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Guidance for Industry

Providing Regulatory Submissions in Electronic Format — NDAs

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Dockets Management Branch (HFA-305, Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857). All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Copies of this draft guidance are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>. For questions on the content of the draft document contact the Electronic Submissions Coordinator, Office of Information Technology, email ESUB@CDER.fda.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
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GUIDANCE FOR INDUSTRY¹

Providing Regulatory Submissions in Electronic Format - NDAs

I. INTRODUCTION

This guidance document is intended to assist applicants in submitting an electronic archival copy of a New Drug Application (NDA), including amendments and supplements, to the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA). The guidance is published pursuant to the Electronic Records; Electronic Signatures regulation [21 CFR Part 11]. The regulation provides for the voluntary submission of electronic records instead of paper records. It established public docket 92S-0251 for the Agency to identify specific types of records that the Agency will accept in electronic form. The regulation also states that persons should consult with the Agency for details on how to proceed with the electronic submission (e.g., method of transmission, media, file formats, and technical protocols). This guidance document is intended to reduce the need to consult CDER for details on submitting the archival copy of the NDA, including amendments and supplements to an NDA, in electronic format. Conforming to the guidance in this document will help ensure that electronic submissions can be accessed, handled, reviewed, and maintained efficiently.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (the act) requires FDA approval of an NDA before a drug may be introduced or delivered for introduction into interstate commerce [21 U.S.C. 355]. Regulations implementing the new drug application provision are set forth under 21 CFR 314.50-90. Although NDA records have historically been submitted as paper documents,² applicants are encouraged to submit electronic NDAs.

The NDA regulations require the applicant to submit archival, review, and field copies of the application. The archival copy is a complete copy of the application intended to serve as the official reference source for the Agency. After an application is reviewed and an approval decision reached, the archival copy is retained by FDA and serves as the sole file copy of the application.

¹ This guidance has been prepared by the Office of Information Technology in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents CDER's current thinking on providing 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.

² FDA has published *Formatting, Assembling, and Submitting New Drug and Antibiotic Applications* (2/1/87) to guide applicants in submitting paper NDA documents.

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The review copy is a duplicate of the six technical sections included in the archival copy for use by the Agency's scientific reviewers and is not archived when the review is completed. The six technical sections of the NDA review copy include the following items as listed in FDA form 356h:

- Item 4 Chemistry, Manufacturing and Controls (CMC) Section
- Item 5 Nonclinical Pharmacology and Toxicology Section
- Item 6 Human Pharmacokinetics and Bioavailability Section
- Item 7 Clinical Microbiology Section
- Item 8 Clinical Section
- Item 10 Statistical Section

An archival copy provided in electronic format can serve as source, or a partial source for the primary review of the submission. However, at this time, many reviewers prefer to use a paper copy when reading text and other heavily used parts of the application. Therefore, even when a submission is provided in electronic format, applicants must provide paper review copies for some of the technical sections.

The field copy is a duplicate of the Chemistry, Manufacturing and Controls section of the NDA. U.S. applicants send the field copy directly to their home FDA district office. Non-U.S. applicants send the field copy to CDER. The field copy is not archived and is not addressed by this guidance.

To aid in the review of the submission, an applicant may elect to provide review aids in addition to the electronic archival and paper review copies. For example, parts of the submission may be provided in word processor format and data in electronic format to be used with a specific software program. Such aids are not considered part of the archival submission. The decision to provide review aids should be made on a case-by-case basis with the concurrence of the appropriate review division(s). Review aids are described in section VII of this document.

This guidance on the submission of NDAs in electronic format is the first in a series that will be issued on providing regulatory submissions in electronic format. Subsequent guidance documents will be developed for the ANDA, IND, and other submissions. In the future, applicants, investigators, and CDER may develop more effective procedures for providing electronic submissions. As a result, this guidance will be updated periodically as appropriate.

III. ARCHIVAL COPY IN ELECTRONIC FORMAT

Archival submissions in electronic format may include both documents and data sets. Electronic documents include any part of a submission that could otherwise be required on paper. Electronic data sets include data provided in an electronic format that can be used in spreadsheet, database, and/or statistical analysis programs.

This section describes the file formats and organization for electronic documents and data sets that CDER is prepared to accept instead of paper for the archival copy of a submission. CDER may not be able to archive and review a submission that does not conform to this guidance and, therefore, may be unable to file the submission in electronic format. As with a paper submission, CDER may refuse to file an application if it is not submitted as required in 21 CFR 314.101.

A. *File Formats for Documents Submitted in Electronic Format for the Archival copy*

Electronic documents must have the ability to generate accurate and complete paper copies in both human readable and electronic form suitable for inspection, review, and copying by the Agency [21 CFR Part 11].

Documents submitted in electronic format should (1) display a clear, legible, easily viewed copy of the information; (2) provide the ability to print a copy of each page as it would have been printed in a paper submission, including retaining fonts, special orientations, table formats and page numbering; (3) include a well-structured table of contents and provide the ability to easily navigate through the submission; and (4) offer the ability to electronically copy text and images. These goals can be accomplished by using Adobe Acrobat Portable Document Format (PDF). PDF has been accepted as a standard for providing documents in electronic format by the International Conference on Harmonisation (ICH).

The following general recommendations will help applicants create electronic documents in PDF that CDER can handle efficiently.

- **Fonts**

Select fonts carefully. Ideally, all fonts used in a PDF document should be available on a reviewer's computer. If a font is not available to a reviewer, it is replaced automatically by another font, and this could affect the document's appearance and structure. To ensure that the correct fonts are always available, they should be embedded in the PDF files. To limit the storage space used by embedded fonts, use as few fonts as possible (preferably five or fewer fonts in each PDF file). Only True Type or Adobe Type 1 fonts should be used, and the use of highly customized fonts is discouraged. If only a small percentage of the characters of a

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particular font are used in the document, only those actually used should be embedded. For example, if Adobe Distiller is used, the font setting should have “embed all fonts” turned on, “Subset Fonts” turned on, and the subset threshold set to 99.

Font sizes should be restricted to 10 points or greater for text and 8 points or greater for tables.

- Page Orientation

To make it easier to read PDF files, the pages should be properly oriented. For example, page orientation becomes a problem when pages originally oriented in landscape mode are presented in portrait mode. To ensure correct page presentation for the reviewer, set the page orientation of these pages to landscape prior to saving the PDF document in final form.

- Page Size and Margins

Pages should be 8.5 inches wide and 11 inches long. The margins should be at least one half (1/2) of an inch on all sides. This will help avoid errors if the pages are printed and avoid obscuring information if the page is subsequently bound.

- Source of Electronic Document

To produce the highest quality electronic document, use an electronic source document to produce PDF documents whenever one is available. Scanned images of paper source documents should be used only if an electronic form is unavailable.

- Methods for Creating PDF Documents

Choose the methods for creating electronic documents carefully. For example, the use of Acrobat Distiller is preferable to Acrobat PDF Writer because of its ability to provide a more precise replication of the printed page. The PDF document will be the same as the paper document if the same PostScript file is used to print and distill the document.

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. Because of file size constraints, the use of gray scale or color is discouraged. If black and white photos are required, consider 8-bit gray scale images. If color photos are required, consider 24-bit RGB images.

- Hypertext Linking and Bookmarks

Hypertext links and bookmarks are techniques used to improve navigation through PDF documents. In general, for all documents with a table of contents, the

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applicant should provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices. These bookmarks are essential for the efficient navigation through documents. Hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page.

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.

See section IV for additional recommendations on bookmarks and hypertext.

