
Guidance for Industry

Providing Regulatory Submissions in Electronic Format — General Considerations

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)
January 1999
IT 2**

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TABLE OF CONTENTS

I.	INTRODUCTION	4
II.	BACKGROUND	4
III.	WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DOCUMENTS?	6
	A. Version	7
	B. Fonts	7
	C. Page Orientation	8
	D. Page Size and Margins	8
	E. Source of Electronic Document	8
	F. Methods for Creating PDF Documents and Images	8
	G. Hypertext Linking and Bookmarks	9
	H. Page Numbering	10
	I. Document Information Fields	10
	J. Open Dialog Box	10
	K. Naming PDF Files	10
	L. Security	11
	M. Indexing PDF Documents	11
	N. Plug Ins	11
	O. Electronic Signatures	12
IV.	WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DATASETS ?	12
	A. SAS System XPORT Transport Format (Version 5 SAS Transport Format)	12
	B. Other Dataset Formats	13
V.	WHAT ARE THE PROCEDURES FOR SENDING ELECTRONIC SUBMISSIONS FOR ARCHIVE ?	14
	A. CDER	14
	B. CBER	14
VI.	WHAT TYPE OF MEDIA SHOULD I USE?	15
VII.	HOW SHOULD I PREPARE THE MEDIA FOR ELECTRONIC SUBMISSIONS FOR ARCHIVE ?	15
VIII.	HOW DO THE CENTERS PROCESS ELECTRONIC SUBMISSIONS FOR ARCHIVE?	16
	A. CDER	16
	B. CBER	16
IX.	WHAT IF I HAVE A QUESTION ?	17
	A. CDER	17
	B. CBER	17

GUIDANCE FOR INDUSTRY¹

Providing Regulatory Submissions in Electronic Format — General Considerations

I. INTRODUCTION

This is one in a series of guidance documents intended to assist you when making regulatory submissions in electronic format to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA). This guidance discusses general issues common to all types of electronic regulatory submissions. In some cases, the guidance for one center differs from that for the other center because of differences in procedures and in the computer infrastructures in the centers. We will work to minimize these differences wherever possible.

Agency guidance documents on electronic regulatory submissions will be updated regularly to reflect the evolving nature of the technology involved and the experience of those using this technology.

II. BACKGROUND

In the *Federal Register* of March 20, 1997 (62 FR 13430), the FDA published the Electronic Records; Electronic Signatures regulations (21 CFR Part 11). This regulation provided for the voluntary submission of parts or all of regulatory records in electronic format without an accompanying paper copy. Publication of this regulation resulted in a series of related actions:

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on regulatory submissions in electronic format. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

On June 1, 1998, the President instructed all Federal agencies to ensure the use of plain language in all new documents. This guidance reflects Agency efforts to comply with the President's plain language initiative.

March 1997:

The Agency established public docket number 92S-0251 to provide a permanent location for a list of the Agency units that are prepared to receive electronic submissions and the specific types of regulatory records that can be accepted in electronic format (62 FR 13467, March 20, 1997). This docket can be accessed on the Internet at

<http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm>.

September 1997:

CDER published a guidance for industry entitled *Archiving Submissions in Electronic Format — NDAs* (62 FR 49695, September 23, 1997) to assist applicants wanting to make electronic submissions of case report forms (CRFs) and case report tabulations (CRTs) as part of the NDA archival submission.

April 1998:

CDER issued a draft guidance for industry, *Providing Regulatory Submissions in Electronic Format — NDAs*, which expanded on the September 1997 guidance by providing information on submitting a **complete** archival copy of the NDA in electronic format (63 FR 17185; April 8, 1998).

June 1998:

CBER published the following draft guidances to assist applicants in their efforts to submit electronic documents to the Center for review and archive as part of their BLA or PLA/ELA submissions:

Electronic Submissions of a Biologics License Application (BLA), Product License Application (PLA) /Establishment License Application (ELA) to the Center for Biologics Evaluation and Research (63 FR 29741, 6/1/98).

