CENTER FOR TOBACCO PRODUCTS

Frequently Asked Questions (FAQ) & Common Errors That Delay Submission Processing
Revised: 02/07/2018

The four most common errors that delay submission processing are:

1. **File path is too long**. The filename plus the names of the folder and subfolders where the file is saved must be less than 180 characters in total. The filename should be abbreviated, descriptive, and about 50 characters long. The following example file path is acceptable at 88 characters:

   c:\FredsFiles\SubmissionFolder987\AmendmentFolder5\ToxSection\ToxData\toxdatefile678.xpt
2. **Filename includes special characters**. Use of special characters or foreign language characters that are not recognized by CTP's Windows operating system cause processing to fail.

   a. **/, \, @, %, <, >, “, ?, |, :, ;** *(colon and semicolon)*
   b. non-English characters such as **ä,é,î,ð,ñ,ü,æ**

3. **Non-standard file types**. FDA can accept 28 different file types or file formats but cannot accept all. Files that open with proprietary software can't be opened if FDA does not have the software.

4. **Very large submissions** (>10 Gigabytes) could be processed more easily if:

   a. The Table of Contents is provided in advance
   b. The filename of the main application document is identified in the TOC
   c. The main application document and TOC are submitted on a separate disk or drive

Frequently Asked Questions (FAQ):

<u>As a center within FDA, the Center for Tobacco Products…</u>

1) strives to remain consistent with existing FDA submission models, file formats and standards, and precedence;

2) must leverage, as much as possible and where appropriate, existing FDA guidance on eSubmissions and data standards;

3) will apply lessons and knowledge from existing FDA experience;

4) will continue to pursue eSubmissions models that are geared toward regulatory review, and therefore, the reviewer as the primary user, *i.e., reviewer oriented models;*

5) will continue down the FDA path toward structured, standardized, well organized content;

6) is constrained by FDA IT infrastructure and IT security policies in what and how it can accept electronic documents;

7) is constrained by regulations and statutes for what and how it can recommend and proceed with regard to approaches, standards, and formats*, (Good Guidance Practice (21CFR10.115) and Paperwork Reduction Act (44 U.S.C. 3501 et seq); and*

8) encourages early consultation by persons intending to submit electronically for the first time and in accordance with 21 CFR §11.2(2), various eSubmitter guidance, and meetings with industry.

As a Federal Agency, the FDA Center for Tobacco Products…

1) is constrained by external regulations for what it can accept and recommend with regard to submission standards and formats, *(sustainable, legible, non-proprietary, NARA regulations under 36CFR1236); and*

2) is constrained by federal security standards for the kind of content it can receive and process – such as no embedded files, executables or other active content, *(Federal Information Security Management Act of 2002)*.

Confidentiality and protection of Trade Secret Information:

1) FDA has an over 100-year history of protecting company trade secret information across thousands of companies in its regulation of food, drugs and biologics, devices, blood derived products, and veterinary medicines.

2) Several laws govern the confidentiality of information submitted to FDA, including sections 301(j) and 906(c) of the Act (21 U.S.C. 331(j) and 387f(c)), the Trade Secrets Act (18 U.S.C. 1905), and the Freedom of Information Act (FOIA) (5 U.S.C. 552), as well as FDA regulations. Section 906(c) of the Act (21 U.S.C. 387(f)) prohibits FDA from disclosing any information reported to or otherwise obtained by FDA under section 904 among other provisions, if that information is confidential commercial or trade secret information exempt from disclosure under FOIA Exemption 4 (5 U.S.C. 552(b)(4)).

Relevant Published CTP Guidance and Letters:

1) Guidance for Industry and FDA Staff: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products). Jan 2011.
Encourages electronic submission, lists submission content.

2) Draft Guidance for Industry: Modified Risk Tobacco Product Applications. Mar 2012.
Discusses content and organization, encourages electronic submission, requests an index, pdf format for text documents, OCR text when possible, hypertext linking, discusses the Electronic Submissions Gateway (ESG), Webtrader, and electronic media.

