ELECTRONIC SUBMISSION
FILE FORMATS AND SPECIFICATIONS

Orientation and Best Practices
for
Data Formats and Submissions
to
The Center for Tobacco Products

For questions regarding this document,
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ELECTRONIC SUBMISSION FILE FORMATS AND SPECIFICATIONS

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ELECTRONIC SUBMISSION FILE FORMATS AND SPECIFICATIONS

INTRODUCTION

This document provides an overview, technical file formats, and data specifications related to submitting electronic files to the Food and Drug Administration's (FDA) Center for Tobacco Products (CTP). This document speaks directly to the mechanisms and data formats associated with electronic submissions (eSubmissions) to CTP. The goals of this document are as follows:

1. Provide specific information and recommendations on data types, file sizes and formatting issues.
2. Explain tools available for creating and transmitting an eSubmission.
3. Help avoid common problems before they occur.
4. Provide answers to common questions regarding eSubmissions.
5. Provide information to technical, administrative, and regulatory persons involved in the creation of eSubmissions or data systems supporting eSubmissions.

AUDIENCE

The target audience for this document has computer and information technology skills and is involved in the creation and transmission of eSubmissions to CTP. Proficiency in data standards, eCommerce, electronic document formats, operating systems, and transmission protocols may be needed to understand fully the information presented in this document.

This document is intended as a reference and provides strategies and considerations for creating and submitting electronic files to CTP. It provides information about file types and eSubmissions technical standards that CTP may reference in various industry guidances and user guides. CTP guidances may cite content within this document, especially where such guidances discuss the submittal of data[1] and eSubmissions so that they can be received, processed, reviewed, and archived by CTP.

For the purposes of this document, the use of the word "supports" means that CTP has processes and technology infrastructure to enable it to receive, process, review, and archive files in the specified formats. Specifications within this document do not supersede guidances, should there be a conflict.

The technical specifications outlined in this document, like FDA guidance documents, do not establish legally enforceable requirements or responsibilities. Any use of the word *should* in these specifications means that something is suggested or recommended but not required.

GENERAL CONSIDERATIONS

The technical specifications outlined in this document are intended to facilitate electronic submissions to CTP. As part of FDA, CTP intends to be consistent where applicable with existing paradigms, file formats, and data standards developed by other FDA Centers. FDA and industry have both benefited from the use of technical standards in the past. Such benefits have included improved reliability, usefulness, accuracy, and assurance that the files within an eSubmission can remain accessible and legible into the future per FDA's records retention schedule. Standards have also facilitated the development of commercially available tools and services that support eSubmission creation and review.

Submissions must be free of security risks such as viruses and files of an active nature. As a first step in limiting security risks, we recommend that submissions be self-contained. Electronic submissions should be in a format that CTP can safely receive, process, review, and archive on the FDA network.

INDEX OF THE FILES WITHIN A SUBMISSION

Because eSubmissions can be complex and, in some cases, very large, providing a list of files included in the eSubmission is important. Such a list may be in the form of a table of contents (TOC) within the narrative body of a submission document or a separate index of files outside of the TOC in a format appropriate for data (e.g., csv of Excel file). This will enable all parties to confirm that all files have been included and received.

A sample TOC for tobacco product submissions modeled after the Electronic Common Technical

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[1] For the purposes of this document, "data" are defined to be static, real values and information contained within a file that do not change or derive upon opening. For example, calculated cells within a spreadsheet using embedded formulas would not be considered data but would instead be considered formulas supporting a defined process or method; however, the numeric values resulting from such formulas would be data in support of a submission to CTP.

Document (eCTD) is presented in Appendix A. The eCTD is an international data standard developed by the International Conference on Harmonization (ICH) for capturing the content and organization of a submission and subscribing to the Common Technical Document (CTD) structure for regulatory applications for a pharmaceutical product.[2]

FDA eSUBMITTER

eSubmitter is software that helps users create an eSubmission to FDA. It is provided by FDA as free, stand-alone software that is downloaded and run on a Windows computer by the person who will be creating the submission. eSubmitter guides the user through the process of entering information and attaching files. It provides screens and functions for capturing data about the applicant, application, and products, and allows the attachment of files. The eSubmitter software and all associated data and files reside locally on the user's computer, allowing users to build their submission packages offline and reuse information from a prior eSubmitter submission file when creating a new submission. eSubmitter does not enable FDA to access or view the submission information on the user's computer.

eSubmitter then packages all data and attachments into zip files that the user can upload to CTP via CTP Portal or ESG/WebTrader. For large submissions, eSubmitter creates multiple zip files constituting a single submission. When applicable, it is helpful for the contact information within the eSubmitter submission to match the contact information within the CTP Portal account.

More information on eSubmitter and how to download it is located on the FDA website at http://www.fda.gov/ForIndustry/FDAeSubmitter/.

Table 01 provides a list of key data elements and their data type characteristics captured by eSubmitter for each submission package.