Electronic Submissions of Case Report Forms (CRFs), Case Report Tabulations(CRTs) and Data to the Center for Biologics Evaluation and Research (63 FR 29739; 6/1/98).

Pilot Program for Electronic Investigational New Drug (eIND) Applications for Biological Products (63 FR 29740; 6/1/98).

Instructions for Submitting Electronic Lot Release Protocols to the Center for Biologics Evaluation and Research (63 FR 29742; 6/98).

January 1999:

CDER and CBER finalized this joint guidance on general considerations for electronic submissions. Subsequent guidances will focus on specific submission types.

The Agency envisions the series of guidance documents on electronic regulatory submissions to provide guidance on the following:

- General considerations for all electronic submissions (e.g., file formats)
- NDAs to CDER (including supplements and amendments)
- Marketing Applications to CBER (e.g., BLAs, PLAs, ELAs, NDAs)
- Abbreviated New Drug Applications (ANDAs)
- Postmarketing Safety Reports
- Investigational New Drug Applications (INDs)
- Annual Reports
- Drug Master Files (DMFs)
- Launch Material
- Advertising
- Other

As individual documents are completed, they will be issued first in draft for comment, then finalized and added to the series. The guidances will be updated regularly to reflect the continuously evolving nature of the technology and experience of those using this technology.

III. WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DOCUMENTS?

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 in Portable Document Format (PDF). CDER and CBER are prepared to archive documents provided as PDF files. PDF is an open, published format created by Adobe Systems Incorporated (<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 International Conference on Harmonisation (ICH).

The following recommendations will help you create PDF files that we can review and archive.

A. Version

We should be able to read all PDF files with version 3.0 of the Acrobat Reader with the search plug in. We should not need any additional software to read and navigate the PDF files.

B. 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 include:

- Limiting the number of fonts used in each document
- Using only True Type or Adobe Type 1 fonts
- Avoiding customized fonts

Resizing a document because the contents are too small to read is inefficient. We believe that Times New Roman, 12-point font, the font used for this document, is adequate in size for reading narrative text. Although sometimes tempting for use in tables and charts, fonts smaller than 12 points should be avoided whenever possible.

We recommend the use of a black font color. Blue font may be used for hypertext links (preferred for submissions to CBER). If a font color other than black is used, avoid light colors that do not print well on grayscale printers. You can test the color reproduction prior to submission by printing sample pages from the document using a grayscale printer.

C. 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.

D. Page Size and Margins

The print area for pages should fit on a sheet of paper that is 8.5 inches by 11 inches. You should allow a margin of at least 1 inch on all sides to avoid obscuring information if the pages are subsequently printed and bound.

E. Source of Electronic Document

PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents are more difficult to read and do not allow us to search or copy and paste text for editing. They should be avoided if at all possible. If you use optical character recognition software, you should verify that all imaged text converted by the software is accurate.

F. Methods for Creating PDF Documents and Images

Choose a method for creating PDF documents that produces the best replication of a paper document. You can ensure that the paper and PDF version of the document are the same by printing the document from the PDF version.

Documents that are available only in paper should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed. At the same time, you should also limit the file size. We recommend scanning at a resolution of 300 dots per inch (dpi) to balance legibility and file size. We discourage the use of grayscale or color because of file size. After scanning, avoid resampling to a lower resolution.

When creating PDF files containing images, you should not resample images. Resampling does not preserve all of the pixels in the original. For PDF images, you can use one of the following lossless compression techniques (with the

exception that, when submitting to CBER, standard radiographic images, PET, and SPECT images should not be compressed).

- For lossless compression of color and grayscale images, use Zip/Flate (one technique with two names). This is specified in Internet RFC 1950 and RFC 1951 (<http://info.internet.isi.edu/in-notes/rfc/files/rfc1950.txt>).
- For lossless compression of black and white images, use the CCITT Group 4 Fax compression technique. It is specified as CCITT recommendations T.6 (1988) - *Facsimile coding schemes and coding control functions for Group 4 facsimile apparatus*.

Paper documents containing handwritten notes should be scanned at 300 dpi. Handwritten notes should be done in black ink for clarity.

