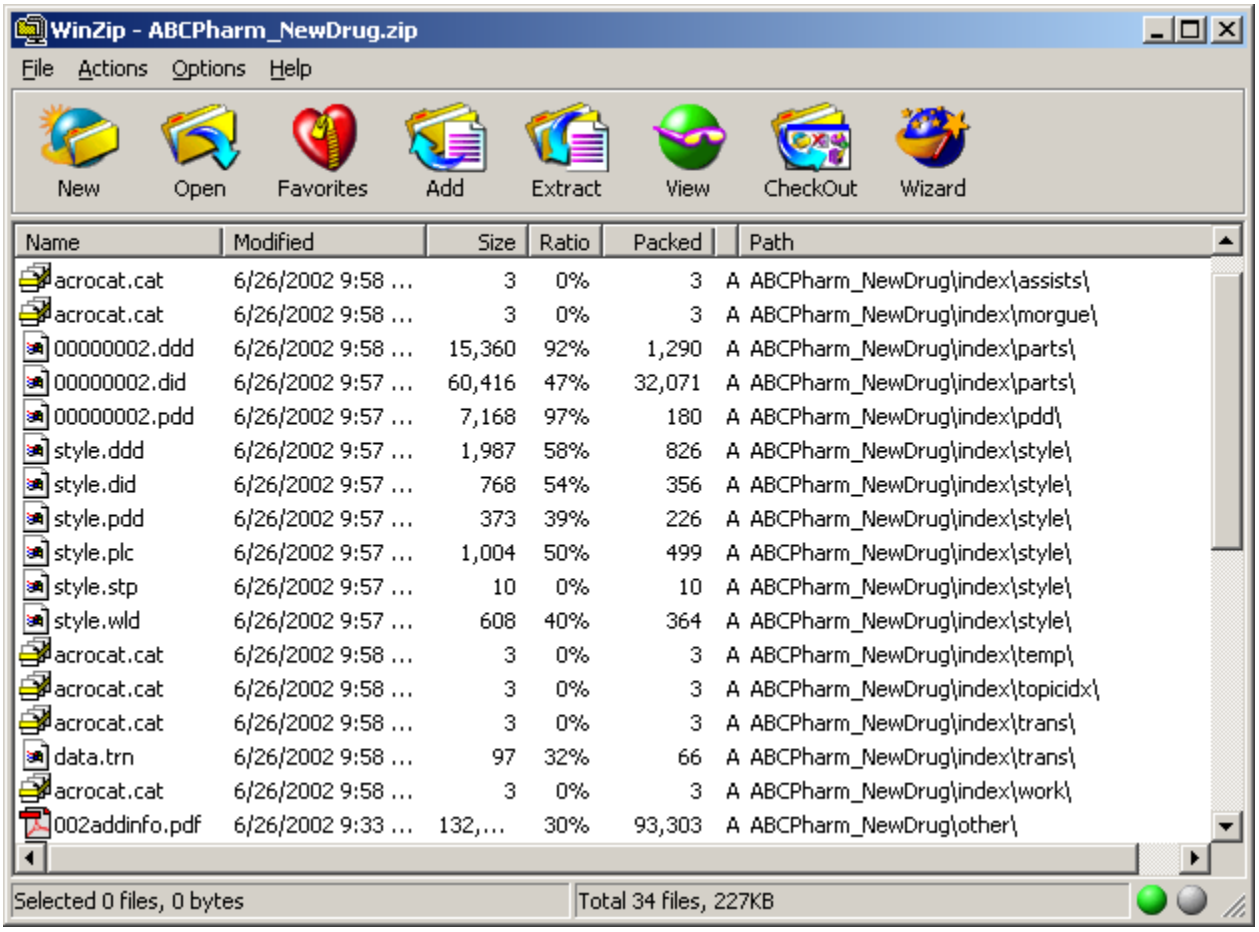
Figure 3.2.1-1-Example IND Amendment Structure



3.2.2 Preparing IND Zip File Structure

To prepare IND Zip file structure users must remove the Form FDA 1571(es) from the main IND folder and then add the entire folder to a Zip file. The roadmap.pdf and Form FDA 1571(es) should not be included in the Zip file. The IND folder should have the same name as the main IND folder so that it is recognized as part of the original IND. The Zip file does not need to be labeled similarly to the main IND folder. Figure 3.2.2-1 depicts the accepted IND amendment Zip file structure showing the inclusion of the full path.

