CVM Recommended File Specifications for eSubmitter

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Introduction

Regulations in 21 CFR Part 11 require that the Agency be able to generate from any document provided in electronic format an accurate and complete paper copy that is both legible ("human readable") and suitable for inspection, review, and copying. Therefore, documents submitted in electronic format should:

- Enable the user to easily view a clear and legible copy of the information
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers
- Include a well-structured table of contents and allow the user to navigate easily through the submission
- Allow the user to copy text and images electronically into common word processing documents

To achieve the above goals, you should submit all electronic documents, that don't include data needed for further processing in Portable Document Format (PDF). PDF is an open, published format created by Adobe Systems Incorporated and accepted as an ISO standard under ISO 32000. (http://www.adobe.com). You do not need to use a product from Adobe or from any specific company to produce your PDF documents. PDF has been accepted as a standard for providing documents in electronic format by the Veterinary International Conference on Harmonization (VICH).

For data files, CVM recommends that either eXtensible markup language (XML) file format or SAS XPORT (XPT) be used. The file specifications contained within this manual are recommendations from CVM and over time may evolve to accommodate a changing technology.

Portable Document Format (PDF) Specifications

PDF Area	Recommended PDF Specification
Version	The PDF files should be created to support the PDF/A standard. Everything needed to render or print a PDF/A file must be contained within the file. This includes all visible content like text, raster images, vector graphics, fonts, color information, and much more. It also means that a wide range of external content references are disallowed, including audio and video content, JavaScript, and executable files. All embedded fonts must be legally embeddable for unlimited, universal rendering. The PDF files also must be compatible with Adobe Acrobat 8.0 or greater without the use of additional plug-ins other than those provide by Adobe as part of Acrobat. We should not need any additional software to read and navigate the PDF files. CVM currently is running Adobe Acrobat X so if you are planning on submitting PDF files generated by a newer version of Adobe Acrobat, please contact technical support at cvmesubmitter@fda.hhs.gov to ensure you do not use a feature that is unsupported.
Plug Ins	It is acceptable to use plug-ins to assist in the creation of a submission. However, the review of the submission should not require the use of any plug-ins other than any provided by Adobe as part of Acrobat, and must be compatible with Adobe Acrobat 8.0 or greater.
Page Size and Margins	The print area for pages should fit on a sheet of paper that is 8.5 inches by 11 inches, unless the source document is of a different size then the size of the source document should be preserved within the PDF file. When possible, you should allow a margin of 1 inch on the left margin and 1 inch on all other sides to avoid obscuring information should the pages ever need to be printed. However, for files that contain images of labeling page size should be commensurate with the size of the label being presented. You should present the label image in the size as if the labeling was in front of you.
Page Orientation	Pages should be properly oriented. For example, you should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation. Landscape pages (including tables) should be oriented such that the header and footer of the document align with the right edge of the page.

PDF Area	Recommended PDF Specification
Fonts	PDF viewing software automatically substitutes a font to display text if the font used to create the text is unavailable on the reviewer's computer. Font substitution can affect a document's appearance and structure, and in some cases it can affect the information conveyed by a document. We cannot guarantee the availability of any one font. Therefore, you should embed all fonts you are using in the PDF files to ensure that those fonts will always be available to the reviewer. When embedding fonts, all characters for the font should be embedded (not just a subset of the fonts being used in the document). One problem associated with embedding fonts is that embedding requires additional computer storage space. Three techniques to help limit the storage space taken by embedding fonts: • limit the number of fonts used in each document • use only True Type or Adobe Type 1 fonts • avoid customized fonts Resizing a document because the contents are too small to read is inefficient. We believe that Verdana, 10-point font, is adequate in size for reading narrative text. This is the preferred font. Although sometimes tempting for use in tables and charts, fonts smaller than 10-points should be avoided whenever possible. We recommend the use of a black font color. Blue font may be used or hypertext links. If a font color other than black is used, avoid light colors that do not view well on computer screens. In addition to font colors, keep formatting simple in tables. When extracting a table from the PDF document, the use of light or white font color will not allow the transfer of text back into some word processing documents.
Page Numbering	If a submission includes more than one file, you need not provide pagination for the entire submission. Pagination should occur on an individual attached file basis.
File Size	An electronic submission can have one or multiple file attachments. The tested limit of file size through FDA's ESG is 12 GB, however each file within the submission should be limited to 100 MB in size. There are several ways to compress file size, including but not limited to: performing Optical Character Recognition, reducing file size in Adobe and creating logical section breaks. The maximum size of the eSubmitter ZIP file should not exceed 2 GB. If you have questions about file size, please contact technical support at cvmesubmitter@fda.hhs.gov to ensure the file size is acceptable.

