CVM ESUBMITTER USER GUIDE

CVM ESUBMITTER SIGNING PACKAGING

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I. INTRODUCTION

CVM requires that the firm (i.e., sponsor) provide, within their submission, the name and the digital signature of the individual who is authorized to make legal representation on behalf of the firm before the agency (i.e., the responsible official) (see 21 CFR §514.1(a)). Once the submission is received, the digital signature captured on the administrative cover sheet is validated against authorized stakeholders within the CVM Electronic Submission System (ESS).

II. OVERVIEW OF SIGNING OPTIONS

After completing the data entry of the submission in CVM eSubmitter you are ready to sign and package the files into a zip format for transmission to CVM. CVM has implemented two options regarding how Responsible Official signatures are applied by industry stakeholders to the Administrative Cover Sheet.

A. Option 1 – Sign During Packaging

Responsible Official digitally signs the submission within eSubmitter during the submission packaging step.

During the submission packing step, the responsible official provides their digital signature and eSubmitter generates a signed Administrative Cover Sheet and automatically includes it within the submission package. This approach requires the responsible official perform the packaging step.

Note: This is the original approach that has been in place since the release of CVM eSubmitter.

B. Option 2 – Externally Sign

Responsible Official digitally signs the Administrative Cover Sheet externally from eSubmitter and attaches it during the submission packaging step.

The Administrative Cover Sheet is output from eSubmitter and provided to the responsible official to digitally sign externally from the eSubmitter application. Once signed, the cover sheet is attached during the eSubmitter packaging step. Using this approach, the responsible official does not have to be present during the submission packaging process.

The firm contact information and key identifying details related to the submission must be available within the submission prior to outputting the cover sheet for external signing, and the key information, as captured at the time of the output, must remain unchanged. Otherwise, the cover sheet will need to be output and signed again, or it will be rejected during the packaging step.

III. CREATING THE ADMINISTRATIVE COVER SHEET

A. Output Menu

To generate an Administrative Cover Sheet, access the "Output" option from the menu bar and select "Administrative Cover Sheet".

Outline	Package Submission <u>Files</u>	
Report Type: ONA	Structured Product Labeling	
Submission Name: Beta	Administrative Cover Sheet	
	Submission Data Report	
	Missing Data/Validation Issues Report	
<u>File Edit View Table</u>	Output Tools Help	_
and the second		

A confirmation dialog box will be presented that describes the two options for applying digital signatures to eSubmitter submissions. Select "Continue" to generate the Administrative Cover Sheet.

Administrative Cover Sheet Output Dialog	×
Administrative Cover Sheet Output - Confirmation	
By outputting the Administrative Cover Sheet, you are planning to digitally sign the submission using option 2, as described below. Do you wish to continue?	
CVM requires that the firm (i.e., sponsor) provide within their submission the digital signature of the individual who is authorized to make legal representation on behalf of the firm before the agency (i.e., the responsible official) (see 21 CFR §514.1(a)).	
The submission "Administrative Cover Sheet" is the document digitally signed by the responsible official for inclusion in the submission package. There are two approaches to digitally signing the Administrative Cover Sheet:	
• Option 1: Responsible Official digitally signs the submission within eSubmitter during Submission Packaging	
• Option 2: Responsible Official digitally signs the Administrative Cover Sheet externally from eSubmitter and it is attached during Submission Packaging	
Option 1: Responsible Official digitally signs the submission within eSubmitter during Submission Packaging During the submission packaging step, the authorized representative provides their digital signature and eSubmitter generates a signed cover sheet and automatically includes it within the submission package. This approach requires the authorized representative perform the packaging step.	
Option 2: Responsible Official digitally signs the Administrative Cover Sheet externally from eSubmitter and it is attached during Submission Packaging	
The Administrative Cover Sheet is output from eSubmitter and provided to the responsible official to digitally sign externally from the eSubmitter application. Once signed, the cover sheet is attached during the eSubmitter packaging step. Using this approach, the responsible official does not have to be present during submission packaging.	
However, there are constraints to this process. The Firm contact information and key identifying details related to the submission must be available within the submission prior to outputting the cover sheet for external signing, and the key information (i.e., as captured at the time the administrative cover sheet was output) must remain unchanged. Otherwise, the cover sheet will need to be output and signed again, or it will be rejected during packaging.	
View Guide Book on Digital Signing Continue Continue	

B. Required Data Elements

There are critical data elements that are required to generate a complete Administrative Cover Sheet. Depending on the type of submission you are creating, there are unique required data elements. Table 1 below indicates which data elements are required by submission type:

ONADE Required Elements	ONADE ABCT	ONADE Communication – Informal	ONADE Communication – Early Response
		Communication	Letter
Document Type	Document Type	Type of Communication	Type of Communication
Currently Established File or Application	Currently Established File or Application	Document Type	Document Type
Document Number	Document Number	Document Number	Document Number
Submission Type	Submission Type	Firm Name	Firm Name
Submission Classification Code	Submission Classification Code	Review Division	Review Division
Review Division	Review Division	Responsible Official	Purpose of Submission
Purpose of	Purpose of	Purpose of	-
Submission	Submission	Submission	
Firm Information	File/Application Owner	-	-
Are you a U.S. Company	Responsible Official or U.S. Agent/U.S. Employee	-	-
Responsible Official or U.S. Agent/U.S. Employee	Submitter Information	-	-
Submitter Information	-	-	-

Table 1: Required Data Ele	ements by Type	of Submission
----------------------------	----------------	---------------

Note: The Purpose of Submission data element is created uniquely for most submissions. Contact CVM if you have questions about a specific submission type.

If any of *these* critical elements are missing, an error message will be generated informing you of the required elements that are missing.

Th be	ne following information must be completed before the Administrative Cover Sheet can e output:
	Document Type
	 Is this submission for a currently established file or application? (under Document Information)
	Submission Type
	 Submission Classification Code
	Review Division
	 Purpose of Submission (Note: The purpose of submission is submission type specific, contact CVM if you need details on how the purpose of submission is generated for a specific submission type)
	Firm Information
	 Are you a U.S. Company? (under Firm Information)
	 Responsible Official or U.S. Agent/U.S. Employee Information
	 Submitter Information

C. File Location

Once the Administrative Cover Sheet is generated successfully, a dialog box will present the user with a confirmation as well as a link directly to the document. The file will always be saved to the location designated for the Output folder in the application preferences.

ie Adri	inistrative Cover Sheet was generated for the open submission.
You I allow extern subm	ave successfully generated an Administrative Cover Sheet for the open submission. This for the submission cover sheet to be digitally signed by the firm's authorized representative ally from the eSubmitter application. The signed cover sheet can then be attached by the ission preparer during the eSubmitter packaging step.
By di that t (see	pitally signing externally from the application, the signer of the submission is acknowledging ney are authorized to make legal representation on behalf of the firm before the agency. 21 CFR §514.1(a)).
The f	le name of the generated Administrative Cover Sheet is:
Beta-	DS-49 CoverSheet.pdf
Click	the link above to open and view the generated Administrative Cover Sheet file.
The / desig	Administrative Cover Sheet file is located within the application 'Output' working folder, as nted within the application preferences (i.e., C:\Users\Public\CVM_eSubmitter_Home\output\)

IV. PACKAGING

Select the Package Files for Submission option of the Output menu of the menu bar or click the Package button on the tool bar. If data is missing, a warning message will be displayed requiring you to correct any issues before proceeding. If the submission has all

the required data, the Packaging Files for Submission dialog is displayed that will lead you through a series of steps to complete the packaging process.

A. Step 1: Overview and Package File Information

- 1. **Specify the Package File Name:** The Package File Name (.zip) text box identifies the name of the zip file to be generated for the submission. CVM eSubmitter automatically defaults the name of the zip file to match the name used for the submission data file.
- 2. **Specify the Package Output Location:** The Package Output Location identifies the file folder where the zip file is generated. To change the location, click the file folder icon and navigate to the new location.

Make note of the package file name and location so it will be easier to locate the package file when it comes time to transmit the file to CVM. Once completed, click the Next button to proceed to the file attachment verification step.

Packag	ing Files Dialog	
	Pa	ckaging Submission Files
	Step 1 Overview and Package File	Information
Wha	t Submission Packaging Entails	
Afte subr Dur com gene For	r completing the submission and verifi mission. " <u>Click</u> " the hint option (i.e. li ing the packaging process, you will v plete submission file. The packaging rated by CVM eSubmitter should not detailed instructions on packaging you	ying there is no missing information you are ready to package the files for <u>ght bulb icon</u>) for additional information on each step of the process. erify all file attachments, provide your digital signature, and produce a process will result in a single ZIP file per submission. The ZIP file be altered in any way prior to transmitting to CVM. ar submission files, see the <u>CVM eSubmitter Packaging Quick Guide</u> .
Gene	eral Submission Package Information	<u> </u>
•	Package File Name	Sample_Submission
ŀ	Package Output Location	C:\DevData\eSub_Home\package\
<u>C</u>	ancel	Previous <u>N</u> ext Done

B. Step 2: File Attachment Verification

This screen lists all file attachments used in the submission. In addition, a check is performed to ensure all files contained within the submission are accessible for inclusion in the final submission package. Review all files listed and their file size. If all are correct, click the Next button to continue to the packaging step. Otherwise, click the Cancel button to exit the packaging process and return to the submission to correct any issues.