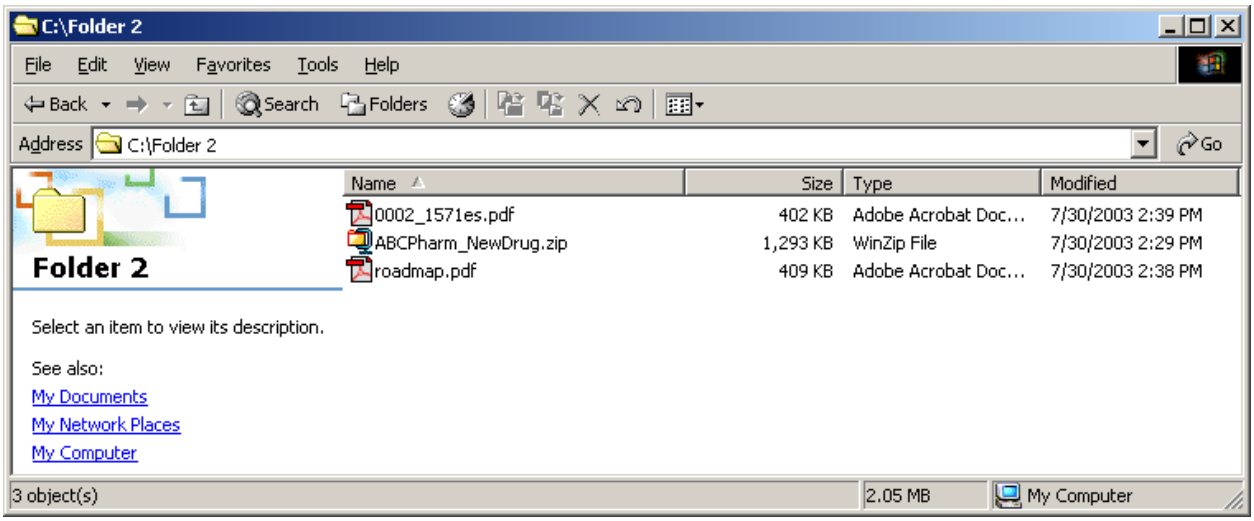
Figure 3.2.2-1- IND Amendment ZIP File Structure



3.2.3 Create ESM IND Amendment Package

The package should consist of three files: the Zip file containing the main IND folder, the Form FDA 1571(es), and the roadmap.pdf. The Form FDA 1571(es) file must be named XXXX_**1571es.pdf**, where XXXX represents the serial number and es represents using the electronic form. If this naming convention is not followed, the IND amendment will be rejected. This file should NOT be modified in any manner after it has been signed. Figure 3.2.3-1 depicts the structure for sending IND amendments via ESM using the electronic form.

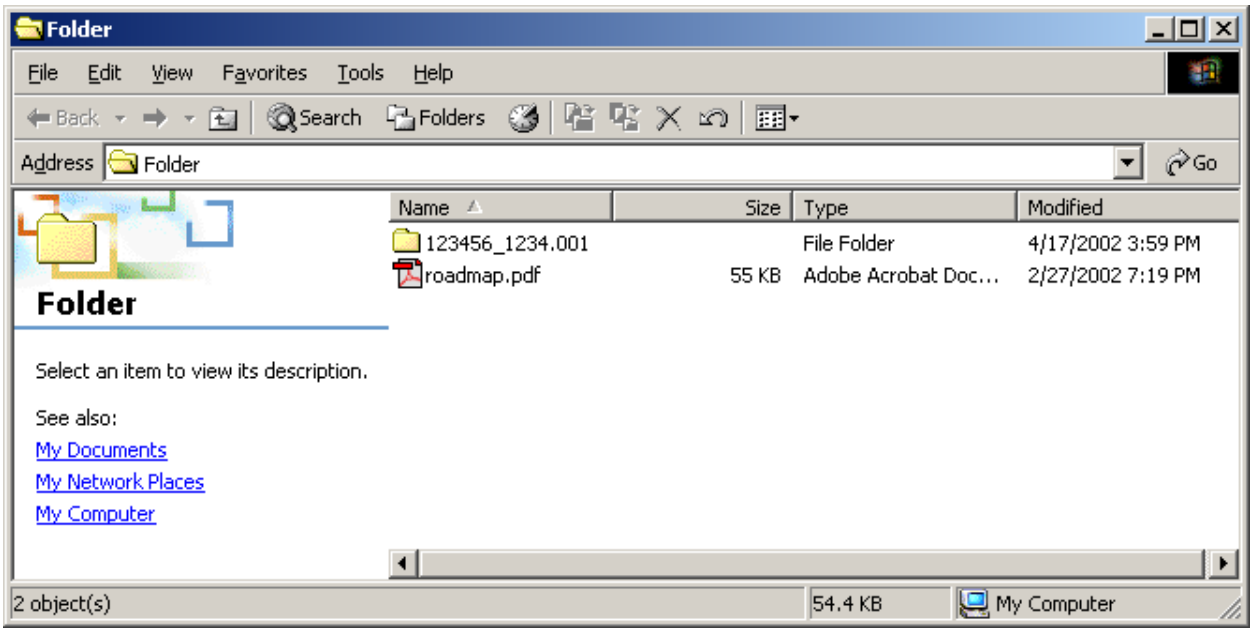
Figure 3.2.3-1- IND Amendment Package



3.2.4 BLA Amendment Structure

All BLA amendment files and folders except the roadmap.pdf should be contained in the main amendment folder (i.e., 123456_1234.001). Each BLA amendment main folder should be unique to prevent overwriting of previously sent amendments. The roadmap.pdf must reside at the same level as the main amendment folder. Figure 3.2.4-1 provides an example of how the BLA amendment should look.