- Document Information Fields

The document information fields are used to search for individual documents and to provide the name of the document when found.

See section IV for guidance on filling in the document information fields.

- 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.

- Naming PDF Files

At this time, limitations in CDER prevent the use of long file names. For this reason, file names of no more than 8 characters should be used with PDF as the extension (e.g., report12.pdf). Avoid punctuation, underscores, spaces, or other nonalphanumeric symbols. For uniformity, it is recommended that specific naming conventions be used for certain files in some submission types.

See section III.C for further guidance on file naming conventions.

- Security

Security settings or password protection for PDF files should be avoided. Allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. The integrity of the files will be secure since they will be archived directly to tape, and a read-only copy will be provided to the reviewer.

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- Indexing PDF Documents

Full text indexes are used to help find specific documents and/or search for text within documents. When a document or group of documents are 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 Exchange. Portions of a document that are imaged are not indexed. Even if the file only contains images, 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. All indexes should be placed in the folder for the item being indexed.

An item's table of contents file should be associated with the corresponding full text index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

See section III. C for additional guidance on the use of indexing.

B. File Formats for Data Sets Submitted in Electronic Format for the Archival copy

The decision to provide data sets in electronic format as the archival copy should only be made with the concurrence of the appropriate review division(s).

CDER currently is prepared to archive data sets submitted as SAS Version Five Transport File Format (SAS transport files) as a replacement for paper. The SAS transport format is an open format published by the SAS Institute. The description of the SAS transport file is in the public domain. Data can be translated to and from the SAS transport format to other commonly used formats without the use of programs from SAS Institute or any specific vendor.

SAS Version Five Transport Files are processed by the XPORT engine in Version 6 of SAS Software and later, and by PROC XCOPY in Version 5. SAS technical support document TS-140 provides the record layout of a SAS transport file. This document and additional information can be found on the SAS world wide web page at <http://www.sas.com>.

Data sets provided as part of a submission as SAS transport files will be imported into the software tool used by the reviewer. The most commonly used tools are database, spreadsheet, and statistical analysis programs. To aid reviewers in using the data sets, the applicant may also want to provide the reviewer with a desk copy of the data set in the

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format of the software tool used by the reviewer. This copy of the data sets cannot serve as the archival copy. See section VII on Review Aids for additional information.

SAS transport file names should be limited to 8 characters with the three-character extension XPT to be compatible with the current CDER network environment. The files should not be compressed. Create an individual transport file for each data set. Example data sets should be submitted to the review division prior to the NDA to ensure that the files open properly.

Additional guidance on providing data sets in electronic format for archiving are found in section V of this guidance document.

C. Organizing the Archival Copy Provided in Electronic Format

1. Organizing the main folder of the submission

All documents and data sets for the archival copy in electronic format should be placed in a main folder using the NDA number, in the form of N123456, as the folder name.



Inside the main folder, all of the documents and data sets should be organized by NDA item described on page 2 of FDA form 356h. Each item has an assigned subfolder where all of the documents and data sets that belong to an item are placed. See table 1 for a description of the items, folder organization, and regulatory reference.

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Table 1: Items of an NDA as described in Form 356h			
Item	Description	regulatory reference	subfolder name
1	Table of contents (Index)	21 CFR 314.50 (b)	main folder
2	Labeling	21 CFR 324.50	labeling
3	Summary	21 CFR 314.50 (c)	summary
4	Chemistry section	21 CFR 314.50 (d)(1)	cmc
5	Nonclinical pharmacology and toxicology section	21 CFR 314.50 (d)(2)	pharmtox
6	Human pharmacokinetics and bioavailability section	21 CFR 314.50 (d)(3)	cpbio
7	Clinical Microbiology	21 CFR 314.50 (d)(4)	micro
8	Clinical section	21 CFR 314.50 (d)(5)	clinstat
9	Safety update report	21 CFR 314.50 (d)(5)	update
10	Statistical section	21 CFR 314.50 (d)(6)	clinstat
11	Case report tabulations	21 CFR 314.50 (f)(1)	crt
12	Case report forms	21 CFR 314.50 (f)(2)	crf
13	Patent information	21 U.S.C. 355 (b) or (c)	other
14	Patent certification	21 U.S.C. 355 (b)(2) or j(2)(A)	other
15	Establishment description	21 CFR Part 600	other
16	Debarment certification	FD&C Act 306 (k)(1)	other
17	Field copy certification	21 CFR 314.50 (k)(3)	other
18	User fee cover sheet	Form FDA 3397	other
19	Other	specify	other

The applicant should provide a cover letter as a PDF file named cover.pdf inside the main folder . This cover letter should also be included with any paper portion of the archival copy. In addition to appropriate regulatory information as described in *Formatting, Assembling, and Submitting New Drug and Antibiotic Applications*, the cover letter should include:

1. A description of the submission.
2. A description of which portions of the submission are presented only in paper, only in electronic format, or in both paper and electronic format.
3. A description of the electronic submission including the contents of the media, their number and format, a description of the file types, and the total size of the submission (e.g., megabytes, gigabytes).
4. Verification that the submission is virus free with a description of the software used to check the files for viruses.

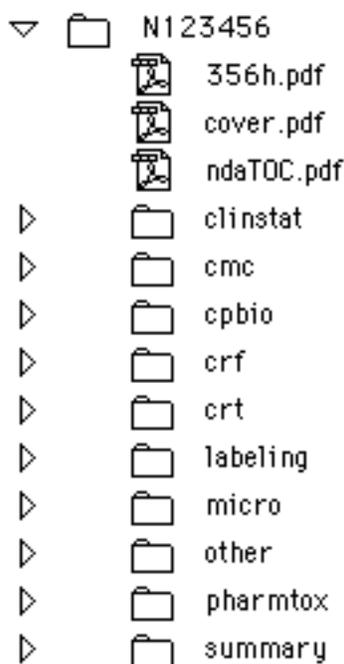
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5. A description of any deviation from the specifications in this guidance document.

The applicant also should provide FDA form 356h as a pdf file inside the main folder. On page 2 of the form, the applicant should note by each item if the documents for the item are in paper format, electronic format, or both paper and electronic format.

Inside the main folder, the applicant should provide a table of contents for the submission named ndaTOC.pdf. See item 1 below for additional information.

The following is an example of the contents of the main folder for NDA 123456



2. Organizing the subfolders of a submission

The archival copy should contain the documents and data sets for the items listed on FDA Form 356h. The guidance for providing each item in electronic format follows below.

Item 1 Table of Contents (Index)

Item 1 is the table of contents for the entire submission. (In FDA form 356h, this item, while called an “index,” is virtually synonymous with a table of contents of the submission and should not be confused with a full text index described in section III. A). The table of contents should list all items of the NDA found on page 2 of FDA form 356h (see table 2 below). If the archival copy of the item is in paper format, the number of the volume that holds the first document of the item should be provided. If the archival copy is in electronic

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format, the folder name containing the files should be provided. If portions of the item are both in paper and electronic format, both the volume number and folder name should be provided.

In the example of the table of contents for the electronic archival copy below, portions of the archival copy of the nonclinical pharmacology and toxicology sections are in paper and electronic format. The paper portion starts in volume 5. The electronic portion can be found in the pharmtox folder. The archival copy of the chemistry section is only provided in paper and starts in volume 1. There is an index of the entire submission in both paper and electronic format. The archival copy for all other items is only provided in electronic format.