Table 01: Specifications of Key Data Elements within eSubmitter

Data Element	Type	Data Element	Type
Establishment Name	VARCHAR(50)	Zip Code	INTEGER(5)
FDA Establishment Identified (FEI)	VARCHAR(10)	Zip Code Ext	INTEGER(4)
DUNS Number	VARCHAR(9)	Province/Territory	VARCHAR(100)
Product Name	VARCHAR(120)	Postal Code	VARCHAR(10)
Submission Tracking Number (STN)	VARCHAR(9) *(XX1234567)*	Country Code	VARCHAR(3) *NGA GENC 3*
First Name*	VARCHAR(100)	Phone Area Code	INTEGER(3)
Middle Name	VARCHAR(100)	Phone Exchange	INTEGER(3)
Last Name	VARCHAR(100)	Phone Line Number	INTEGER(4)
Title Name	VARCHAR(4)	Phone Ext	INTEGER(5)
Address Line 1	VARCHAR(100)	Phone International	VARCHAR(20)
Address Line 2	VARCHAR(100)	File Name	VARCHAR(255)
City	VARCHAR(100)	File Title	VARCHAR(400)
State Code	VARCHAR(5)	Dates (of any kind)	DATE

* Note: First name, last name, and the other contact information fields are captured separately for each contact type (e.g., U.S. agent, owner, authorized representative).

SECURITY AND ENCRYPTION

The Federal Information Security Modernization Act of 2014 (44 U.S.C. § 3551–58) requires FDA to ensure the integrity, confidentiality, and availability of its electronic records. In addition, sections 301(j) and 906(c) of the FD&C Act require that FDA ensures the confidentiality of trade secrets and certain other information provided by its regulated parties. Toward this end, electronic files received by FDA must be free of computer viruses and spyware that could introduce vulnerabilities and compromise record integrity as well as impede FDA's ability to process the records. Due to the security risk, FDA cannot access submission files stored in external sources (e.g., on third-party, file-storage platforms such as Dropbox). FDA scans all media and files it receives for security risks. Among other concerns associated with files that are found to contain security risks, such files could result in difficulty receiving additional files from that submitter in the future. Including a statement within each submission confirming that it is virus-free, along with a description of the scanning software (name, version, and company) used, can help avoid such issues.

[2] http://estri.ich.org/eCTD/

Security settings, encryption, links to external storage spaces, and password protection can render files (e.g., PDFs) inaccessible or unmanageable for review, storage, and retrieval by FDA. Such settings can also render content difficult to search, copy, and print. FDA forms in PDF format, available from the FDA website, may contain security settings established by FDA that prevent the end user from changing the essential elements of the form; however, the security settings on these FDA forms do not impede their use, search, and storage. Additional file security features added by an end user can impede the receipt, review, and archiving of an eSubmission by FDA.

For reasons of information technology security and Federal records and redaction requirements, FDA generally cannot receive and process files that are of an active or dynamic nature, such as files that contain macros (active files), executables (.exe), command files (.com), Visual Basic scripts, and JavaScript. However, accommodations may be made in advance of receipt when such files, for example promotional materials that include smartphone apps, are required for regulatory review.

FILE FORMAT TYPES

CTP is able to receive, process, review, and archive many commonly used file types, also referred to as file formats. This helps ensure that an appropriate file format is available for each of the different kinds of content an applicant may want to include in its eSubmission. Table 02 lists formats most appropriate for each kind of content.

Table 02: Supported File Format List with Descriptions

File Format Description	Filename Extension(s)	Appropriate Uses
ASCII Text	TXT	Supporting data and data tables, extracted text from documents, programming code and procedures
Bitmap Graphics	BMP	Photographs, graphs, charts, exemplar images of labeling and promotional materials
Cascading Style Sheets	CSS	Documents, consumer web page content
Chemical Markup Language	CML	Open standard using XML format for molecular and chemical data
Comma Separated Values	CSV	Supporting data and data tables with delimiters, table of contents and small data sets
Data Type Definition	DTD	Definition of data submitted within XML datasets; for study data as well as electronic submission standards for content, e.g., eCTD backbone, SPL
Excel	XLS, XLSX	Alternative file format for data and formulas
Extensible Markup Language	XML	Study data, table of contents, electronic submission standards for content, e.g., eCTD backbone, SPL; define files for data submitted in SEND, SDTM, or ADaM format
Extensible Stylesheet Language	XSL	Layout, formatting of content for display that has been provided in XML file format
GIS Data format	KML*	Geographic Information System standard for geographic location data in XML format
Graphic Interchange Format (CompuServe)	GIF	Photographs, graphs, charts, exemplar images of labeling and promotional materials
Hypertext Markup Language	HTM, HTML	Documents, consumer web page content
JPEG Image	JPG, JPEG	Photographs, graphs, charts, exemplar images of labeling and promotional materials
Molecular Design Limited MOL file	MOL	Information about a molecule, e.g., atoms, bonds, connectivity and coordinates
Moving Picture Experts Group	MPG, MPEG	Video , molecular rotation
MPEG Audio Stream, Layer III	MP3	Audio