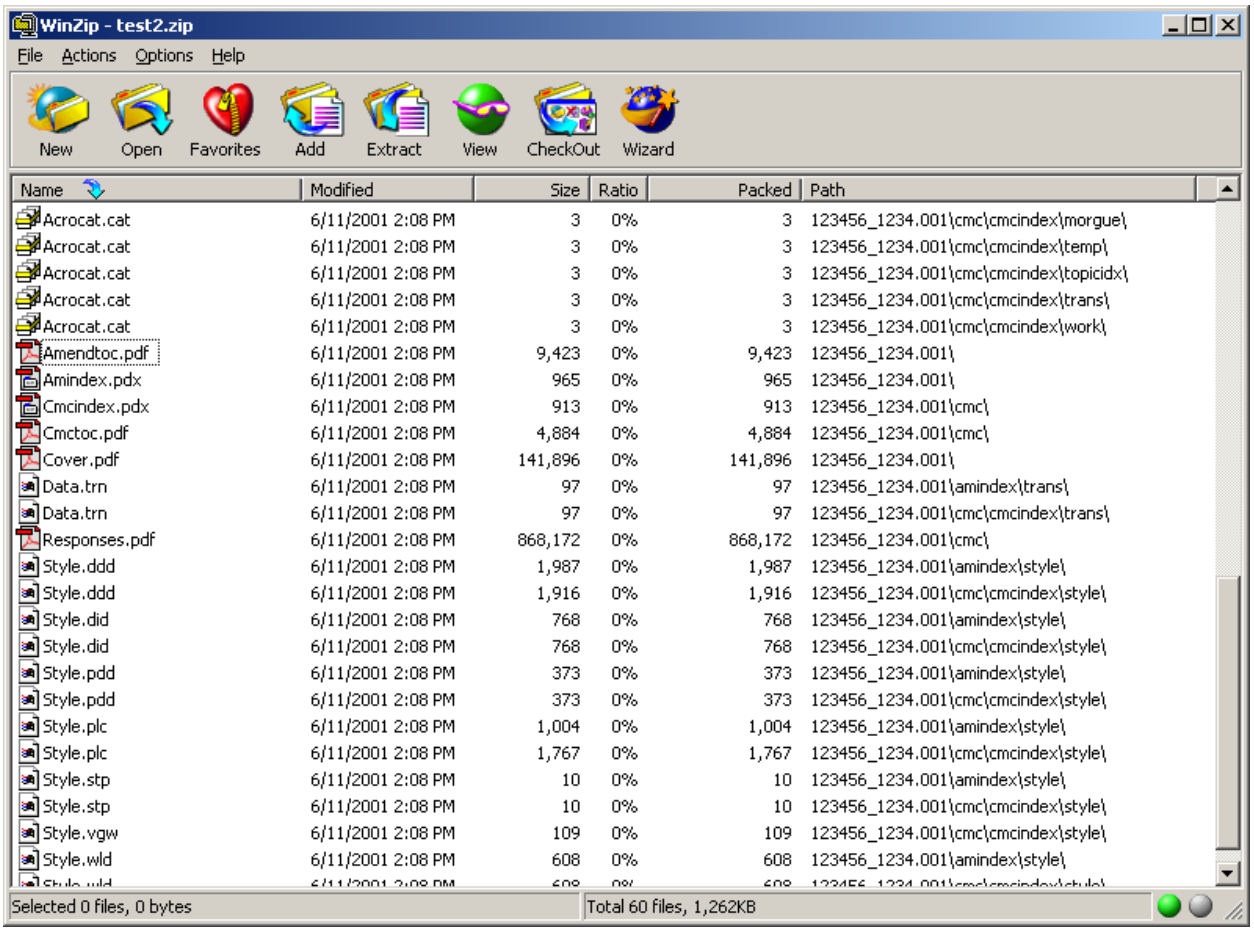
Figure 3.2.4-1- Example BLA Amendment Structure



3.2.5 Preparing BLA Zip File Structure

First, remove the Form FDA 356H(es) from the main amendment folder, then add the entire folder to a Zip file. The roadmap.pdf and Form FDA 356H(es) must not be included in the Zip file. The Zip file is not required to have the same name as the main amendment folder (e.g., 123456_1234.001) but if desired to so, it will still be accepted by CBER. Figure 3.2.5-1 depicts the accepted BLA amendment Zip file structure with inclusion of full path.