Item	Description	Paper volume number	Folder name
1	Table of contents (Index)	1	main folder
2	Labeling	n/a	labeling
3	Summary	n/a	summary
4	Chemistry section	1	n/a
5	Nonclinical pharmacology and toxicology section	5	pharmtox
6	Human pharmacokinetics and bioavailability section	n/a	cpbio
7	Clinical Microbiology	n/a	n/a
8	Clinical section	n/a	clinstat
9	Safety update report	n/a	n/a
10	Statistical section	n/a	clinstat
11	Case report tabulations	n/a	crt
12	Case report forms	n/a	crf
13	Patent information	n/a	other
14	Patent certification	n/a	other
15	Establishment description	n/a	other
16	Debarment certification	n/a	other
17	Field copy certification	n/a	other
18	User fee cover sheet	n/a	other
19	Other	n/a	other

The table of contents should be provided as a single PDF file. The table of contents for the original NDA should be named ndaTOC.pdf. The table of contents for an amendment should be named amendTOC.pdf. The table of contents for a supplement should be named supplTOC.pdf.

A hypertext link should be provided from this table of contents to the corresponding table of contents for each item. These links are essential for establishing a comprehensive table of contents for the electronic submission.

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Some items, such as item 3 (the submission summary) and items 13 to 18, are single documents and are not associated with a table of contents. For these items, the hypertext link from the submission table of contents should be directly to the document.

Item 2 Labeling

Labeling is item 2 on page 2 of FDA form 356h. Under 21 CFR 314, the applicant shall submit copies of the label and all labeling for the drug product. The content and format of what is referred to in this section as **labeling text** is defined in 21 CFR 201.57 and includes all text, tables, and figures used in the package insert.

All documents for this section should be included in a single folder named labeling, and each label or labeling document should be provided in a single PDF file. There is no specific guidance for the file name of these PDF files.

The labeling text (see above) should be provided in a document that is letter size (8.5 by 11 inches) with font sizes 10 points or greater for text and 8 points or greater for tables and figures whenever possible. The labeling text should be in portrait orientation without any columns. Because PDF documents cannot be easily edited or compared electronically, labeling text should be provided in a word processing format (e.g., Microsoft Word) as well as in PDF. The word processing file will not be archived and should be handled as a review aid (see section VII). Since the labeling text will be used as the reference for labeling content, the submission of final printed labeling should be accompanied by a letter certifying that the labeling text and the final printed package insert are identical in content including text, bolding, figures, and tables. Content in figures and tables does not include such variations as line size, color, or shading.

The Title field of the Document Information fields for each PDF file should include the NDA number, the type of labeling (e.g., labeling text, package insert, container, carton), the date of labeling, and whether the labeling is draft, changes being effected or approved. For draft or changes being effected labeling, the date of labeling is the submission date, and for approved labeling, the date of approval. NDA numbers are in the form of N123456 and dates are in the form of 01jan1997. For example, a final printed package insert approved on January 10th of 1996 would be characterized in the Title field as:

N123456, package insert, approved, 10jan1996

The draft labeling text for N123456 submitted on May 5, 1995 would be:

N123456, labeling text, draft, 05may1995.

The manufacturer label code may be included in the subject field.

A table of contents for all PDF files in this section should be in the form of a PDF file. The labeling table of contents should include a list of all of the labeling examples provided.

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Hypertext links should connect documents listed in the table of contents with corresponding PDF files. The table of contents should be named labelTOC.pdf and placed in the labeling folder.

Item 3 Summary

The summary of the submission is item 3 on page 2 of FDA form 356h. Additional information about the content of the summary can be found under 21 CFR 314.50(c)(1).

The information for the summary section should be provided in a single PDF file named summary.pdf and placed in a folder named summary. It should also be identified in the Document Information Title field as submission summary.

There should be a hypertext link from the submission table of contents directly to the summary.pdf file.

For all documents with a table of contents, including the summary document, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices.

In the annotated label, hypertext links should be provided between all annotations and the appropriate sections of the summary or other items in the NDA.

Item 4 Chemistry, Manufacturing, and Controls (CMC) Section

The chemistry, manufacturing and controls section is item 4 from page 2 of FDA form 356h. Additional information about the content of this section can be found under 21 CFR 314.50(d)(1).

A single PDF file should be provided for each document in this section and all documents pertaining to drug substance, drug products, and environmental impact placed in folders named substan, product, environ, respectively. Place all of these folders in a single folder named cmc.

For documents dealing with drug substance, include *ds* in the Document Information Title field, the name of the active ingredients and a brief description of the document. The description should be limited to a couple of words. For documents dealing with a drug product, include *dp* in the Document Information Title field, the name of the drug product, and a brief description of the document. For documents dealing with environmental assessment, include *ea* in the Document Information Title field, the name of the drug product, and a brief description of the document.

A table of contents for all files in this section should be provided in the form of a PDF file. In the table of contents for the CMC section, list all documents included in the section. The location of the file with the file name and folder(s) should be included. The documents can be listed under the following headings:

2353dft.doc
6APR1998

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A. Drug Substance

1. Description & Characterization
2. Manufacturer
3. Synthesis/Method of Manufacture
4. Process Controls
5. Reference Standard
6. Specifications/Analytical Methods
7. Microbiology
8. Container/Closure System
9. Stability

B. Drug Product

1. Components/Composition
2. Specifications & Methods for Drug Product Ingredients
3. Manufacturer
4. Methods of Manufacturing and Packaging
5. In-process Controls & Tests
6. Specifications/Analytical Methods
7. Container/Closure System
8. Microbiology
9. Stability

C. Environmental Assessment

Hypertext links should connect documents listed in the table of contents with the corresponding pdf file. Name the table of contents cmcTOC.pdf and place in the cmc folder.

For all documents with a table of contents, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures and appendices.

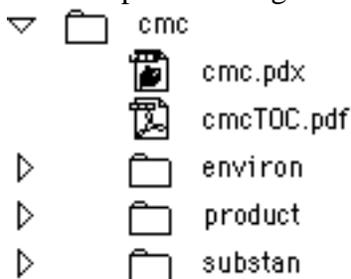
To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page.

Providing the following links, possibly in a summary document or table, can also improve the efficiency of the review: batch numbers to stability data, drug product batch numbers to formulation composition, clinical protocol numbers to the appropriate batch numbers, formulation composition to drug substance batch numbers, stability studies to description of container/closure systems, impurity profile to forced degradation data, impurity profile to synthetic source of impurity, specifications to validation reports, packaging components to DMF letters of authorization, names of chemical substances/degradents to their structures, chemical names to chemical abstract registry numbers.

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An index of the full text and the Document Information fields of all documents in this section should be provided. Name the index definition file `cmc.pdx`, and place this file and all associated index files in the `cmc` folder. Associate the `cmcTOC.pdf` file with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

An example of the organization of this item is below:



Item 5 Nonclinical Pharmacology and Toxicology Section

The nonclinical pharmacology and toxicology section is item 5 on page 2 of FDA form 356h. Additional information on the content of this section can be found in 21 CFR 314.50(d)(2).

All documents included in this section should be placed in a single folder named `pharmtox`.

The entire summary of the nonclinical pharmacology and toxicology section should be placed in a single PDF file named `pharmsum.pdf`. The summary should be identified in the Document Information Title field as `pharmtox summary`. The summary document should provide a hypertext link between each reference to a data summary table or figure supporting a conclusion and the corresponding data table or figure (whether located in a study report or elsewhere).