MPEG-4 Video	MP4	Video
Portable Document Format	PDF	Documents, formal reports containing narrative text and images
Portable Network Graphics	PNG	Photographs, graphs, charts, exemplar images of labeling and promotional materials
QuickTime movie file	MOV	Video , molecular rotation
SAS Transport	XPT, XPORT (not CPORT)	Data and data tables and SAS program code (see more information below in Analysis Datasets section)
Scalable Vector Graphics	SVG	Images
Structured Data File	SDF	For the chemical data structure, wraps MDL
Windows Media File	WMV	Video
Windows Waveform Sound	WAV	Audio
XML Schema	XSD	Layout, formatting of content provided in XML format

FILE and FOLDER NAMING CONVENTION

A submission may contain hundreds of individual files; therefore, clear and consistent naming of files and folders (directories) is helpful for both industry and the FDA reviewers. The submission file that contains the main TOC is called main since it is the starting or entry point to begin navigation and review. This main submission file may also contain the bulk of the narrative. Clearly naming this file as "Main-TOC.pdf" will help ensure that all parties know which file to begin with and navigate from.

The use of certain characters can cause problems in processing submissions and cross-referencing files. Characters to avoid include spaces and special characters such as **/**, ****, **@**, **%**, **;** , non-English letters, and other non-alphanumeric symbols. The FDA ESG and the ICH eCTD specification[3] provide additional information on use of special characters in file names.

Descriptive and unique filenames and folders across the entire eSubmission aid in locating information and communicating with the submitter about specific files. Unique file names also help prevent the overwriting of files upon upload into review systems that may use different folder or directory structures.

Concise, abbreviated filenames of less than 50 characters followed by the file extension indicating file format is usually sufficient to describe and distinguish files. 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 environment and on the Internet; thus, both the submitter and FDA must operate under this constraint. However, FDA uses 75 characters of this path length when loading files into its own subfolders and systems. Therefore, submitters can use up to 180 characters in naming file paths within eSubmissions.

RAW and ANALYSIS DATASETS

Raw data as well as data organized and defined for use in analysis by statistical tools (analysis datasets) are commonly part of submissions to CTP. The SAS Institute's SAS transport file (.XPT) format has been a recommended format by FDA since 2004.[4] SAS transport is an open format and may be created with the XPORT engine in SAS Version 6 and later, or by using PROC XPORT in SAS Version 5 format. XPORT is an open format, while CPORT is a proprietary format that cannot be processed or archived by the FDA. The following link provides additional information for preparing XPT files to meet FDA submission standards:
<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

A comma-separated values (CSV) file is an alternative to SAS transport files and is a text file where data are separated by a comma delimiter with carriage returns at the end of each row. If other delimiters are used to separate values, it is important to identify the delimiter in the body of the submission or in the file index so that the data can be properly parsed and utilized. It is common for the first row in a CSV file to contain column headers naming the data domain of each data column.

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[3] FDA ESG Submission Process: High Level Technical Validation, https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm577609.htm

[4] FDA's Study Data Specifications version 2.0, the original version 1.0, originally published in 2004, https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm312964.pdf

FILE SIZE AND SUBMISSION SIZE

File size recommendations across FDA guidances can vary because of technical limitations inherent in different file types, modes of transmission, a user's computer, and a Center's own experience with problems processing and reviewing regulatory applications. For example, Centers have found it difficult to open PDF file sizes greater than 500MB, resulting in the need to resubmit a portion of the submission. Individual datasets and files containing large images can exceed 500MB, but problems can occur beyond 2GB.

Because CTP Portal and FDA ESG only accept submissions that were created using eSubmitter, and because eSubmitter splits a submission into multiple smaller files to ensure that they can be transmitted, size limitations are largely determined by eSubmitter.

eSubmitter has been validated to create submissions of up to 150GB, in which each file within the submission does not exceed 5GB. Such a submission, for example, may take several hours for eSubmitter to package and will result in multiple zip files, each usually under 2GB, where the combined size of all zip files equals 150GB. The total submission size possible can be larger or smaller depending upon available memory and hard drive space of a user's computer.[5] Also, performance is improved when all files to be attached reside locally on the PC running the eSubmitter software.

The resulting eSubmitter submission, which may include multiple zip files, can then be uploaded through CTP Portal or FDA ESG. CTP Portal will upload them one by one until all files have been uploaded. Should a problem or timeout occur during the upload process, CTP Portal will continue the upload where it last left off. Upon CTP's receipt, the multiple zip files will be uncompressed and restored into a single submission. Upload speed will vary depending upon local Internet service provider speed.