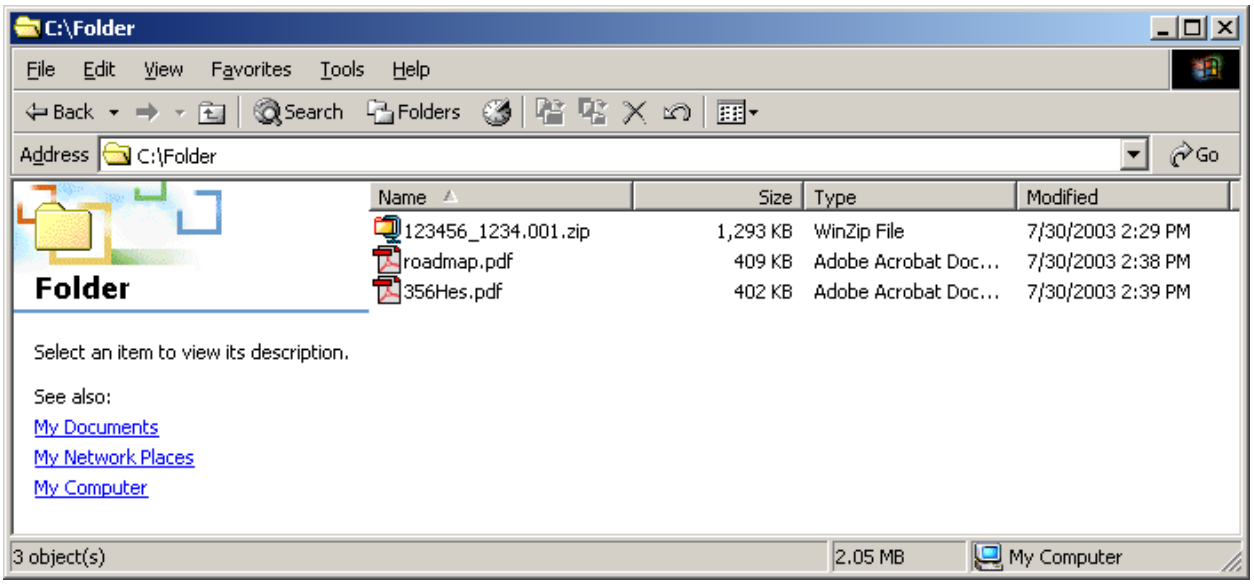
Figure 3.2.5-1- BLA Amendment Zip File Structure



3.2.6 Create ESM BLA Amendment Package

The package should consist of three files: the Zip file containing the main amendment folder, the Form FDA 356Hes, and the roadmap.pdf. The Form FDA 356H(es) file must be named **356Hes.pdf**, where es represents using the electronic form. If this naming convention is not followed, the BLA amendment will be rejected. This file should NOT be modified in any manner after it has been signed. Figure 3.2.6-1 depicts the structure for sending BLA amendments via ESM using the electronic form.