	Packaging Submission F	ïles	
Step 2 File Attachme	nt Verification (may not be relevant for all Subn	nission types)	
File Attachment List			
File Name	File Tille	Question Count	Filt
Attachment1.pdf	Supporting Information	1	10/13/2004 0

C. Step 3 Option 1: Signing During Packaging

This section contains the steps for reviewing the submission report, applying a digital signature, and producing the submission package. Follow the instructions below:

- 1. **Review Submission Report**: Click the **Review Submission Report** button to open the submission report. Review and ensure the submission report is accurate and then close the report and return to the packaging dialog.
- 2. **Select Digital Signing Approach**: Select "Provide Digital Signature" from the drop-down list in the "Select Digital Signing Approach" question.
- 3. Attach Digital Signature: Click the folder button, locate the signature file using the file browser dialog, and select the appropriate digital signature file (.pfx). Once selected, CVM eSubmitter will maintain the file name and location for future packaging processes.
- 4. **Provide Digital Signature Password**: Type in the password for the digital signature attached. The entry of the password is required for each packaging attempt, but it will not be maintained by CVM eSubmitter for future packaging processes.
- 5. **Package and Sign Submission**: Click the **Package & Sign Submission Files** button to initiate the generation of the submission package (zip file).

ckaging Files Dialog	
Pa	ackaging Submission Files
Step 3 Digital Signature and Package	• Creation
Review Submission Report	
Submission Report	Open Submission Report
Digitally Sign Submission	
Select Digital Signing Approach	Provide Digital Signature 🗸
Attach Signed Cover Sheet	6 & 3
Attach Digital Signature	C:\CVM_eApps\CVM_eSubmitter_TestJohnSmith.pfx
Digital Signature Password	
Produce Submission Package	9
After completing all steps to this point, package file.	click the "Package & Sign Submission Files" button below to begin creating the
Package & Sign Submission Files	0%
Package & Sign Submission Files	0%
Cancel	Previous Next Done

After initiating the package generation process, CVM eSubmitter will verify that the password for the digital signature is valid. An error message will be displayed if the password is invalid, and control will return to the packaging dialog to allow for the password to be corrected.

After successful verification of the password, a Certification Agreement dialog is displayed. You must click the **Accept** button for the certification agreement before CVM eSubmitter will generate the final submission package file.

🔛 Certi	fication Agreement Dialog
2	Please read the following certification message regarding the responsibilities of the submitter with respect to this submission type. Choose 'Accept' if you agree to the terms and conditions specified and wish to continue to package the submission.
I certif	ly that:
	 I have personally reviewed this submission (or received assurances from qualified personnel) and determined that this submission and all supporting data are true, accurate, and complete to the best of my knowledge and belief, For any information submitted by reference in this submission, I/we have submitted to FDA documentation granting the right of reference and I/we have confirmed to the best of our ability that the information contained in the referenced file is true, accurate, and complete, No services of any person debarred under section 306(a) of the Federal Food, Drug, and Cosmetic Act have been used in any capacity related to this submission, and I am aware there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing and willful violations (18 U.S.C. § 1001).
Furthe	r, I agree:
	 To comply with all applicable statutes and regulations governing the investigational use and approval of new animal drugs.
<u>C</u> an	cel Accept

Once accepted, all files to be included within the submission package will be collected and the package file created. A "Complete" message is displayed if the package was created successfully. Otherwise, a "Failed" message is displayed. Click the **Next** button to continue to the transmission instructions step.

s	tep 3 Digital Signature and Pa	ackage Creation
Digita	ally Sign Submission	
•	Submission Report	Review Submission Report
•	Attach Digital Signature 🔹 🔍	C:\eSubSource\gov/fda\cdrh\apps\sub\deploy\JohnSmith
•	Digital Signature Password 🥥	******
	After completing all steps to this the package file.	point, click the "Package & Sign Submission Files" button below to begin creating
	ckage & Sign Submission Files	Complete.
Pa	ickage & Sign Submission riles	
Pa	ickaye a siyii submission mes	
Pa	ichage a sign submission mes	

D. Step 3 Option 2: Attaching Signed Administrative Cover Sheet

If you have a signed Administrative Cover Sheet that you wish to attach, select "Attach Signed Administrative Cover Sheet" from the drop-down list in the "Select Digital Signing Approach" question.