Each study report, including all appendices (except for the individual animal line listings), should be provided as a single PDF file. Include the study number in the name of the file. For example, study 1234 can be named `1234.pdf`. The individual animal line listings for the study should be provided as a separate file. Include the study number in the name of the file and add *d* to the file name for the animal line listings. For example, the animal line listings for study 1234 can be named `1234d.pdf`. For each study, place the two PDF files in a folder whose name includes the study number and place the folder in the `pharmtox` folder. The Title portion of the Document Information field of each study report should be designated study and followed by the study report number and the study type. Helpful information that may also be included in the Title field is the species and treatment duration. For example, study 2001, a 12-month toxicity study in dogs, should be identified as: study 2001, toxicity study, dog, 12 month. For the file that has the animal line listing, the

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word data should be added to the Title field. For the above example, the animal line listing file would be identified as: study, data, toxicity study, dog, 12 month

All publications should be provided in a single PDF file, and each publication should be designated *ref* and included in the reference number for each publication in the file name. For example, a publication that is designated as reference number 12 would be identified as ref12.pdf. If there is more than one reference per number, add letters for subsequent references. For example, for a series of publications under reference 12, designate the first as ref12.pdf and subsequent publications as ref12a.pdf, ref12b.pdf, etc. The Title portion of the Document Information field for each publication file should be designated as reference and followed by the reference number and brief description (couple of words) or the title of the publication.

A table of contents for all files in this section should be provided in the form of a PDF file named pharmTOC.pdf. The pharmtox table of contents should list all study reports, data (including study report numbers), publications, and the summary document provided in the pharmtox section. The location of the file with the file name and folder(s) should be included. Hypertext links should be provided between the documents listed in the table of contents and the corresponding PDF file. Place the pharmTOC.pdf file in the pharmtox folder.

For all documents with a table of contents, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page.

An index of the full text and the document information fields of all documents in this section should be provided. The index definition file should be named pharmtox.pdx, and this file and all associated index files should be placed in the pharmtox folder. Associate the pharmTOC.pdf file with this index so that whenever the pharmtox table of contents is opened, the associated index is automatically added to the available index list.

Animal line listings as data sets

The purpose of this part of the guidance is to describe how to submit the archival copy of individual animal line listings in electronic format that allows reviewers to use their own data analysis tools. **The decision to provide data sets in electronic format as the archival copy, instead of a paper or PDF format, should be made on a study-by-study basis and only with the prior agreement of the review division.**

In general, data sets should include both raw and derived data that normally would be provided in the paper or PDF individual animal data listings. Just as data for each domain

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(e.g., labs, histopathology) is provided as a table in a paper or PDF submission, with electronic data sets submissions, each domain is provided as a single data set.

The following information is intended to be the basis for discussions with the review division on the presentation of data in electronic format. The extent of the data needed by reviewers varies and more specific information can be obtained from the review division at the time of the pre-NDA meeting or earlier in the drug development process.

FORMAT OF THE DATA SETS:

As described in section II of this guidance document, data sets provided as SAS transport files, version 5, can be archived by CDER as a replacement for paper documents.

Data sets provided as SAS transport files will be imported into the software tool used by the reviewer. The most commonly used tools include: database programs, spreadsheet programs, and various statistical programs.

Example data sets should be submitted to the review division prior to the NDA to ensure that the files open properly. Data set files should be less than 25MB per file. The files should not be compressed. Each data set should be saved as an individual SAS transport file.

ORGANIZATION OF DATA SETS:

The type and amount of data vary from indication to indication, and the organization of the data should be discussed with the reviewing division prior to submission. In general, data from each study should be divided into data set files such as: clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, histopathology.

Data sets can be divided further to achieve a size less than 25 MB. For example, lab data may be further divided by specific lab tests. Additional data sets should be provided as needed. File names should be limited to 8 characters with the three character extension XPT to be compatible with the current CDER network environment.

All data sets for an individual study should be placed in a folder identified by the study name and all folders placed in a single folder called datasets. The datasets folder should be placed in the pharmtox folder.

A data set table of contents should list all data sets included in the submission with a full description of the contents of the data set. The table of contents should be provided as a PDF file named dataTOC.pdf and placed in the datasets folder.

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GENERAL CONSIDERATIONS FOR DATA SETS:

The efficient use of the data sets by the reviewer can be significantly improved if some basic principles are followed in setting up the data sets.

- Each animal should be identified with a single, unique number for the entire application. This unique number should be provided in each data set. This is essential for joining different data sets.
- For a data table, each data element should be represented as a single column heading. Each row should contain a single observation or result for an individual animal, allowing for multiple rows per animal.
- When at all possible, the same data element names and codes should be used across studies. This is helpful when combining data sets and reduces the time for learning the data sets. For example, if glucose is checked in a number of studies, the same name should be used to describe this variable in all of the studies.
- Include variable descriptions and codes in the column header. For example, for the variable name SEX include the following information “sex of the animal: m = male, f = female.”
- Duration is frequently part of an analysis. To save the reviewer time, start and stop times and dates should also be provided as duration of treatment based on the start of study treatment and expressed in minutes, hours, or days, whichever is appropriate. When expressed in days, the following formula should be used to calculate study day [(test date)- (date of first dose) + 1].
- Results are frequently analyzed based on treatment assignment, dose and sex of the animals. To save time for the reviewer, each data set should include these variables.

CONTENT OF SPECIFIC DATA SETS:

The exact data elements needed by the reviewer will vary, and the content of the data sets should be discussed with the review division as early in the drug development process as possible. As an example, the clinical chemistry data set might include the following data elements: lab test name, lab test date/time, study day of test, lab test result, baseline value of lab test, change from baseline.

DOCUMENTATION OF THE DATA SETS:

The key elements of documentation are in the data definition table. The data definition table includes an organized listing of all variable names, descriptive narrative, data types, codes (and decodes). Data definition tables should be provided as a single PDF file named

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variable.pdf and include a hypertext link from the listing in the data set table of contents to the appropriate data definition table.

Most of this information can also be included in the description field in the SAS transport file. For each variable, include a narrative description and any codes that were used to describe the information in each cell. If the codes cannot fit into the description field, then include a separate column with the text of the cell.

Item 6 Human Pharmacokinetics and Bioavailability Section

The human pharmacokinetics and bioavailability section is item 6 on page 2 of FDA form 356h. Additional information on the content of this section can be found under 21 CFR 314.50(d)(3).

All documents and folders for this section should be placed in a single folder named cpbio and a single PDF file for each document (e.g., study reports and summaries) should be provided and placed in the cpbio folder.

The summary document for the clinical pharmacology and biopharmaceutics section should be named cpbiosum.pdf and placed in the cpbio folder. The summary document should provide a hypertext link between each reference to a data summary table or figure supporting a conclusion and the corresponding data table or figure (whether located in a study report or elsewhere). The summary should be identified in the Document Information Title field as cpbio summary.

The cpbio folder should contain subfolders named biopharm, PK, PD, subpops, drugint, invitro, assay and pubs. The following table summarizes the documents to be included in each subfolder.

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Documents included in each subfolder	
Folder name	Should contain studies
biopharm	addressing relative bioavailability, bioequivalence, food-effects, dissolution, and in vitro - in vivo correlation related to bioavailability
PK	related to pharmacokinetics
PD	related to pharmacodynamic results and PK/PD assessments
subpops	evaluating the effects of age (elderly and pediatrics) or gender on the pharmacokinetics or pharmacodynamics. Studies involving sub-populations such as patients with renal disease and patients with hepatic disease should be included in this folder. If the sub-population listed above is the primary target population, then studies should not be filed under the folder Subpops, but should be included in the main folders as appropriate.
drugint	related to drug interactions
invitro	related to in vitro work such as protein binding, RBC distribution and drug metabolism
assay	containing assay descriptions and their validation reports including cross validation of assays
pubs	from publications supporting the submission

The Document Information Title field for the studies should include the type of study (e.g., biopharm, pk, pd, subpops, drugint, invitro, assay, pubs) and the study number. For example, the report for study 201, a pharmacokinetic study should be designated as pk, study 201.