Figure 3.2.6-1- BLA Amendment Package

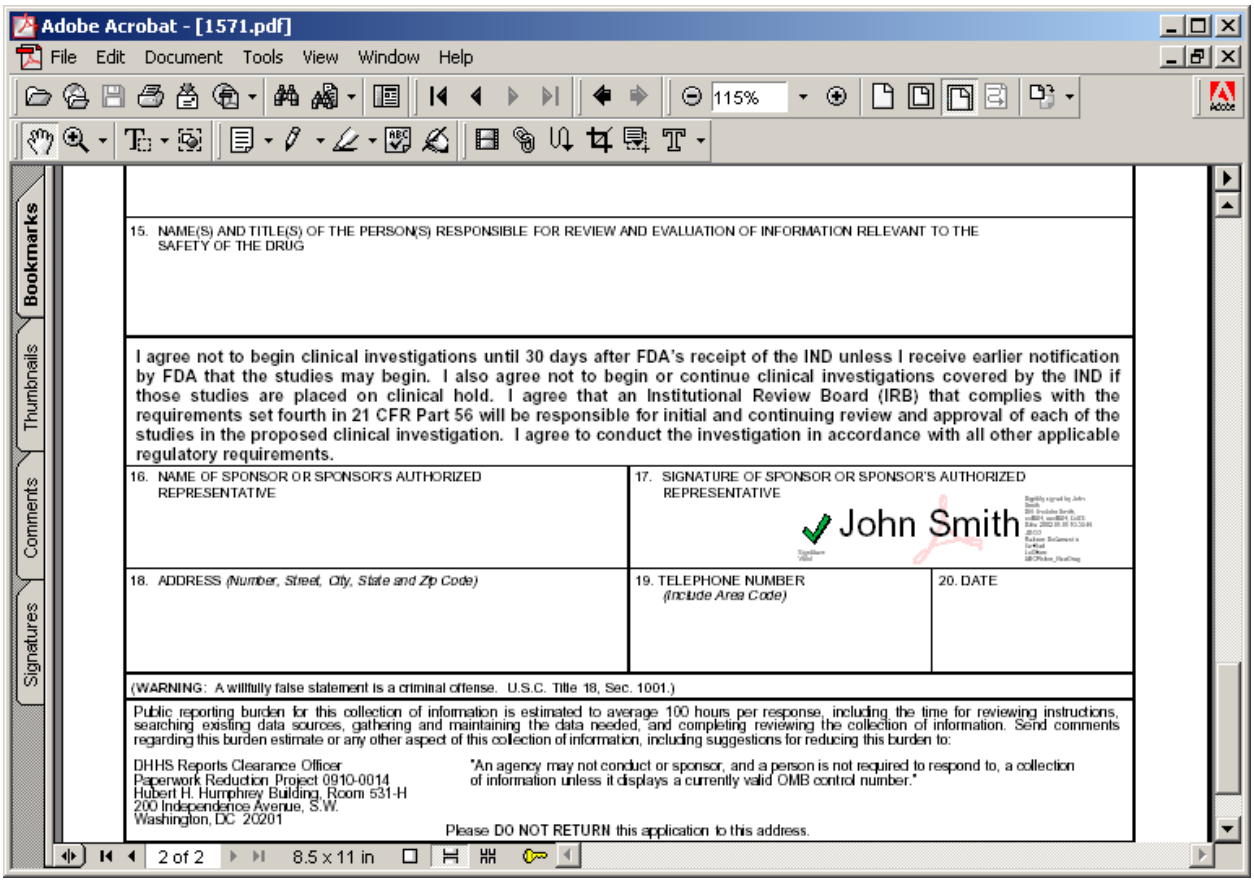


3.2.7 Electronically Sign Form FDA 1571/Form FDA 356H

The following provide the steps to electronically sign the Form FDA 1571/Form FDA 356H standard form.

Electronically sign the Form FDA 1571/Form FDA 356H using the Adobe Acrobat Self-Sign certificate that has been sent to and certified by CBER. When electronically signing the Form FDA 1571/Form FDA 356H, it is required that the document be signed in the **SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE** field. Figure 3.2.7-1 depicts a sample signature appearance of an electronic signature block on a Form FDA 1571.

Figure 3.2.7-1- Signature Appearance



3.2.7.1 Steps to Electronically Sign Form FDA 1571/Form FDA 356H

The following steps are needed to electronically sign the Form FDA 1571\Form FDA 356H Form:

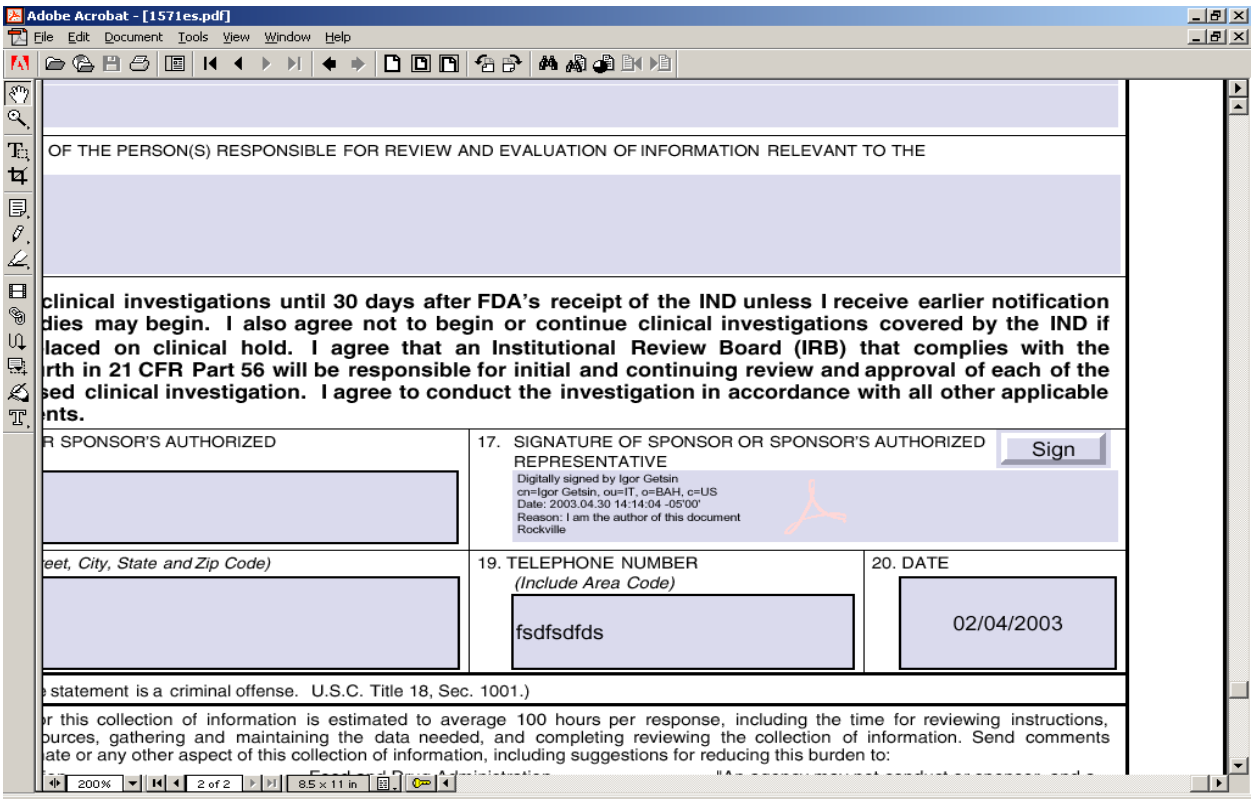
1. Launch Adobe Acrobat.
2. From the File menu bar, open the Form FDA 1571/Form FDA 356H form.
3. From the Tools menu bar, select **Self-Sign Security** followed by **Log In** from the drop down list.
4. Log into the Self-Sign Security with the appropriate profile.
5. From the Tools menu bar, select **Digital Signatures** followed by **Sign Document** from the drop down list. The Digital Signature – Alert screen will appear.
6. Follow the instructions within the Digital Signature – Alert screen.