PDF Area	Recommended PDF Specification
Document Properties: Description Tab	Document properties are used to search for individual documents and to identify the document when found. To modify document properties, from the tool bar navigate to File Document Properties.
Document Properties: Initial View Tab	In the Document Properties box, the Initial View tab can also be found. In the Document Options section, all PDF files should set the Show field as Bookmarks Panel and Page. If there are no bookmarks, set the initial view as Page only. Set the Page Layout and Magnification fields to default.
Document Properties: Security	PDF files are stored as original documents and will not be altered from their original form. Remove any security settings, read-only, or password protection used on the files. Files submitted with security settings will not be accepted.
Indexing PDF Documents	Full text indexes are used to help find specific documents and/or to search for text within documents. When a document or group of documents is indexed, all words and numbers in the file and all information stored in the Document Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat. Portions of a document that are imaged are not indexed. Even if the document only contains images, the text in the Document Information fields of the file will be indexed. All PDF files should be full-text searchable prior to submitting to the FDA.

PDF Area	Recommended PDF Specification
Bookmarks and Hypertext Links	Bookmarks and hyperlinks should be used to assist the reviewers in navigating through the content of the submission. If you used either bookmarks or hypertext links, consider the following: • Use meaningful bookmarks (e.g., the title of the section, name of a study, data set, or facility). This will aid the reviewer in locating information and navigating the submission. • Bookmark references can be created for the heading of a section, subsection or title of figures and tables within the document. In general, including a bookmark to the main table of contents for a submission or item is helpful. Make the bookmark hierarchy identical to the table of contents. • Use hyperlinks within the file. Hyperlinks are used to improve navigation through PDF documents and are encouraged. Hyperlinks can be designated by rectangles using thin lines or by blue text or you can use invisible rectangles for hypertext links in a table of contents to avoid obscuring text. Hyperlinks throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page are helpful and improve navigation efficiency. When creating bookmarks and hyperlinks, the magnification setting should be set to Inherit Zoom so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document. Important Note: Hyperlinks between individual PDF document files are not currently supported and any absolute links that reference across files will not work. In general, for documents with a table of contents, provide bookmarks and hypertext links for each item listed in the table of contents including all tables, figures, publications, other references, and appendices. These bookmarks and hypertext links are essential for the efficient navigation through documents.

PDF Area	Recommended PDF Specification
Optical Character Recognition	PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document such as MS Word. Scanned documents are more difficult to read and do not allow the reviewers to search or copy and paste text for editing or re-use. The use of scanned documents should be avoided if at all possible. If scanning cannot be avoided, the following is highly recommended: • Perform optical character recognition (OCR) on all scanned documents so that the text is searchable. If using the OCR capabilities within Adobe Acrobat, select 'Searchable Image (Exact)' as the OCR setting. If this processes is used, remediation of the OCR'd document is not necessary. If the source document is only available on paper, it should be scanned at resolutions that will ensure the pages are legible on the computer screen. At the same time, remember to limit the file size to be less than 100 MB. We recommend scanning at a resolution of 300 dots per inch (dpi) to balance legibility and file size. After scanning, avoid re-sampling to a lower resolution. For files with images and photographs: Also, when creating PDF files containing images, you should not resample images. Re-sampling does not preserve all of the pixels in the original. For photographs, the image should be obtained with a resolution of 600 dpi. If black and white photos are submitted, consider 8-bit gray scale images. If color photos are submitted, consider 24-bit RGB Color Model images. A captured image should not be subjected to non-uniform scaling (i.e., sizing). Files with scanned images and photographs tend to be large in file size. Please do not exceed 100 MB for a single file. Consider multiple files for these types of documents. Note: Scanned tables and graphs cannot be extracted easily if scanned. Most OCR programs will distort the data in tables and graphs. Convert MS Word documents to PDF, as this method usually retains the formatting. For a paper document with handwritten notes: Paper documents containing handwritten notes should be scanned at 300 dpi. There is no need to OCR PDF files from handwritten notes. These handwritten notes should be made in black ink for clarity. If you have questions about creating electronic copies, please contact technical support at cvmesubmitter@fda.hhs.gov.