A table of contents for all files in this section should be provided in the form of a PDF file. In the clinical pharmacokinetics and bioavailability table of contents, all study reports (including study report numbers) and all other documents should be listed. The location of the file with the file name and folder(s) should be included. Hypertext links should be provided between the documents listed in the table of contents and the corresponding PDF file. The table of contents should be named cpbioTOC.pdf and placed in the cpbio folder. The documents can be listed under the following headings:

- Summary
- Biopharmaceutics
- Pharmacokinetics
- Pharmacodynamics
- Subpopulation Studies
- Drug Interactions
- In Vitro Studies
- Assay
- Publications

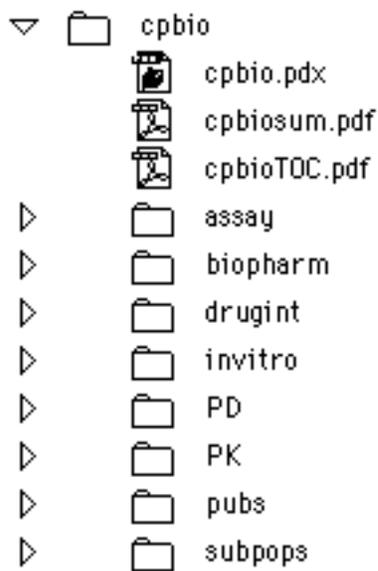
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For all documents with a table of contents, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page.

An index of the full text and the document information fields of all documents in this section should be provided. The index definition file should be named `cpbio.pdx` and the `cpbio.pdx` file and all associated index files placed in the `cpbio` folder. Associate the `cpbioTOC.pdf` file with this index so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

An example of the organization of this item is below:



Item 7 Clinical Microbiology

The clinical microbiology section is item 7 on page 2 of FDA form 356h. Additional information on the content of this section can be found under 21 CFR 314.50 (d)(4).

All documents for this section should be placed in a single folder named `micro` and a single PDF file provided for each document. The types of studies provided depend on whether the drug is an anti-infective drug product, antiviral drug product, or an immunomodulator. For an anti-infective drug product, the `micro` folder should contain subfolders named `preclinical` and `clinical`. The following tables summarize the documents to be included in each subfolder.

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Documents to be included in the subfolders for anti-infectives	
Folder Name	Should contain studies
Preclinical	Mechanism of action, antimicrobial spectrum of activity, intracellular antimicrobial concentration assessment, mechanism(s) of resistance, susceptibility test methods, pharmacokinetics, pharmoacodynamics, bioavailability, prophylactic and therapeutic studies, and provisional interpretative criteria.
Clinical	Organism relevance to pending indications, susceptibility test quality control data, dilution disc diffusion correlation, bacteriological efficacy studies,

The summary document for the clinical microbiology section should be named *microsum.pdf* and placed in the *micro* folder. The summary documents should provide hypertext link between each reference to a data summary table or figure supporting the conclusions and the corresponding data table or figure (whether located in a study report or elsewhere).

The summary should be identified in the Document Information Title field as *micro summary*. For studies, the Title portion of the Document Information field should include the type of study and the appropriate reference number.

A table of contents for all files in this section should be provided in the form of a PDF file. The microbiology table of contents should list all documents included in the section. The location of the file with the file name and folder(s) should be included. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided and the table of contents named *microTOC.pdf* and placed in the *micro* folder. For an anti-infective drug product, the documents can be listed under the following headings:

1. Summary
2. *In vitro* Preclinical Data
 - A. Mechanism(s) of Action
 - B. Antimicrobial Spectrum of Activity
 - C. Intracellular Antimicrobial Concentration Assessment
 - D. Mechanism(s) of Resistance Studies (Phase 1 to Phase 3)
 - F. Susceptibility Test Method(s) Analysis
3. *In vivo* Human and Animal Data
 - A. *In vivo* Phase 1 and Phase 2 Data
 - B. Provisional Interpretive Criteria

For all documents with a table of contents, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices.

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To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related section, references, appendices, tables, or figures that are not located on the same page.

An index of the full text and the Document Information fields of all documents in this section should be provided. The index definition file should be named *micro.pdx* and the *micro.pdx* file and all associated index files placed in the *micro* folder. Associate the *microTOC.pdf* file with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

Item 8 Clinical Section

The clinical section is item 8 on page 2 of FDA form 356h. Additional information on the content of this section can be found under 21 CFR 314.50 (d)(5), the guidance on the *Format and Content of the Clinical and Statistical Sections of NDAs*, and the ICH E3 *Structure and Content of Clinical Study Reports*.

All documents in this section should be placed in a single folder named *clinstat*. Subfolders should be provided for each indication, if applicable. A single PDF file should be provided for each document. The case report tabulations (individual patient data listings) and the case report forms (sections 16.3 and 16.4 of the E3 *Structure and Content of Clinical Study Reports*, respectively) should not be included with the study reports and should be included in items 11 and 12, respectively. Include the study number, *iss*, or *ise* in the file name, as applicable. For example, study 1234 should be named *1234.pdf*.

As an alternative, each study report and integrated summary can be divided into two separate PDF files instead of one file as described above. The first PDF file should include the body of the study or summary report, all tables, figures, and graphs referred to but not included in the body of the study report, the reference list, the protocol with all amendments, and a sample case report form. This is sections 1 to 16.1.2 of the clinical study report as defined in the E3 *Structure and Content of Clinical Study Reports*. Include the study number, *iss*, or *ise* in the file name, as applicable. As noted above, the case report tabulations (individual patient data listings) and the case report forms should only be included in item 11 and 12, respectively. The second PDF file should contain the remaining appendices (sections 16.1.3 to 16.2 as defined by the E3 *Structure and Content of Clinical Study Reports*). Include the study number, *iss*, or *ise*, as applicable and add *app* to the file name. For each study, place the two PDF files in a folder whose name includes the study number. For the Integrated Summary of Safety and the Integrated Summary of Efficacy, place the two PDF files in folders named *iss* and *ise*, respectively. Place all folders in the *clinstat* folder.

The Title portion of the Document Information field should include a brief description of the document, usually consisting of a couple of words. All study reports should include the study number as a description. For example, the report for study 201 should include study 201 in the title field. The Integrated Summary of Safety and the Integrated Summary of Efficacy use *iss* and *ise*, respectively.

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A table of contents for all files in this section should be provided in the form of a PDF file. The clinstat table of contents should list all study reports (including study report numbers) by indication, formulation, population (such as adult, pediatric) and type of trial (such as controlled clinical trials, open label trials), as appropriate. All other documents in the clinical section should be listed with a brief description of the document. The location of the file with the file name and folder(s) should be included. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided and the table of contents named clinTOC.pdf and placed in the clinstat folder.