- 1. **Review Submission Report**: Click the **Review Submission Report** button to open the submission report. Review and ensure the submission report is accurate and then close the report and return to the packaging dialog.
- 2. **Select Digital Signing Approach**: Select "Attach Signed Administrative Cover Sheet" from the drop-down list in the "Select Digital Signing Approach" question.
- 3. Attach Signed Cover Sheet: Click the folder button, locate the signed Administrative Cover Sheet file using the file browser dialog, and select the appropriate file (.pdf).
- 4. **Package and Sign Submission**: Click the **Package & Sign Submission Files** button to initiate the generation of the submission package (zip file).

	P	ackaging Submission Files			
S	tep 3 Digital Signature and Packag	e Creation			
Revie	ew Submission Report				
•	Submission Report	Open Submission Report			
Digita	ally Sign Submission		_		9
•	Select Digital Signing Approach	Attach Signed Administrative Cover Sheet			-
•	Attach Signed Cover Sheet	C:\Users\Public\CVM_eSubmitter_Home\output\2020-9-	0	2	0
•	Attach Digital Signature		C	Q	ি
•	Digital Signature Password				
Prod	uce Submission Package				~
	After completing all steps to this point, package file.	click the "Package & Sign Submission Files" button below to	begin cr	eating	the
Pa	ckage & Sign Submission Files	0%			

- 5. **Validation**: Once the **Package and Sign the Submission Files** button is selected, validation will be performed on the attached signed Administrative Cover Sheet to ensure that it is the correct file.
 - a. **Valid Cover Sheet**: eSubmitter validates that the attached file is an eSubmitter generated file. You will get the following error message if another PDF file is attached.

an error occurred when validating the attached cover sheet
The cover sheet file does not match the structure of an eSubmitter generated cover sheet. To attach a signed cover sheet during packaging, the cover sheet must have first been generated by eSubmitter during the preparation of the submission.

b. **Submission Content**: If any of the submission critical content has been modified after the Administrative Cover Sheet was generated, the following error message will be displayed. The information inside the parenthesis will show you the cover sheet information, followed by current submission information. The corrective action for this error is to modify the submission or generate an updated Administrative Cover Sheet.

erro	r occurred when validating the attached cover sheet
The ype atta gen	cover sheet file does not appear to match the open submission (e.g., document /number, submission type/classification code). Either an incorrect cover sheet was ched or the submission changed significantly since the cover sheet was first erated. You will need to regenerate and sign the new cover sheet before attempting epackage to ensure the cover sheet matches the submission content.
The	following issues were detected:
	Cover sheet Document Type does not match the open submission (I: G).
	Cover sheet Document Number does not match the open submission (111111: 111112).

c. **Signed**: eSubmitter will validate that a digital signature has been applied to the attached Administrative Cover Sheet. The corrective action for this error is to sign the file and reattach.

Administrative Cover Sheet Issues Dialog	
n error occurred when validating the attached cover sheet	
The Administrative Cover Sheet was not signed. Ensure the authorized representative has approved the content of the submission and have them sign the cover sheet before re-attempting to package the submission	
Close	

d. **Completion**: Once all data elements pass validation, the following confirmation dialog box will be presented. This dialog box requests that the user confirm that the signature was applied by the responsible official designated within the submission.

🔛 Acknowledgement Dialog	×
Verify the digital signature within the Administrative Cover Sheet.	
Verify that the digital signature used to sign the Administrative Cover Sheet is representative of the individual who is authorized to make legal representation on behalf of the firm before the agency (i.e., the responsible official) (see 21 CFR §514.1(a)).	
Choose 'Accept' if you agree to acknowledge the signature and continue to package the submission. Administrative Cover Sheet	
Click the link above to open and view the attached Administrative Cover Sheet file.	
Dr. John A. Smith	
Cancel	כ

E. Step 4: Transmit Submission Package

This section contains either the final instructions for transmitting the submission package to CVM (packaging process successful), or an explanation of any issues detected during the process (packaging process failed). Click the Done button after reviewing the message to close the dialog.