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 images. A captured image should not be subjected to nonuniform scaling (i.e., sizing).

Gels and karyotypes should be scanned directly, rather than from photographs. Scanning should be at 600 dpi and 8-bit grayscale depth.

Plotter output graphics should be scanned or captured digitally at 300 dpi.

High-pressure liquid chromatography or similar images should be scanned at 300 dpi.

G. Hypertext Linking and Bookmarks

Hypertext links and bookmarks are techniques used to improve navigation through PDF documents. Hypertext links can be designated by rectangles using thin lines or by **blue text** (the latter is preferred by CBER). In CDER, you can use invisible rectangles for hypertext links in a table of contents to avoid obscuring text. Recommendations for hypertext linking and bookmarks are provided in the guidance for the specific submission type.

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. 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. Avoid using bookmark levels in addition to those present in the table of contents.

Each additional level increases the need for space to read the bookmarks. We recommend using no more than 4 levels in the hierarchy.

Hypertext links 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. Use relative paths when creating hypertext linking to minimize the loss of hyperlink functionality when folders are moved between disk drives. Absolute links that reference specific drives and root directories will no longer work once the submission is loaded onto our network servers.

When creating bookmarks and hyperlinks, choose the magnification setting *Inherit Zoom* so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document.

H. Page Numbering

If a submission includes more than one document, you need not provide pagination for the entire submission. Include page numbers only for individual documents.

It is easier to navigate through an electronic document if the page numbers for the document and the PDF file are the same. To accomplish this, the initial page of the paper document should be numbered page 1.

I. Document Information Fields

Document information fields are used to search for individual documents and to identify the document when found. Recommendations for the document information fields will be provided in the guidance for the specific submission type.

J. Open Dialog Box

The open dialog box sets the document view when the file is opened. The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, set the initial view as *Page* only. Set the *Magnification* and *Page Layout* to default.

K. Naming PDF Files

We are recommending names for folders and selected files in individual guidances for specific submission types. For uniformity, we hope that you use our specific naming conventions when they are provided. Reviewers are trained to look for these folders and files, and using the recommended names should help

avoid misunderstandings, improve communication, and speed the review of a submission.

When we do not specify a file name, you can use file names up to 32 characters in length with a 3-character extension. Avoid using punctuation, spaces, or other nonalphanumeric symbols in file names.

L. Security

You should not include any security settings or password protection for PDF files. Allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. Our internal security and archival processes will maintain the integrity of the submitted files. A read-only copy of the files, generated from the submitted files, will be provided to the reviewer.

M. Indexing PDF Documents

We use full text indexes to help find specific documents and/or 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.

These full text indexes should not be confused with a table of contents. Adobe Acrobat Catalog is one example of a tool that can be used to index PDF documents. Indexes should not require extensions or additions to off-the-shelf Acrobat programs.

With many submissions, we ask that you associate the table of contents file for a section with the corresponding full text index file. By associate, we mean that when the table of contents file is opened, the index file is automatically added to the available index list and is ready to be used.

Further recommendations for full text indexes will be provided in guidance for the specific submission types.

N. 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, in addition to those provided with Acrobat Reader 3 because we are not prepared to archive additional plug-in functionality.

O. Electronic Signatures

We are developing procedures for archiving documents with electronic signatures. Until those procedures are in place, documents for which regulations require an original signature, such as certifications, must be accompanied by a paper copy that includes the handwritten signature and the submission identifier (e.g., NDA number).

IV. WHAT FILE FORMATS SHOULD I USE FOR ELECTRONIC DATASETS ?

Regulations in 21 CFR Part 11 require all datasets provided in electronic format to provide an accurate and complete copy of the data suitable for inspection, review, and copying. Currently, we are able to accept and archive datasets in SAS System XPORT transport format (Version 5 SAS transport file). We plan on providing guidance for additional file format types for datasets. See Section B, below. See also recommendations provided in guidance for the specific submission types.