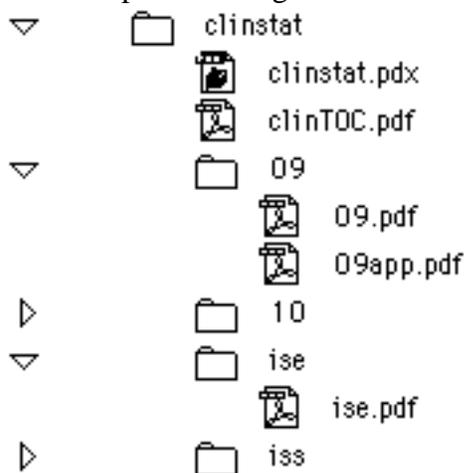
For all documents with a table of contents, the applicant should provide bookmarks for each item in the document's table of contents including all tables, figures and appendices (even if included in a separate file).

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables or figures that are not located on the same page.

For study reports, a bookmark to the appropriate case report tabulations that are found in the domain and/or profile folder should be provided. This bookmark may consist of a single link that would take the reviewer to the place in the domain or profile table of contents where the study's case report tabulations are listed or to the single file that contains the appropriate domain or patient profiles. A similar bookmark should be included for the case report form table of contents located in the *crf* folder.

An index of the full text and the Document Information fields of all documents in this section should be provided. The index definition file should be named clinstat.pdx and the clinstat.pdx file and all associated index files placed in the clinstat folder. Associate the clinTOC.pdf file with this index so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

An example of the organization of this item is below.



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Item 9 Safety Update

The safety update is item 9 on page 2 of FDA form 356h. Additional information about the contents of this section can be found in 21 CFR 314.50 (d)(5). The guidance for this section is similar to the clinical section guidance.

All documents for this section should be placed in a single folder named update and a single PDF file provided for each document.

A table of contents for all files in this section should be provided in the form of a PDF file. The safety update table of contents should list of all documents included in the section. The location of the file with the file name and folder(s) should be included. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided and the table of contents named updatTOC.pdf and placed in the update folder.

An index of the full text and the Document Information field of all documents in this section should be provided. The index definition file should be named update.pdx and the update.pdx file and all associated index files placed in the update folder. Associate updatTOC.pdf with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

Item 10 Statistical Section

This section should be identical to the clinical section. Documents describing statistical methods and the like should be included in item 8. For this item, the submission table of contents should be linked to the clinTOC.pdf.

Item 11 Case Report Tabulations (CRTs)

Case report tabulations are item 11 on page 2 of FDA form 356h. Additional information on the content of this section can be obtained from 21 CFR 314.50(f)(1). CRTs can be provided in two forms, patient profiles and domain profiles (see table 3 below). Patient profiles can be provided as PDF files. Domain profiles can be provided as PDF files and/or SAS transport files. Consult with the reviewing division to determine if both patient profiles and domain profiles are needed and to determine which file format(s) should be used for the domain profiles.

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CRT	Description	Format
Patient profiles	Patient profiles contain all of the study data collected for an individual patient organized by time.	PDF
Domain profiles	Commonly referred to as patient line listings or patient data listings, domain profiles consist of all data collected for a single CRF domain (such as demographics, vital signs, adverse events, laboratory measurements, efficacy measures) from one study.	PDF SAS Transport

Patient profiles as PDF files

There are three methods for organizing the patient profiles. One method is to include all patient profiles for an entire study in a single file. Another is to provide all patient profiles for a single site in one file. The term study site is also commonly identified as the study center or individual investigator. Including the study or site number in the file name of the patient profile will help identify the file. A third method is to provide each individual patient's complete patient profile as a single PDF file. Including the patient ID in the file name will help identify the file.

If each patient's profile is provided as a single PDF file, then all patient profiles for a single study site should be placed in a folder identified with the site number. All site folders should be placed in a single folder identified by the study number. For example, all patient profiles for site 3 for study 301 would be placed into a folder named 3, which then would be placed in a folder named 301. In the Document Information Title field include *pp*, the study number, the site identification and the patient's unique ID number. The unique patient ID number should be composed of elements of the study number, site number, and patient number, or a functional equivalent. For example, the patient profile for patient 001 in study 2001 at site 003 would have the following in the Title field: *pp*, study 2001, site 003, PID 2001-003-001.

If all patient profiles from a single site are included in one file, then all files for a particular study will be placed in a single folder identified by the study number. Place all of these study folders in a single folder named *profile*. The Document Information fields for each file should contain *pp*, the study number, and the site identification in the Title field

If all patient profiles for a study are placed in a single file, then place these files directly into the *profile* folder. The document information fields for each of these files should contain *pp* in the Title field and the study number.

Place the *profile* folder into a folder named *crt*.

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Provide a table of contents of all patient profiles in the form of a PDF file. If the profiles for a study are included in a single file, the patient profiles table of contents should list all of the studies and provide a hypertext link between the study listing in the table of contents and the corresponding study patient profile PDF file. If the profiles for a single site are included in a single file, the table of contents should also list all of the sites. If each patient profile is provided as an individual file, the patient profiles table of contents should list the unique patient ID numbers by study and site. The location of the file with the file name and folder(s) should be included. Hypertext links between the patient listings in the patient profiles table of contents and the corresponding patient profile PDF files should be provided. The table of contents files should be named pptoc.pdf and placed in the profile folder.

An index of the full text and the Document Information field of all documents in this section should be provided. The index definition file should be named profile.pdx, and the profile.pdx file and all associated index files placed in the profile folder. Associate ppTOC.pdf with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

Domain profiles as PDF files

There are two methods for organizing the domain profiles. One method is to include all domain profiles for an entire study in one file. When using this method, the applicant should provide a bookmark to each individual domain profile. Including the study number in the file name of the domain profile will help identify the file.

Alternatively, a single PDF file can be provided for each CRF domain. Including the name of the domain in the file name will help identify the file.

All domain profiles for a single study should be placed in a folder identified with the study number. For example, domain profiles for study 301 should be placed into a folder named 301. Place all of these folders in a single folder named domains and place this folder into a folder named *crt*.

If all domains for a study are included in one file, the Document Information fields for each file should include *dp* in the Title field and study number. If each domain is in a separate file, also include the appropriate CRF domain name. For example, the domain profiles for vital signs in study 2001 would have the following in the Title field: dp, study 2001, vital signs.

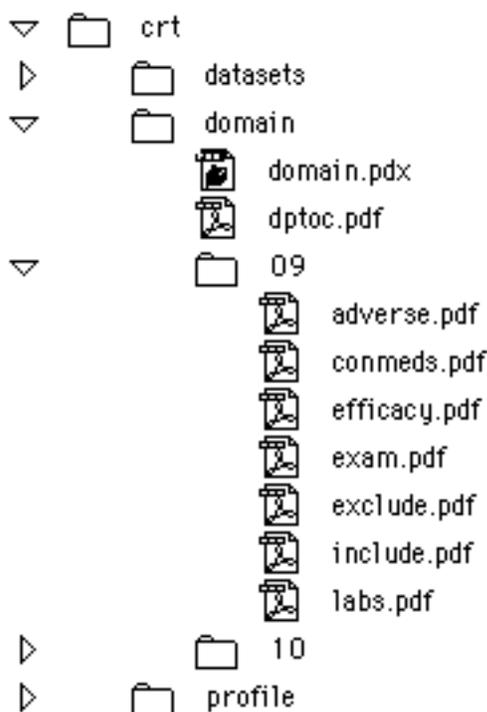
Provide a table of contents for all domain profiles in the form of a PDF file. If the domain profiles for a study are in a single file, the domain profiles table of contents should list all of the studies and provide a hypertext link between the study listing in the table of contents and the corresponding study domain profile PDF file. If each domain profile for a study is provided as an individual file, all CRF domains should be listed by study. The location of the file with the file name and folder(s) should be included. Hypertext links between the

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CRF domain listing in the domain profiles table of contents and the corresponding CRF domain profiles PDF files should be provided. The domain profiles table of contents should have the file name dpTOC.pdf and be placed in the domain folder.