FONTS

The selection of fonts to be used within an eSubmission is an important consideration, as font selection can help ensure or degrade content integrity and legibility. The FDA eSubmissions program has historically supported a variety of common font families that are available across computer operating systems (see Table 03). Word processors and document-viewing software can automatically substitute fonts to display textual content if the specified font is unavailable on the user's computer. Font substitution can affect a document's appearance and formatting, and in some cases, can appear to alter the information contained within a document. This means that, in such instances, FDA reviewers reading a document submitted in standard PDF format may see content that is not exactly as the applicant intended or even appears different than when previously viewed.

If non-standard fonts are used, embedding the fonts can ensure that content is displayed correctly, as intended by the applicant. When fonts are embedded, it is helpful to include all characters defining the font set, not only a subset of the fonts used in the document. Some listed fonts may not be available within SAS Unix; however, selecting Helvetica for PDF output of graphs will help ensure the fewest problems, as most viewers will substitute with Arial, which is within the same sans serif family.

Font sizes of at least 9 point ensure legibility. The Times New Roman and Calibri font families, 12 point, are most common for narrative content. The Arial and Calibri font families provide optimal legibility on-screen and in print, consume less ink to print, and facilitate more accurate optical character recognition (OCR) when pages require scanning. When choosing a font size for tabular information, considerations of font size may be offset by the advantages of presenting the table across as few pages as possible to facilitate data comparisons. Font sizes of 9 to 10 point are common for tables and data sets when data must be presented within the narrative body of a submission in PDF format. Small sizes are commonly used for footnotes. Font size does not pertain to data file formats such as csv, txt, xml, and datasets.

Resizing scanned images and scanned text can shrink and deform the content, thus reducing legibility and printability. Black and high-contrast colors against an opposing background facilitates legibility. Light colors display poorly against light backgrounds and print poorly on grayscale printers.

[5] The submission size that can be created using eSubmitter can vary. The 150GB submission was created on a computer running Windows 10 with 16GB RAM and at least 200GB free hard drive space and required 3 hours to package. All other software applications were closed during packaging. Time and capability will vary depending on available memory and CPU speed.

Table 03: List of FDA Standard Fonts

Font type	**Font Family**
Serif	Times New Roman
	Garamond
Sans Serif	Arial
	Calibri
Monospace	Courier New
Other	Symbol, e.g., αλμσπϕφθζηγψ
	Wingdings, e.g., ♦■❖◆●🖂❒⌘♓♏♋♎♑♒
	Webdings, e.g., ⏵▲⏭⏮⊖ⓘ?🛇⃠🚌✦

PAGE ORIENTATION

Page orientation can vary from page to page as needed for the most appropriate viewing and printing within a submission. Appropriate page orientation eliminates the need for reviewers to rotate pages or monitors to read content. For example, setting page orientation of a wide table to landscape prior to saving into a document format such as PDF or printing can ensure that all columns fit onto one wide page and that the page is displayed in a top-to-bottom orientation that does not require rotation to read on a monitor.

PAGE SIZE AND MARGINS

Formatting pages to fit on a sheet of paper that is 8.5x11 inches (letter size) or 8.5x14 inches (legal size) facilitates viewing on standard monitors and printing. A margin of at least 1/2 inch on each side for portrait orientation provides more information on-screen but avoids obscuring information should pages need to be printed and bound. For pages in landscape orientation, a 3/4 inch margin at the top allows more information to be displayed legibly on the page. Header and footer information should not invade the specified margins (i.e., header and footer information should not appear within 3/8 inch of the edge of an 8.5x11 inch page), so the text will not be lost upon printing or binding. These margins allow printing on A4 as well. Oversized documents (e.g., facility and process flow diagrams) and promotional advertising and labeling materials submitted in an image or document format should be created according to their actual page size.

SCANNING OF PAPER DOCUMENTS

Electronic document files produced by scanning paper documents initially result in photographic images of text and data that are not recognizable as functional text on a computer. This means the text cannot be searched, selected, or extracted (copy/pasted), and is susceptible to issues that can impact photography. Additional processing is necessary for scanned text images to be recognized as words and numbers through a process called optical character recognition (OCR). Such scanning of a submission enables important functionality in the course of a review, such as the ability to quickly search and find content as well as extract text and data for use in a review. However, OCR may produce documents of poor quality, with problems such as missing or incorrect characters underlying the images of words. The sensitivity and specificity of OCR software varies, and some OCR software allows the ability to adjust parameters and validate the resulting text. The resulting file size of scanned documents is significantly larger than equivalent PDF documents generated directly from their source programs or printed to a PDF printer driver.

FDA has recommended minimum image resolutions for scanned documents, depending upon the nature of the content[6] (see Table 04), and these are also suitable for submissions to CTP. Scanning documents at a resolution of 300 dots per inch (dpi) ensures that document pages are legible both on the computer screen and when printed and, at the same time, minimizes the file size. The use of grayscale and color significantly increases the file size and should be used only when these features improve the reviewability of the material. After scanning, avoid resampling to a lower resolution. A captured image should not be subjected to non-uniform scaling (i.e., sizing).