7. Electronically sign the Form FDA 1571/ Form FDA 356H in the **SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE** field. Close the document. The form should NOT be modified in any manner after it has been signed. Doing so will invalidate the signature and cause the amendment to be rejected.

3.2.8 Electronically Sign Form FDA 1571es

Electronically sign the Form FDA 1571es using the Adobe Acrobat Self-Sign certificate that has been sent to and certified by CBER. When electronically signing the Form FDA 1571es, it is required that the document be signed in the **SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE** field. Figure 3.2.8-1 depicts a sample signature appearance of an electronic signature block on a Form FDA 1571es.

Figure 3.2.8-1-Form FDA 1571es Signature Appearance



3.2.8.1 Steps to Electronically Sign Form FDA 1571es

1. Launch Adobe Acrobat.
2. From the File menu bar, open the Form FDA 1571es form.
3. Enter the required data into the Form FDA 1571es form and select the **Save Data** button.

4. Electronically sign the Form FDA 1571es form by selecting the **Sign** button in the SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESANTIVE field.

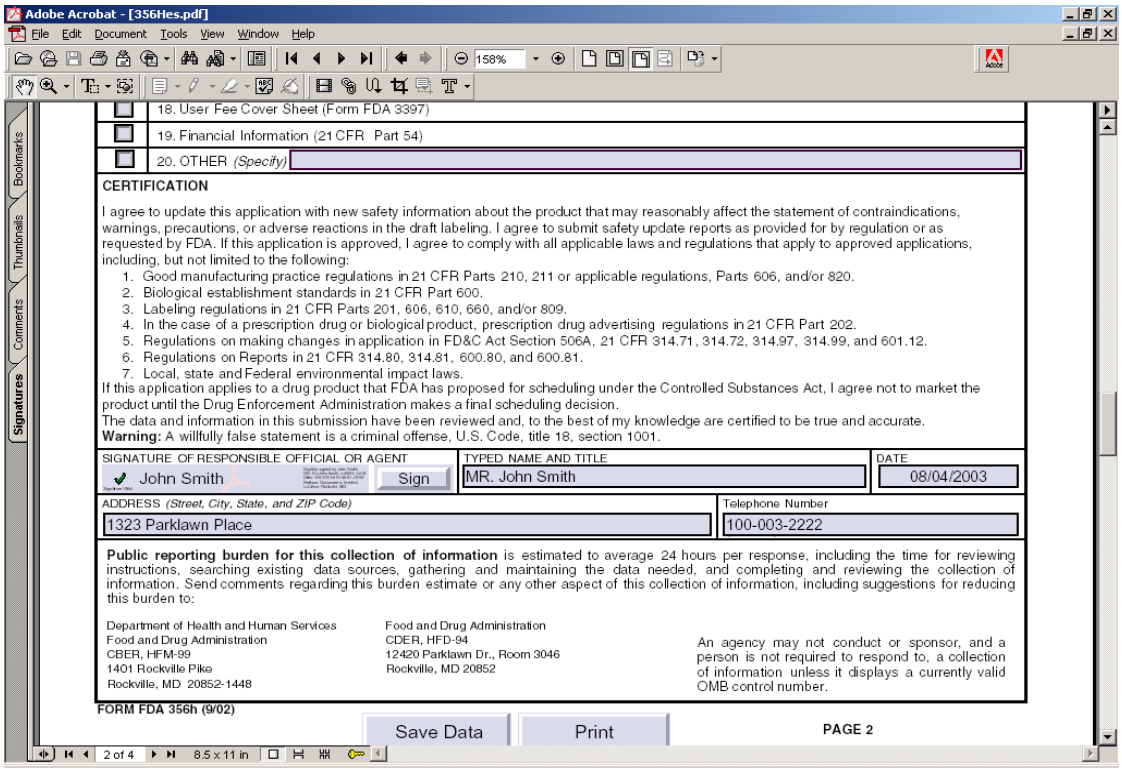
5. Click within the SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESANTIVE field and follow the instructions within the **Adobe Self-Sign Security** screen.