An index of the full text and the Document Information field of all documents in this section should be provided. The index definition file should be named domain.pdx and the domain.pdx file and the associated index files placed in the domain folder. Associate dpTOC.pdf with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

An example of the organization of this item is below.



Domain profiles as data sets

The purpose of this part of the guidance is to describe how to submit the archival copy of domain profiles in electronic format that allows reviewers to use their own data analysis tools. **The decision to provide data sets in electronic format as the archival copy should be made only with the prior agreement of the review division.**

In general, data sets should include both raw and derived data that normally would be provided in the paper or PDF domain profiles (individual patient data listings) described above. Just as each case report form domain is provided as a table in a paper or PDF submission, with electronic data sets submissions, each case report form domain is provided as a single data set.

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The following information is intended to be the basis for discussions with the review division on the presentation of data in electronic format. The extent of the data needed by reviewers varies and more specific information can be obtained from the review division at the time of the pre-NDA meeting or earlier in the drug development process.

FORMAT OF THE DATA SETS:

As described in section II of this guidance document, data sets provided as SAS transport files, version 5, can be archived by CDER as a replacement for paper documents.

Data sets provided as SAS transport files will be imported into the software tool used by the reviewer. The most commonly used tools include: database programs, spreadsheet programs, and various statistical programs.

Illustrative data sets should be submitted to the review division prior to the NDA to ensure that the files open properly. Data set files should be less than 25MB per file. The files should not be compressed. Each data set should be saved as an individual file.

ORGANIZATION OF DATA SETS:

The type and amount of data vary from indication to indication and the organization of the data should be discussed with the reviewing division prior to submission. In general, data from each study and data supporting the integrated summary of safety and efficacy should be divided into the data set files as shown in table 4. Data sets can be divided to less than 25 MB. For example, lab data may be further divided by specific lab tests. Additional data sets should be provided as needed. File names should be limited to 8 characters with the three character extension XPT to be compatible with the current CDER network environment.

Background information		Results	
File name	Description	File name	Description
demog.xpt	Demographics	exposure.xpt	Drug exposure
include.xpt	Inclusion criteria	dispos.xpt	Disposition
exclude.xpt	Exclusion criteria	efficacy.xpt	Efficacy results
conmeds.xpt	Concomitant medication	adverse.xpt	Adverse Events
medhist.xpt	Medical history	lab_chem.xpt	Lab - chemistry
		lab_heme.xpt	Lab - hematology
		lab_urin.xpt	Lab - urinalysis
		ECG.xpt	ECG
		vitals.xpt	Vital signs
		exam.xpt	Physical examination

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All data sets for an individual study should be placed in a folder identified by the study name and all folders placed in a single folder called datasets. The datasets folder should be placed in the *crt* folder.

A data set table of contents should list all data sets included in the submission with a full description of the contents of the data set. The table of contents should be provided as a PDF file named dataTOC.pdf and placed in the datasets folder.

GENERAL CONSIDERATIONS FOR DATA SETS:

The efficient use of the data sets by the reviewer can be significantly improved if some basic principles are followed in setting up the data sets.

- Each patient should be identified with a single, unique number for the entire application. This unique number needs to be provided in each data set. This is essential for joining different data sets.
- For a data table, each variable should be represented as a single column heading. Each row should contain a single observation or result for an individual patient, allowing for multiple rows per patient.
- When at all possible, the same variable names and codes should be used across studies. This is helpful when combining data sets and reduces the time for learning the data sets. For example, if glucose is checked in a number of studies, use the same name to describe this variable in all of the studies.
- Include variable descriptions and codes in the column header. For example, for the variable name SEX include the following information: “patient’s sex, f= female, m = male”.
- Duration is frequently part of an analysis. To save the reviewer time, start and stop times and dates should also be provided as duration of treatment based on the start of study treatment and expressed in minutes, hours, or days, whichever is appropriate. When expressed in days, the following formula should be used to calculate study day: [(test date)- (date of first dose) + 1].
- Results are frequently analyzed based on the study, center/site, treatment assignment, sex, age, and/or race of the subjects. To save time for the reviewer, each data set should include these variables.
- For treatment assignment, all placebo patients should be 0, and in fixed dose studies, the treatment assignment variable should be the prescribed dose.

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CONTENT OF SPECIFIC DATA SETS:

The following lists contain suggested data elements for the individual data sets. This listing is meant to serve as a starting point for discussion between the applicant and the review division on the content of the data sets and, therefore, are not all inclusive. The extent of the data needed by the reviewer will vary, and more specific information should be obtained from the review division at the time of the pre-NDA meeting or earlier in the drug development process.

Demographics

- age
- sex
- race
- weight
- height
- country
- (additional variables)

Inclusion criteria

- vary by protocol

Exclusion criteria

- vary by protocol

Concomitant drugs

- drug name
- drug start date
- drug stop date
- drug started before study (yes/no)
- drug type
- (additional variables)

Medical history

- medical condition
- past condition (yes/no)
- current condition (yes/no)
- body system
- (additional variables)

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Disposition

- screen (yes/no)
- enrolled (yes/no)
- randomized (yes/no)
- received at least one treatment (yes/no)
- completed study (yes/no)
- reason for discontinuation
- treatment at time of discontinuation
- cumulative dose at time of discontinuation
- duration of treatment at time of discontinuation
- (additional variables)

Exposure

- dose
- dose start date/time
- dose end date/time
- duration of dose
- treatment sequence number for cross over, titration, dose adjustments, etc. (1,2,3...)
- study phase (titration, maintenance, taper, washout, etc.)
- randomization date/time
- study day
- baseline weight
- (additional variables)

Efficacy data

- vary by protocol

Physical exam

- exam date/time
- study day of exam
- visit number
- exam on scheduled visit (yes/no)
- reason for exam
- timing of exam in relationship to last dose of study treatment
- exam parameter
- body system
- abnormal (yes/no)
- baseline exam (yes/no)
- change from baseline (improvement, worsening, no change)
- past condition (yes/no)
- (additional variables)

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Adverse events

- preferred term
- reported term
- body system
- start time of event
- stop time of event
- duration
- course (continuous or intermittent)
- severity (mild, moderate, severe)
- seriousness (yes/no)
- seriousness type (death, life threatening, permanently disabling, hospitalization, cancer, overdose, congenital anomaly)
- action taken (none, decrease dose, discontinuation, etc.)
- outcome (recovered, alive with sequelae, died, ongoing, persisting, unknown)
- causality (possible, probable, remote, unrelated)
- study day
- visit number
- timing of onset in relationship to last dose of study treatment
- study treatment at time of event
- dose of treatment in absolute amount at the time of event
- drug concentration
- duration of treatment
- concomitant treatment
- (additional variables)

Vital signs

- vital sign date/time
- study day of vital sign
- visit number
- vital signs taken on scheduled visit (yes/no)
- vital signs used as the baseline value (yes/no)
- reason for vital signs
- vital signs parameter value
- baseline value of vital signs parameter
- change from baseline
- abnormal (yes/no)
- vital sign related discontinuation (yes/no)
- duration of treatment at the time of vital signs
- dose of treatment at the time of vital sign
- timing of vital signs in relationship to last dose of study treatment
- (additional variables)