kaging Files Dialog			
	Packaging Submission Files		
Step 4 Transmit Subn	ission Package		
Review Submission Package 1	ransmission Instructions		
Submission Package Cre	ated Successfully		
 Locate the submission ZIP file on your computer's hard drive. The file is stored in the Package folder designated within eSubmitter (i.e., the Package location specified under File->Preferences). Follow the instructions provided on the ESG website <u>http://www.fda.gov/esg/</u> to properly transmit the ZIP file via the Gateway. 			
 Locate the submissio designated within eS Follow the instructio file via the Gateway. 	IZIP file on your computer's hard drive. The file is stored in the P bmitter (i.e., the Package location specified under File->Preference s provided on the ESG website <u>http://www.fda.gov/esg/</u> to proper	ackage folder es). ly transmit the ZIP	
 Locate the submission designated within eS Follow the instruction file via the Gateway. 	I ZIP file on your computer's hard drive. The file is stored in the P bmitter (i.e., the Package location specified under File->Preference s provided on the ESG website <u>http://www.fda.gov/esg/</u> to proper	ackage folder es). Iy transmit the ZIP	
 Locate the submissio designated within eS Follow the instructio file via the Gateway. 	I ZIP file on your computer's hard drive. The file is stored in the P bmitter (i.e., the Package location specified under File->Preference s provided on the ESG website <u>http://www.fda.gov/esg/</u> to proper	ackage folder es). ly transmit the ZIP	
 Locate the submissio designated within eS Follow the instructio file via the Gateway. 	I ZIP file on your computer's hard drive. The file is stored in the P bmitter (i.e., the Package location specified under File->Preference s provided on the ESG website <u>http://www.fda.gov/esg/</u> to proper	ackage folder es). ly transmit the ZIP	

F. Large Submission Packages

Very large submissions (i.e., over 1 GB) will be broken up into multiple smaller packaged ZIP files. The individual ZIP files will all use the same file name with an index number attached to the end. The standard manifest file included within each package contains a singular reference that links the files so that they can be processed together once all are received by CVM. The individual package files do not need to be sent or received in index order to be successfully processed.



V. RECOMMENDATIONS TO SPEED UP PACKAGING

There are three standard configurations for setting up eSubmitter within a sponsor environment (see the CVM eSubmitter Preferences Quick Guide for additional details):

- Option 1: User workstation install with each user working completely independent.
- Option 2: User workstation install with users sharing resources on a shared network drive (recommended).
- Option 3: Network install with users sharing the application and resources across a shared drive.

Submission size categories:

- Small: Less than 10 MBs (most of all submissions)
- Medium: 10 MBs to 30 MBs
- Large: 30 MBs to 100 MBs
- Very Large: 100 MBs to several GBs (where submissions over 1 GB are split into multiple submission parts)

The three items that have the largest impact on the time required to package a submission within eSubmitter are:

- Submission size: The cumulative size of all the attached files included within a submission.
- The location of the files included within a submission (i.e., local drive or network share).
- The location of the "packaging" folder where the submission package is generated (i.e., local drive or network share).

Below are tables of packaging sample test results based on common use and setup configurations:

Submission Size	Location of Packaging Folder	Location of Submission Files	Packaging Time (hrs:min:sec)
8 MB	Local Drive	Local Drive	<00:00:01
20 MB	Local Drive	Local Drive	00:00:02
80 MB	Local Drive	Local Drive	00:00:05
620 MB	Local Drive	Local Drive	00:00:40
2500 MB (2.5 GB)	Local Drive	Local Drive	00:02:46

Table 3: Packaging folder on the local drive and submission files on a network share

Submission Size	Location of Packaging Folder	Location of Submission Files	Packaging Time (hrs:min:sec)
8 MB	Local Drive	Network Share	00:00:05
20 MB	Local Drive	Network Share	00:00:07
80 MB	Local Drive	Network Share	00:00:24
620 MB	Local Drive	Network Share	00:03:33
2500 MB (2.5 GB)	Local Drive	Network Share	00:20:31

Table 4: Both packaging folder and submission files located on a network share

Submission Size	Location of Packaging Folder	Location of Submission Files	Packaging Time (hrs:min:sec)
8 MB	Network Share	Network Share	00:13:44
20 MB	Network Share	Network Share	00:32:38
80 MB	Network Share	Network Share	02:15:10
620 MB	Network Share	Network Share	>17 hrs
2500 MB (2.5 GB)	Network Share	Network Share	>70 hrs

As can be seen by the sample testing results, the largest bottleneck in packaging is when the "package" folder is located on a network share. Thus, CVM's recommendation is to set the packaging folder to a local drive and to manually copy the package file to a network share after the packaging process has completed.

VI. VERSION HISTORY

September 29, 2020 – Original version.

May 15, 2024 – Revised to update the document format and include specific validation requirements based on the type of submission being created.

November 15, 2024 – Revised to include recommendations to speed up the packaging process.