3) CTP eSubmitter Webpage, Quick Guide, User Manual, and templates. Since March 2011.
Requests pdf format for text documents, establishes some level of organization of content, and asks for descriptions of any files an applicant may attach.
<http://www.fda.gov/ForIndustry/FDAeSubmitter>

4) Guidance for Industry: Tobacco Health Document Submission. Apr 2010.
Requests pdf, tiff, eSubmitter, ESG, metadata, OCR, content structure, and asks for descriptions of any files an applicant may attach.
<http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm208913.htm>

5) Guidance- "Meetings with Industry and Investigators on the Research and Development of Tobacco Products". May 2012.
Suggests ESG and eSubmitter, "We encourage you to submit the meeting information package electronically."
<http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm305279.htm>

6) Letter: Request for Submissions Related to Menthol. May 2010.
Asks for PDF, searchable pdf, OCR, SAS, no embedded or bundled files, and the use of hypertext.
<http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM284132.pdf>

7) Letter: Request for Submissions Related to Dissolvable Tobacco Products. June 2011.
Asks for pdf, searchable pdf, OCR, metadata, ASCII and SAS formats.
<http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM284119.pdf>

8) Guidance from other FDA centers can be acknowledged and discussed but should be qualified with a statement that they were created prior to CTP and tobacco industry involvement and cannot be enforced. However, their content reveals the current capabilities and constraints within FDA that CTP is considerate of.

9) "October: The Premarket Tobacco Product Application for Electronic Nicotine Delivery Systems (ENDS): A Public Seminar", Oct 2016. Specifically "Primer on CTP Electronic Submissions" (lists file naming, file types, file organization suggestions):
<https://www.fda.gov/TobaccoProducts/Newsroom/ucm517650.htm>

10) CBER/CDER "PDF Specification", Sep. 2016,
<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>

File formats and data standards

1) Existing data definition standards adopted by other FDA centers are acceptable to CTP (*e.g., SDTM, SEND, MedDRA, HL7, etc.*). These are different and go beyond the physical, technical file formats discussed below.

2) Existing file formats accepted by other FDA centers are acceptable to CTP (*e.g., pdf, csv, txt, SAS Transport (xpt), jpg, html, xml, tiff, rtf, mov, avi).*

3) Source data (raw data) are defined by their scope and values, not their format. Raw data include what was captured through original observations, tests, and instruments, regardless of paper or electronic form. Raw data include all values of data collected - not just those used in final reports. In instances where data may be in a proprietary format, such as from laboratory instrumentation, we recommend that in lieu of submitting the instrument files, you submit data files that have been generated for use in analysis.

4) FDA recommends using SAS open transport file (SAS.xpt) format created with the XPORT engine in SAS Version 6 and later, or by PROC XCOPY in SAS Version 5 format. The following link provides additional information for preparing your SAS.xpt files to meet FDA submission standards: <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

5) A data dictionary should be provided along with the data files that describe each variable and the meaning of any coding.

6) Standards and lessons will be borrowed from past and current eSubmission models (*e.g., eCopy, eSubmitter, RoadMap PDF, eCTD, RPS*).

7) Executable "active content" and embedded files are not acceptable by FDA. *(There may be an exception for promotional materials such as iPhone apps and ads but this must be specially arranged with FDA IT and Security.)*

8) eSubmitter provides a means to assemble an electronic submission to CTP; CTP recommends following the User Guide when using eSubmitter. The guide provides information on how to upload and describe each file separately rather than bundling them into a single zip file. <http://www.fda.gov/ForIndustry/FDAeSubmitter>

9) Use of hyperlinking ("open file" not "open webpage" option) and bookmarking has been a mainstay of FDA electronic submissions since the mid-1990s and has proven valuable to regulatory reviewers in facilitating navigation of a submission.

10) A file path is the string of text that specifies the location of each file and includes folders, subfolders, and the full filename. This path is limited to 255 characters in the Windows OS environment. For

example:

"c:\FredsFiles\SubmissionFolder987\AmendmentFolder5\ToxSection\ToxData\toxdatefile678.xpt"

Both the Applicant and FDA will be operating under the 255-character limit, and the FDA will need 75 characters of this path for loading files into its own subfolders and systems. Therefore, file paths within eSubmissions can be up to 180 characters long and still have enough characters left for FDA processing.

General Approach of the FDA eSubmissions program

1) Content should be logically organized and structured.

2) A comprehensive Table of Contents should be provided that lists and describes all files present in a submission.

3) The use of hyperlinking and bookmarks are encouraged; this facilitates navigation throughout the submission and across files.

4) The appropriate eSubmitter template should be used.

5) Sustainable format (preservable/archivable) for files is required by FDA. FDA is obligated to comply with federal electronic records requirements under 36 CFR 1236.

6) Functional PDF, not just scanned images, are preferred. If scanned images are used, they must be OCR.

7) There should be no embedded files or active content.

8) Use of the Advice Letter and Pre-Application Meeting as a means of communication. Keep in mind the communications will be specific to that application or study.

9) FDA Regulations will not include technical details on format and organization. These details will be outlined in guidance documents and adopted industry standards. Historically, independent standards associations have helped drive eSubmission standards and FDA has participated as a member. FDA can then endorse such standards through FR notice. This model of standards development allows for a more flexible, interactive collaboration between FDA and industry and enables vender or market supported outcomes. This model of standards development has also spurred private market solutions.