Table 04: Document and Image Scanning Resolutions

Document Type	**Minimum Resolution** dots per inch (dpi) to ensure legibility
Handwritten notes	300 dpi (black ink)
Plotter output graphics	300 dpi
Photographs – black and white	600 dpi (at least 8 bit grayscale)
Photographs – color	600 dpi (at least 24 bit RGB)
Gels and karyotypes	600 dpi (at least 8 bit grayscale depth)
High pressure liquid chromatography	300 dpi

[6] *Portable Document Format Specification*, CDER/CBER, Sep. 2014, and, *Guidance to Industry- Providing Regulatory Submissions in Electronic Format, General Considerations*, CDER/CBER, Jan. 1999.

IMAGE COLOR MATCHING

Because color varies from monitor to monitor, it is difficult to ensure that the reviewer will see exactly the same color as in the original image. However, for printing, there is more control over the color by using the CMYK (Cyan, Magenta, Yellow, Black) color model as opposed to the RGB (Red, Green, Blue) model. Pantone matching using the color profile provided by CMYK ensures color consistency for printing. The International Color Consortium (ICC)[7] color profile specification is used when PDF documents are printed.

DOCUMENT NAVIGATION

A TOC, hypertext links, and bookmarks assist in navigating an eSubmission. CTP recommends including a hypertext-linked TOC and bookmarks in documents greater than five pages. Hypertext links help a reviewer navigate to references, related sections, appendices, tables, and figures that are not on the same page or within the same file. Hypertext links in text can be designated by rectangles using thin lines or by blue text. A consistent method of designating links in a document avoids confusion. Hypertext links that open a file or document should be set to open the file or document in a new window. A relative path specifies the location of a file from the current directory downward and does not include the specific drive letter and parent directories above the current location. Using relative paths when creating hypertext links minimizes the loss of hyperlink functionality when eSubmissions are loaded onto network servers; both absolute links that reference specific drives and links to root directories do not work once the submission is loaded. This is done within Adobe Acrobat, for example, by choosing the "open file" rather than the "open webpage" option when creating each link.

A TOC in the main body of a submission (e.g., MAIN-TOC.pdf) as well as within each section helps the reviewer navigate and find information of interest. For documents with a TOC, CTP recommends providing bookmarks and hypertext links for each item listed including all tables, figures, publications, other references, and appendices that are essential for navigation through documents. When creating links in TOCs and throughout submission documents, the current Internet standard is to use invisible rectangles and blue text, which avoids obscuring text for hypertext links. Other navigation assistance includes a bookmark hierarchy (up to four levels) identical to the TOC. A sample TOC for tobacco product submissions modeled after the eCTD is presented in Appendix A.

When creating bookmarks and hyperlinks, setting the magnification to "Inherit Zoom" is helpful as it ensures that all pages open and display at the same magnification level of the primary document.

SPECIAL CONSIDERATIONS FOR PORTABLE DOCUMENT FORMAT (PDF)

PDF is an open publishing format created by Adobe Systems Incorporated and later adopted by the International Organization for Standardization as ISO 32000-1:2008. PDF is utilized by FDA in its eSubmissions standards for document content of a narrative nature. Software from a variety of sources can be used to create files in PDF format.[8]

CTP can receive and process PDF versions 1.4-1.7, PDF/A-1, PDF/A-2 and beyond. The readability of PDF files by Adobe Acrobat X, or above is one indicator that these files can be read by CTP. PDF files should not require additional software or plug-ins to be read, navigated, text-searched, text-selected, or printed.

PDF files should not contain: JavaScript; dynamic content that can include audio, video or special effects and animations; attachments; 3D content; or annotations.

Hypertext links in documents should be tested to ensure that they remain active after conversion to PDF/A. Promotional materials (e.g., labeling, advertising) submitted in PDF format may need special consideration to ensure accurate and unaltered presentation.

> Fast Web View Optimization:
> "Optimize the PDF for fast web view" is an option available when generating PDF documents. It provides for a more responsive display of the first page of each PDF when viewing from

[7] International Color Consortium, http://www.color.org/

[8] Reference: ISO 32000-1:2008 - Document management – Portable document format – Part 1: PDF 1.7. ISO.org. 2008-07-01. http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=51502

tools that use a web interface. This can facilitate a reviewer's interaction with the documents as he or she navigates across content, which is beneficial to the review process.

Initial View Settings:
"Bookmarks Panel and Page" is an option under PDF document settings that sets the initial document view upon opening to display an entire page and a left-side panel showing bookmarks to document content, allowing more expeditious navigation. If there are no bookmarks, set the Navigation Tab to "Page Only." Page Layout and Magnification can remain as "Default."