6. Close the document once the Form FDA 1571es is digitally signed. The Form FDA 1571es should NOT be modified in any manner after it has been signed. Doing so will invalidate the signature and cause the amendment to be rejected.

3.2.9 Electronically Sign Form FDA 356Hes

Electronically sign the Form FDA 356Hes using the Adobe Acrobat Self-Sign certificate that has been sent to and certified by CBER. When electronically signing the Form FDA 356Hes, it is required that the document be signed in the **SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT** field. Figure 3.2.9-1 depicts a sample signature appearance of an electronic signature block on a Form FDA 356Hes.

Figure 3.2.9-1-Form FDA 356Hes Signature Appearance



3.2.9.1 Steps to Electronically Sign Form FDA 356Hes

1. Launch Adobe Acrobat.
2. From the File menu bar, open the Form FDA 356Hes form.
3. Enter the required data into the Form FDA 356Hes form and select the **Save Data** button..
4. Electronically sign the Form FDA 356Hes form by selecting the **Sign** button in the SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT field.
5. Click within the SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT field and follow the instructions within the **Adobe Self-Sign Security** screen.
6. Close the document once the Form FDA 356Hes is digitally signed. The Form FDA 356Hes should NOT be modified in any manner after it has been signed. Doing so will invalidate the signature and cause the amendment to be rejected.

3.2.10 Create Email Message

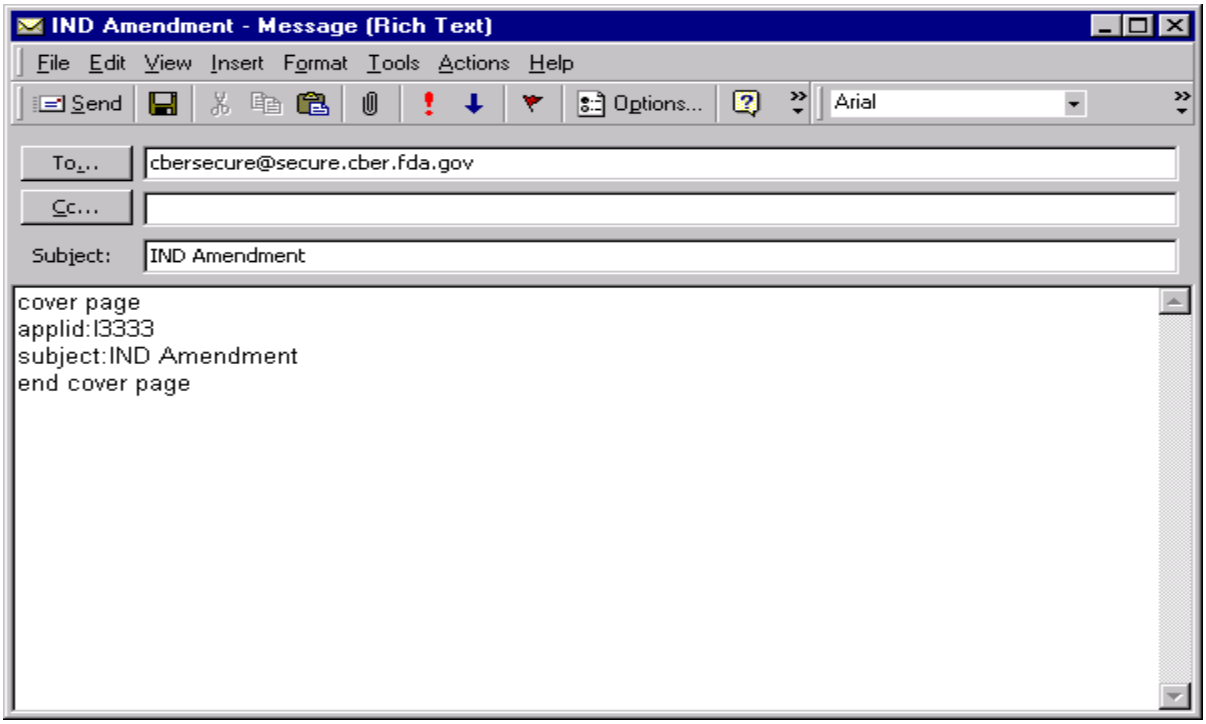
Open and create a new email message. ESM will accept messages from any of the major email applications that are S/MIME compliant (i.e., Netscape, Outlook, Lotus). In the **TO:** field of the message body, type the following email address: **cbersecure@secure.cber.fda.gov**.

Note: When using the Form FDA 1571es/Form 356Hes electronic forms, a cover page is not required. A cover page is only required when using the Form FDA 1571/Form FDA 356H standard form.