PDF Area	Recommended PDF Specification
Naming PDF Files	We suggest uniformity be used when naming files. When naming files, DO NOT use punctuation, spaces, or other non-alphanumeric symbols in file names when naming the files for attachments. For example, do not use slashes (/) (\), tildes (~), asterisks (*), periods (.), brackets [ ], single quotation marks ('), double quotation marks ("), parentheses ( ), hash tag (#), or percent (%). Once the file is attached to a question, it can be selected as an attachment to other questions, if appropriate. The eSubmitter tool supports the following file types: • Portable Document Format Files (.pdf) • Excel Files (.xls, .csv) • SAS System XPORT Files (.xpt) • Media Files (.wmv, .avi) • Image Files (.gif, .tif, .jpg) • Extensible Markup Language Files (.xml, .dtd) • Archive/Compressed Files (.zip) • Standard Generalized Markup Language Files (.sgml) • MDL Molfiles Files (.mol) However, CVM submission will only permit PDF, XML, and/or XPT files. Based on the question you are answering, the question may have restrictions on which file types you are allowed to attach. For example, some questions may allow you to attach any of the three file types permitted by CVM and some may only allow you to attach PDF and XML files as the questions response or supporting documentation.

Facsimile and Final Printed Labeling (FPL) in PDF files

Final printed labeling (FPL) are required to be submitted as part of the animal drug approval submission. However, in lieu of FPL CVM permits the submission of facsimile labeling with the (A)NADA as long as the FPL is submitted prior to marketing the approved product. In the electronic world, facsimile labeling would represent the 2-dimentional aspect of the labeling components, including color, size, and fonts, without the labeling actually being produced. The PDF files with facsimile labeling need to contain the images/graphics of the labeling components without actual pictures of the final printed label components printed on their intended media (bag, foil pouch, syringe, etc.). The PDF files for FPL should contain the actual pictures of the different label component embedded at their actual size and color. To aid in the review of both facsimile and FPL submissions, CVM recommends that both a pantone ruler (for color verification) and a photographic ruler (for size verification) be included in all photographs of final printer labeling.

Extensible Markup Language (XML) Specifications

The use of XML file format within the CVM eSubmitter templates have been limited to either the submission of Stability data or other data questions. One should verify that when an XML file is created, it is not created with proprietary formatting as can occur with many common word processing programs. The created XML file, at a minimum, should be viewable with any of the common web browsers. When creating XML files to support the answers to stability questions, the file should conform to the HL7 standard. For more information visit the CVM eSubmitter webpage:
http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm226816.htm,

SAS Transport (XPT) Specifications

SAS Transport files are use to package both SAS programs as well as SAS data. Currently, CVM has the following recommendations on how these files should be constructed. Stakeholders are encouraged to contact CVM's Biostatistics Teams (HFV-163 and 164) if they wish to discuss these recommendations further.

- SAS programs are to be submitted as XML files. This can be done by selecting "File>Save As>Web files" and specifying an XML extension. Note that other web file extensions are HTM and HTML. Please choose XML.
- SAS logs and output are no longer required for submission. If the sponsor chooses to submit these files, they can be submitted as PDF documents.
- DATA files should be submitted as either XML files or XPORT (XPT) files. CPORT files are basically bundled SAS7BDAT files that need to be opened in an unsecured area for use. We prefer that in SAS programs, you use the data you provide to us.
- XPORT files are easy created and used in SAS. For information regarding, XPORT files use the following links: http://www.sas.com/industry/government/fda/faq.html and Technical Document TS-140.
- If data exist in an EXCEL file, they can be saved as XML file and used in SAS programs. (See SAS 9.2 XML LIBNAME Engine User's Guide for more information.)