Page Numbering:
In general, including the page number on each page of a PDF document, with the initial page of the PDF document numbered as page 1, facilitates navigation of and correspondence about electronic documents. When a document is split because of its size, subsequent files should be numbered consecutively to follow from the preceding file.

SPECIAL CONSIDERATIONS FOR PROMOTIONAL MATERIALS

Content such as promotional materials (e.g., labeling, advertising), schematic diagrams, and process flow diagrams may need special consideration to ensure accurate image representation. Since color can vary from computer to computer, it can be difficult to ensure that the reviewer will see exactly the same color as in the original image. CTP recommends providing images at the highest resolution and depth possible. For photographs, CTP recommends providing the image at a resolution of at least 600 dpi.

When paper source documents must be scanned, high resolution will ensure that pages are legible both on the computer monitor and when printed; at least 600 dpi is usually sufficient. Promotional material submitted according to its actual size, when practical, is most effective in ensuring that it is presented and reviewed as it will actually exist on the market. When an image size is altered, it is important to state the original dimensions so that reviewers can understand how it will appear on the market. Images of three-dimensional promotional pieces constitute multiple sides and components; providing all sides and components of such pieces will help ensure that they can be reviewed.

OTHER DATA STANDARDS THAT MAY IMPROVE AN eSUBMISSION TO CTP

The following data and eSubmission standards may be helpful in facilitating a high-quality, reviewable eSubmission. The data standards listed in Table 05 represent key standards that CTP recommends for use in eSubmissions.

Table 05: Structure and Content Standards*

Standard	Description	Reference
ADaM	Analysis Data Model (ADaM) is a CDISC standard that provides traceability between analysis results, analysis data, and data represented in the Study Data Tabulation Model (SDTM).	https://www.cdisc.org/standards/foundational/adam
AMA CPT	Current Procedural Terminology (CPT®) code set American Medical Association	https://www.ama-assn.org/practice-management/apply-cpt-license
APA Style Manual	American Psychological Association (APA) Style Manual provides a standardized format for cited references.	https://www.apastyle.org/manual/index
eCTD	The Electronic Common Technical Document (eCTD) is an international data standard developed by the International Conference on Harmonization (ICH) for capturing the content and organization of a submission and subscribing to the Common Technical Document (CTD) structure for regulatory applications for a pharmaceutical product.	http://estri.ich.org/eCTD/ http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
ICD	The International Classification of Diseases (ICD) is the international "standard diagnostic tool for epidemiology, health management and clinical purposes."	http://www.who.int/classifications/icd/en/
ISO 8601	The ISO 8601 is an international standard covering the exchange of date- and time-related data. It was	https://www.iso.org/standard/40874.html

Standard	Description	Reference
	issued by the International Organization for Standardization (ISO) and provides an unambiguous and well-defined method of representing dates and times particularly when data are transferred between countries with different conventions for writing numeric dates and times.	
IUPAC	The International Union of Pure and Applied Chemistry (IUPAC) develops recommendations to establish unambiguous, uniform, and consistent nomenclature and terminology for chemical disciplines, including: definitions of terms relating to a group of properties; nomenclature of chemical compounds and their classes; terminology, symbols, and units; classifications and uses of terms; and conventions and standards of practice for presenting data.	https://iupac.org/what-we-do/nomenclature/
LOINC	Logical Observation Identifiers Names and Codes (LOINC) is a database and universal standard for identifying medical laboratory observations.	https://loinc.org/
MedDRA	The Medical Dictionary for Regulatory Activities (MedDRA) is a standard developed through the International Conference on Harmonization (ICH) for medical terminology for use in regulatory communications and evaluation of data pertaining to human medical products.	https://www.meddra.org/
RPS	The Regulated Product Submission (RPS) is an iteration of eCTD (eCTD 4.0) being developed through Health Level Seven International (HL7) that will include enhanced identification of information contained in a submission and two-way message exchange between industry and regulatory agencies.	http://wiki.hl7.org/index.php?title=Regulated_Product_Submissions http://www.fda.gov/ForIndustry/DataStandards/RegulatedProductSubmission/default.htm
SDTM	The Study Data Tabulation Model (SDTM) is a CDISC standard that provides a standard structure for human clinical trial (study) data tabulations and for nonclinical study data tabulations.	https://web.archive.org/web/20080612045554/http://www.cdisc.org/models/sdtm/v1.1/index.html
SEND	The Standard for Exchange of Nonclinical Data (SEND) is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for nonclinical studies, which provides a way to present nonclinical data in a consistent format.	https://www.cdisc.org/standards/foundational/send
SNOMED	The Systematized Nomenclature of Medicine (SNOMED) is a systematic, computer-processable collection of medical terms in human and veterinary medicine; it provides codes, terms, synonyms and definitions that cover anatomy, diseases, findings, procedures, microorganisms, substances, etc.	http://www.snomed.org/
UNII	Unique Ingredient Identifiers (UNIIs) for substances in drugs, biologics, foods, and devices.	https://www.fda.gov/ScienceResearch/HealthInformatics/ucm474551.htm
UCUM	Unified Code for Unit of Measure (UCUM) is a code system intended to include all units of measure currently used in international science, engineering, and business.	https://ucum.nlm.nih.gov/
WHODD	The WHO Drug Dictionary (WHODD) is an international classification of medicines created by the WHO Program for International Drug Monitoring organizations and drug regulatory authorities for identifying drug names in spontaneous ADR reporting (and pharmacovigilance) and in clinical trials	https://www.who-umc.org/