3.2.10.1 Cover Page Format using Standard Form

The cover page header must be the first text entered in the message body when using standard the Form FDA 1571/Form FDA 356H Form. The first line of the cover page header should read '**cover page**'. The second line should have the required attribute '**applid**' and on the third line the attribute '**subject**'. The applid is either the IND Number for the IND submission or the STN for the BLA original submission. The applid attribute must contain the IND number or BLA STN of the original submission preceded by an 'I' (e.g. I3333) for an IND amendment or 'B' (e.g. B222222/0) for BLA amendment. The subject line should contain information about the amendment (e.g. IND Amendment). The last line of the cover page header should read 'end cover page'. If the following cover page format is not followed the email message will be sent to the CBER Exchange Server Trouble Folder. Figure 3.2.10.1-1 depicts a sample cover page for an IND amendment.

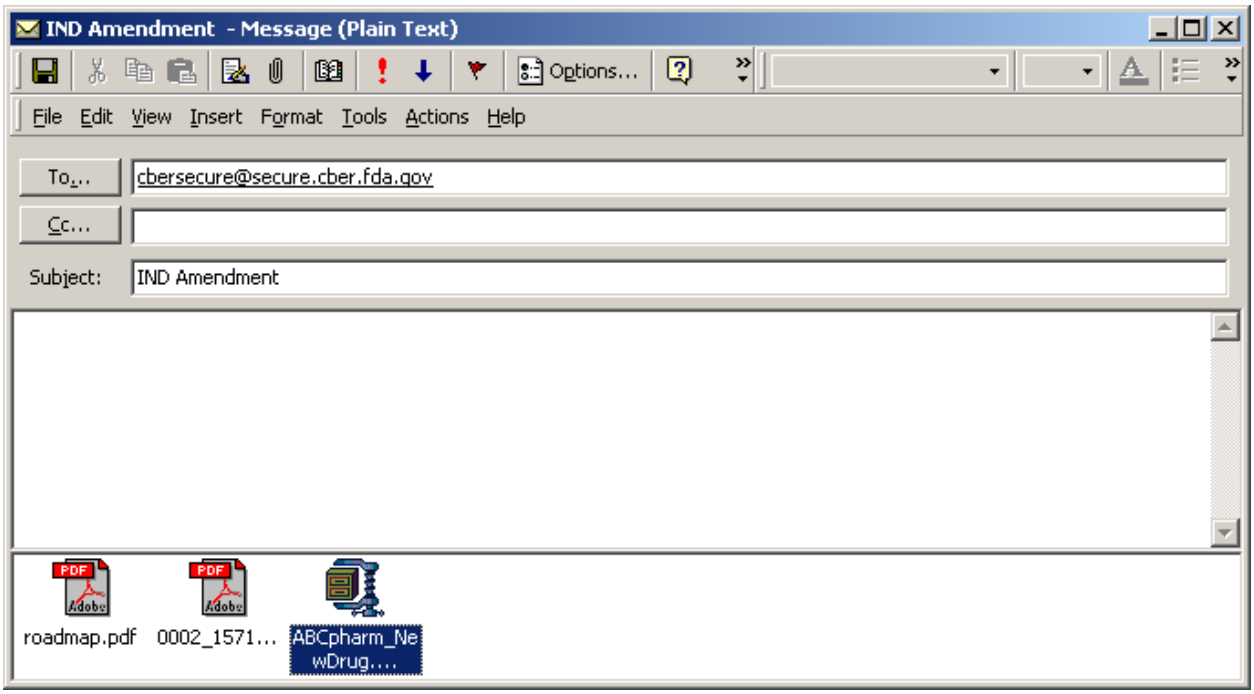
Figure 3.2.10-1-Sample Cover Page



3.2.11 Attach IND/BLA Amendment

Attach the amendment's Zip file, Form FDA 1571(es)/Form FDA 356H(es) Form, and the roadmap.pdf file to the email message. Figure 3.2.10-1 depicts a sample IND amendment message with required attached files.

Figure 3.2.11-1-Sample Message with Required Attachments



3.2.12 Encrypt and Send Email Message

The encryption process varies depending on the technology used to send and receive secure messages. The encryption process is as follows:

- VPN to VPN the MMS server will automatically encrypt the email message.
- S/MIME to VPN, the message must be encrypted with the sender's public key.

Note: Industry participants that are registered with CBER may send secure email messages to the **cbersecure@secure.cber.fda.gov** mailbox. Otherwise, if the secure message is sent to another address, it will not be successfully received by CBER.

4 SECURE MESSAGING CONTACTS

The following names are the points of contact within CBER.

Area	Name	Organization	Telephone
Technical	Joe Montgomery	CBER EDR/ESM Project Officer	301-827-1332
	Dan Offringa	CBER Secure Messaging Administrator	301-827-1385
	Greg Dyer	Contractor ESM Administrator	240-314-5542
Functional/Regulatory	Michael Fauntleroy	CBER Director of Electronic Submissions	301-827-5132