A. SAS System XPORT Transport Format (Version 5 SAS Transport Format)

SAS XPORT transport format, also called Version 5 SAS transport format, is an open format published by the SAS Institute. The description of this SAS transport file format is in the public domain. Data can be translated to and from this SAS transport format to other commonly used formats without the use of programs from SAS Institute or any specific vendor.

You should follow the recommendations in this section to create SAS transport files that we can review and archive.

1. Version

In SAS, SAS XPORT transport files are created by PROC XCOPY in Version 5 of SAS software and by the XPORT engine in Version 6 and higher of SAS Software. We are unable to archive SAS Transport files processed by the CPORT engine.

You can find the record layout for SAS XPORT transport files in SAS technical support TS-140. This document and additional information about the SAS Transport file layout can be found on the SAS world wide web page at <http://www.sas.com/fda-esub>.

2. *Transformation of Datasets*

We use a variety of software tools to analyze the datasets. Stat/Transfer from Circle Systems and DBMS/copy from Conceptual Software Inc., are two programs used to transfer data to various formats used for analysis. SAS Viewer version 7 is used to open SAS transport files directly.

3. *Naming SAS Transport Files*

All SAS transport files should use *xpt* as the file extension.

4. *Compression Of SAS Transport Files*

The SAS transport files should not be compressed.

5. *Content Of Datasets And Organization*

You should provide a single transport file for each dataset. Many of the software tools used by the reviewers require datasets to be loaded into random access memory (RAM) prior to opening the file. Therefore, dataset files should be organized so that their size is generally less than 25 MB per file. The datasets should be accompanied by data definition tables that include the variable name, a description of the variable, the type of variable (e.g., number, character, date), and codes used in the dataset. For derived variables, the method of deriving the variable should also be included in this table. Variable names are limited to 8 characters. You should include a descriptive name up to 32 characters in the label header. Further recommendations for content of SAS Transport files are provided in guidance for each specific submission type.

We recommend that you discuss the content of the datasets with the review division prior to submission.

B. Other Dataset Formats

Although we are not prepared to archive other dataset file formats at this time, additional file formats are being considered, such as structured ASCII for ANDA and postmarketing safety data. Structured ASCII is also being explored for use with the chemistry, biopharmaceutic, and clinical pharmacology data for NDAs. As these projects mature, we will provide additional guidance.

V. WHAT ARE THE PROCEDURES FOR SENDING ELECTRONIC SUBMISSIONS FOR ARCHIVE ?

Submissions should be sent directly to the appropriate center involved. The procedure for handling paper submissions is unchanged from the past.

A. CDER

Send one copy of the electronic regulatory submission for archive to the CDER Central Document Room (CDR) as follows:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

CDER uses this copy to make other copies as needed (see section VIII, below, on processing electronic submissions).

B. CBER

Send two copies of the electronic regulatory submission as described in this guidance to CBER's Document Control Center (DCC) as follows:

Center for Biologics Evaluation and Research
Attn: (Insert "Responsible Office")
HFM-99, Room 200N
1401 Rockville Pike
Rockville, MD 20852-1448

It is essential to communicate with the appropriate CBER office prior to submitting an electronic document, notifying us of your intention to submit an electronic document at least six to eight months in advance of the target date for the submission. At that time, the sponsor should forward a completed copy of the appropriate application specific questionnaire (<http://www.fda.gov/cber/guidelines.htm>).

Subsequent to the receipt of the questionnaire, a teleconference will be scheduled with the appropriate CBER staff. The objective of the teleconference is to convey information relating to the proposed electronic submission's management paradigm, content, format, and structure. Moreover, we will discuss any issues specific to your submission that may not have been fully addressed in the general considerations guidance.

VI. WHAT TYPE OF MEDIA SHOULD I USE?

CDER and CBER are prepared to accept electronic submissions provided on the media listed in the table below. To optimize processing efficiency, we recommend choosing media with a capacity most appropriate to the size of the submission. Whenever possible, applicants should choose media capable of holding the submission on the *fewest* number of units.