* Note: The FDA Data Standards Catalog provides a comprehensive list of standards, formats, and

terminologies pertaining to eSubmissions, although not all are directly applicable to tobacco products: <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

TRANSMISSION MODES

eSubmissions can be sent to CTP via the following modes:

- CTP Portal, which requires an eSubmitter-generated zip file. Refer to this URL for more details: https://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/ucm515047.htm
- ESG/Web Trader, which requires an eSubmitter-generated zip file. Refer to this URL for more details: https://www.fda.gov/tobaccoproducts/guidancecomplianceregulatoryinformation/manufacturing/default.htm (submit online)

TESTING OF CONTENT AND FORMAT PRIOR TO SUBMITTAL TO FDA

Submission testing can help detect issues and resolve problems prior to submission. Such tests may include viewing, navigating, searching within text, selecting text, printing, and clicking on hyperlinks and bookmarks. While many document types may allow files to embed within files, this can create problems for virus scanning or even submission through the FDA ESG and CTP Portal.

CTP encourages early consultation by individuals intending to submit electronically, especially those making an eSubmission for the first time. Individuals are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, file formats, technical protocols) and whether to proceed with the eSubmission, see 21 CFR section 11.2(b)(2).

Technical questions may be submitted to CTPeSub@fda.hhs.gov. In addition, for assistance on seeking meetings with the CTP Office of Science regarding research and development plans related to tobacco products, see Guidance for Industry and Investigators: Meetings with Industry and Investigators on the Research and Development of Tobacco Products.[9]

[9] *Guidance for Industry and Investigators - Meetings with Industry and Investigators on the Research and Development of Tobacco Products (Revised)** June 2020, https://www.fda.gov/media/83420/download

DOCUMENT HISTORY

January 2018: First edition of document posted.

April 2019: Document is revised to include additional information and also reorganized and revised for clarity. Specific revisions include the following:

- FILE SIZE AND SUBMISSION SIZE – Added information about file size and submission size limitations for eSubmitter, ESG, and CTP Portal.
- Table 03: List of FDA Standard Fonts – Revised and condensed table from font names to font families.
- SECURITY AND ENCRYPTION – Added wording and references related to protection of confidentiality of trade secret information. Added wording about scanning for viruses and documenting that it was done.
- TRANSMISSION MODES – Added "flash drives" to physical media.
- FONTS – Added information regarding fonts in SAS Unix.
- Table 05: Structure and Content Standards – Removed reference to ISO11238 **since it may not be applicable to tobacco product submissions to CTP.** Added APA Style Manual and UCUM.
- DOCUMENT NAVIGATION – Added description about how to make hyperlinks in PDF files that work once an eSubmission is loaded.
- SCANNING OF PAPER DOCUMENTS – Added explanation regarding use of scanning and OCR.
- TESTING OF CONTENT AND FORMAT PRIOR TO SUBMITTAL TO FDA – Added information regarding consulting FDA for technical questions.

October 2019: Document is revised to include additional information regarding table of contents and supported file formats. Specific revisions include the following:

- INDEX OF THE FILES WITHIN A SUBMISSION – Added language to reference a sample table of contents modeled after the eCTD (Appendix A).
- Table 02: Supported File Format List with Descriptions – Added additional file extensions for mpeg and jpeg files. Added information under Extensible Markup Language regarding use of Define files for data if submitted using the SEND, SDTM, ADaM data standard.
- DOCUMENT NAVIGATION – Added reference to Appendix A.
- APPENDIX A – Added a sample table of contents heading and hierarchy for capturing the content, structure, and organization of submissions to CTP.

December 2021: Document is revised to include additional language clarifying the self-contained nature and modes of transmission

- INTRODUCTION – removed language referencing data submitted via paper or electronic modes
- AUDIENCE – removed language referencing software vendors
- GENERAL CONSIDERATIONS – added language to reference the self-contained nature of submissions
- FILE SIZE AND SUBMISSION SIZE - removed language referencing physical media
- SECURITY AND ENCRYPTION – added language to reference the self-contained nature of submissions, and to further clarify that links to files stored externally prevent CTP from receiving, processing, reviewing, and archiving submissions
- FDA eSUBMITTER – removed language referencing physical media
- TRANSMISSION MODES – removed language referencing physical media

APPENDIX A:

Sample Table of Contents Heading and Hierarchy for Submissions to the Center for Tobacco Products

A sample table of contents (TOC) heading and hierarchy for capturing the content, structure, and organization of submissions to the Center for Tobacco Products is presented below. This sample TOC is modeled after the Electronic Common Technical Document (eCTD). The eCTD is an international data standard developed by the International Conference on Harmonization (ICH) for capturing the content and organization of a submission and borrowing from the Common Technical Document (CTD) structure for regulatory applications for a pharmaceutical product.[2]

A sample submission with this TOC may include separate document files named by the relevant section (for example, five separate pdf files for 1.1-Submission Form, 1.2-Cover letter, 2.1-Index of all studies, 2.3-Product Description and Manufacturing Summary, and 3.1-Product Design and Specification). Additionally, the applicable sections and content captured by the sample TOC may differ by tobacco product submission type (e.g., substantial equivalence exemption requests, substantial equivalence reports, premarket tobacco product applications, modified risk tobacco product applications, listing of ingredients in tobacco products, tobacco product master files). The recommended or required content for different tobacco product submission types are described elsewhere.[10]

MODULE 1: ADMINISTRATIVE

1.1 Submission Form
1.2 Cover Letter
1.3 Administrative Information
1.4 Industry to FDA Correspondence Regarding Application Status
1.5 Industry to FDA Correspondence - Other
1.6 Meetings with Industry
1.7 Dispute Resolution
1.8 Industry Periodic Report
1.9 Product Labels and Labeling
1.10 Product Promotional Material
1.11 Grandfather Evidence
1.12 FDA to Industry Correspondence
1.13 Master File Authorization
1.14 Health Documents [904(a)(4)]
1.15 Requested Documents [904(b)]

MODULE 2: SUMMARY

2.1 Index of All Studies
2.2 Integrated Summary
2.3 Product Description and Manufacturing Summary
2.4 Target Market for Tobacco Product
2.5 Nonclinical Overview
2.6 Clinical - Individual Health Overview
2.7 Clinical - Population Health Overview
2.8 Environmental Impact Summary
2.9 Index of all Referenced Literature

MODULE 3: PRODUCT DESCRIPTION AND MANUFACTURING

[10] https://www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance

3.1 Product Design and Specification
3.2 Ingredients, Additives, and Constituents
3.3 Product Performance
3.4 Tobacco Product Comparisons
3.5 Tobacco Product Manufacture
3.6 Other Tobacco Product Features
3.7 Referenced Literature

MODULE 4: NONCLINICAL

4.1 Tabular Listing of All Nonclinical Studies
4.2 Nonclinical Studies
4.3 Nonclinical Behavioral Studies
4.4 Nonclinical Abuse Liability Studies
4.5 Nonclinical Study Model or Analysis
4.6 Nonclinical Literature Review
4.7 Other Documents Relating to Research [911(d)(5)] or 910(b)(1)]
4.8 Referenced Literature

MODULE 5: CLINICAL - PRODUCT IMPACT ON INDIVIDUAL HEALTH

5.1 Tabular Listing of Individual Health Studies
5.2 Abuse Liability Study (human) – PK and PD or Subjective Effects
5.3 Actual Use Study - Use Behaviors or Health Outcomes
5.4 Other Clinical Study Reports and Related Information
5.5 Adverse Experience Reports
5.6 Individual Health Literature Review
5.7 Other Documents Relating to Research [911(d)(5)] or 910(b)(1)]
5.8 Referenced Literature

MODULE 6: CLINICAL – PRODUCT IMPACT ON POPULATION HEALTH

6.1 Tabular Listing of All Population Health Studies
6.2 Tobacco Product Perception and Intention Study
6.3 Behavioral Epidemiology (Observational) Study
6.4 Biomarker Epidemiology (Observational) Study
6.5 Health Risk Epidemiology (Observational) Study
6.6 Population Modeling or Analysis
6.7 Postmarket Surveillance and Postmarket Study Plan or Protocol
6.8 Population Health Literature Review
6.9 Other Documents Relating to Research [911(d)(5)] or 910(b)(1)]
6.10 Referenced Literature

MODULE 7: ENVIRONMENTAL IMPACT

7.1 Need for the Proposed Actions
7.2 Potential Environmental Impacts of the Proposed Actions and Alternatives - Manufacturing the New Products
7.3 Potential Environmental Impacts of the Proposed Actions and Alternatives – Use of the New Products
7.4 Potential Environmental Impacts of the Proposed Actions and Alternatives – Disposal of the New Products
7.5 Mitigation of Environmental Effects
7.6 Alternatives to the Proposed Actions
7.7 List of Preparers
7.8 Listing of Agencies and Persons Consulted
7.9 Other Documents Relating to Research [911(d)(5)] or 910(b)(1)]
7.10 Referenced Literature References
7.11 EA Appendices
7.12 EA Confidential Appendices