Recommendations for Media		
Size of Submission	Media and format	Units
Less than 10MB	3.5 inch DOS Formatted Floppy Disks	1 to 10
Less than 3.25GB	CD-ROM ISO 9660	1 to 5 CDs
Greater than 3.25GB	Digital Tape - Digital Equipment Corp. DLT 20/40 and 10/20 GB format using OPENVMS with VMS backup or NT server 4.0 with NT backup or backup exec.	No limit

VII. HOW SHOULD I PREPARE THE MEDIA FOR ELECTRONIC SUBMISSIONS FOR ARCHIVE ?

Send all electronic media adequately secured in a standard binder marked clearly on the outside ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE. CDs should be packaged carefully to ensure that they arrive in a usable condition. Particularly vulnerable are diskettes and CD jewel cases shipped in envelopes without bubble-type protective material or stiff backing. The use of a jiffy-type bag by itself to ship media will not provide adequate protection for shipping electronic media.

The first binder with electronic media should include only a paper copy of the cover letter for the submission, a paper copy of the appropriate FDA form for the submission (e.g., for an NDA/BLA include FDA form 356h), and the electronic media for archiving. Please attach labels to the media including the CD jewel cases. Label the media with the following:

- Submission identifier (e.g., NDA, BLA number)
- Proprietary and generic name.
- Company name
- Submission serial number, if applicable.
- Submission date: in the format of DD-MMM-YYYY (for example, 01-Jan-1997).
- Disk/CD-ROM/tape number (the number should include the total number submitted such as Disk # of #)

When sending CD ROMS to CBER, number them from 0.001 through 0.XXX for the original submission, and 1.001 through 1.XXX for subsequent submissions with additional information.

VIII. HOW DO THE CENTERS PROCESS ELECTRONIC SUBMISSIONS FOR ARCHIVE?

A. CDER

When an electronic submission arrives in CDER, we copy the electronic files to tape to create an archival copy of the submission. We also copy the files to a network server to create a read-only copy for the reviewer. We use internal procedures to track submissions (do not send roadmap files described below with submissions to CDER).

B. CBER

When an electronic submission arrives in CBER, one copy of the media is archived; the second copy of the submission's media is copied to a network server to create a read-only copy for the reviewer.

The structure and content of electronic submissions to CBER should be based upon the application (e.g., BLAs, PLA/ELAs). Subsequent to the delivery of the electronic application, any additional electronic and/or paper information will be added to the existing network copy of the submission and distributed to appropriate reviewers. The root directory of an electronic application should contain a roadmap.pdf file to orient the review team to the original application and to any and all subsequent information added to the application.

CBER suggests that a roadmap.pdf file be used to establish hypertext links to the application's main table of contents, and to the applications folders and files. This *roadmap* or *home page* should be updated and resubmitted as additional information to the application.

The roadmap file should not contribute in any way to the content of what is under review. It is a map, intended to facilitate navigation through the contents of an application. The application's roadmap.pdf file should be easily updated or modified, for example, using the Replace File command under the Document menu option in Adobe Exchange. This function will automatically replace the old hypertext links to previously submitted sections of the application, leaving only the task of creating the new links corresponding to newly submitted information.

In addition to providing a navigable guide to the application, the roadmap.pdf file should include the sponsor's submission date in the DD-MMM-YYYY format

(e.g., 01-Jan-1999). The contents of the original application and any subsequent amendments to that application should be briefly described in a roadmap.pdf table. The location of these files and folders on the submitted media should be indicated in the roadmap.pdf. Where portions of an application have been submitted only as a paper documents, they should be included in the roadmap and table of contents and tagged as *paper only*.

A summation of the electronic document, using at least 40 key words from the main document should be included with all electronic applications delivered to CBER. This summation should be located in the root directory on the CDROM or DLT tape. The file containing the key words should be an ASCII text file entitled *Summary.txt*.

IX. WHAT IF I HAVE A QUESTION ?

A. CDER

You may direct questions regarding the preparation of submissions in electronic format in CDER to the Electronic Submissions Coordinator, email ESUB@CDER.fda.gov.

B. CBER

You may direct questions regarding the preparation of submissions in electronic format in CBER to the Electronic Submissions Coordinator email ESUBPREP@CBER.fda.gov.