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ECG

- ECG date/time
- study day of ECG
- visit number
- ECG taken on scheduled visit (yes/no)
- ECG used as the baseline value (yes/no)
- reason for ECG
- ECG parameter
- ECG parameter value
- baseline value of ECG parameter
- change from baseline
- abnormal (yes/no)
- ECG related discontinuation (yes/no)
- duration of treatment at the time of ECG
- dose of treatment at the time of ECG
- timing of ECG in relationship to last dose of study treatment
- (additional variables)

Labs

- lab test name
- lab test upper limit of normal (ULN)
- lab test lower limit of normal (LLN)
- lab test unit of measure
- lab test date/time
- study day of test
- visit number
- sample taken on scheduled visit (yes/no)
- value used as the baseline value (yes/no)
- lab test result
- baseline value of lab test
- change from baseline
- lab test greater than ULN (yes/no)
- lab test less than LLN (yes/no)
- lab test value in times of ULN
- lab related serious adverse event (yes/no)
- lab related discontinuation (yes/no)
- duration of treatment at time of assessment
- dose of treatment at time of assessment
- (additional variables)

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PROGRAMS AND DERIVED VARIABLES:

Programs and codes used to arrive at the final analysis for principal efficacy and safety data should be provided and placed in the datasets folder. The programs should contain sufficient detail to allow the reviewer to follow the logical flow of the program.

A listing of all derived variables with text describing their creation should be included. This file should be named derived.pdf and placed in the datasets folder.

DOCUMENTATION OF THE DATA SETS:

The critical elements of documentation are the annotated case report form and the data definition table.

The annotated case report form is a blank CRF that maps each blank on the case report form to the corresponding element in the data base. The annotated case report form should provide the table names, field names, and coding. Each page and each blank of the CRF should be represented. The sponsor should write “not entered in data base” in all sections where this applies. Provide the annotated case report form as a PDF file.

The data definition table includes an organized listing of all variable names, descriptive narrative, data types, codes (and decodes). Provide the data definition tables as a single PDF file named variable.pdf and include a hypertext link from the listing in the data set table of contents to the appropriate data definition table. Table 5 gives an example of part of a data definition table for adverse events for study 201.

Variable name	Narrative description	data type	Codes
PATID	unique patient ID number	number	n/ a
SEX	patient's sex	char	f= female, m= male
BDATE	birth date	date	n/ a
TRT	assigned treatment	number	0= placebo, 5= 5mg

Most of this information can also be included in the description field in the SAS transport file. For each variable include a narrative description and any codes that were used to describe the information in each cell. If the codes cannot fit into the description field, then include a separate column with the text of the cell. For example, for the variable concomitant medications, there may be a number code for each type of medication. If all of this information cannot fit into the description field, include a separate column for concomitant medications that has the actual name of the concomitant medication.

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Item 12 Case Report Forms (CRFs)

Case report forms are item 12 on page 2 in FDA form 356h. Additional information on the content of this section can be found under 21 CFR 314.50 (f)(2) and 21 CFR 314.50 (f)(3).

If a paper CRF was used in the clinical trial, the electronically submitted CRF should be an exact image or series of images of the paper CRF that contains all original entries with all modifications, addenda, corrections, comments, annotations, and any extemporaneous additions.

There are three methods for organizing the case report forms. One method is to provide each patient's case report form in a single PDF file. Including the patient ID in the file name will help identify the file. Alternatively, if each patient's CRF is brief, then all CRFs for a single site or study may be placed in a single PDF file as long as the file size is less than 50 MB. The term study site is also commonly identified as the study center or individual investigator. Including the study or site number in the file name of the case report form will help identify the file.

If each patient's case report form is provided as a single PDF file, all case report forms for a single study site should be placed in a folder identified with the site number. All site folders should be placed in a single folder identified by the study number. For example, all case report forms for site 3 for study 301 would be placed into a folder named 3, which would be placed in a folder named 301. If all case report forms from a single site are included in one file, this file should be placed in a single folder identified by the study number. Place all case report form folders in a single folder named *crf*. If all case report forms for a study are placed in a single file, then place this file directly into the *crf* folder.

If all case report forms for a study are included in one file, the Document Information fields for each file should contain *crf* in the Title field and the study number. If all case report forms for a single site are included in one file, add the site identification to the Title field. If each case report form is in a separate file, also include the site number and the unique patient ID number used in the submission. The unique patient ID number should be composed of elements of the study number, site number, and patient number, or a functional equivalent. For example, the case report form for patient 001 in study 2001 at site 003 would have the following in the Title field: *crf, study 2001, site 003, PID 2001-003-001* .

The case report form for patient 12345 in study 2001 at site 1234 would have the following in the Title field: *crf, study 2001, site 01234, PID 2001-1234-12345*.

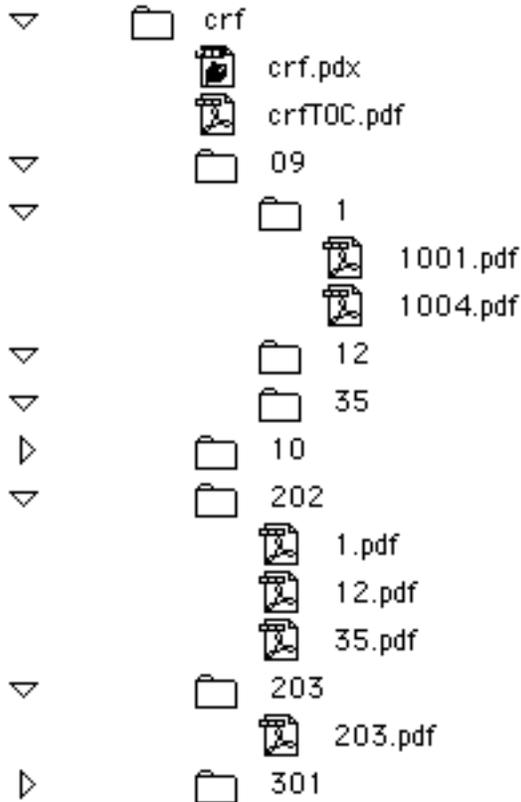
Provide a table of contents of all case report forms in the form of a PDF file. If the case report forms for a study are included in a single file, the case report forms table of contents should list all of the studies and provide a hypertext link between the study listing in the table of contents and the corresponding study case report forms PDF file. If the case report

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forms for a single site are included in a single file, the table of contents should also list all of the sites. If each case report form is provided as an individual file, the case report forms table of contents should list unique patient ID numbers by study and site. The location of the file with the file name and folder(s) should be included. Hypertext links between the listings in the case report forms table of contents and the corresponding case report forms PDF files should be provided. The table of contents should be named *crfTOC.pdf*, and placed in the *crf* folder.

An index of the full text and the Document Information field of all documents in this section should be provided. The index definition file should be named *crf.pdx* and the *crf.pdx* file, and the associated index files placed in the *crf* folder. Associate *crfTOC.pdf* with the index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

An example of the organization of this item is provided below.



Item 13 Patent Information

Item 14 Patent Certification

Item 15 Establishment Description

Item 16 Debarment Certification

Item 17 Field Copy Certification

Item 18 User Fee Cover Sheet

Items 13 through 18 are on page 2 of FDA form 356h. Form 356h provides the appropriate regulatory reference for each of these items. All documents for this section should be placed in a single folder named other and a single PDF file provided for each document. The names for these files are in table 6. For these single documents, no table of contents is needed. There should be a hypertext link between the submission table of contents and the individual PDF file.

Item	Name	File name
Item 13	Patent information	patinfo.pdf
Item 14	Patent certification	patcert.pdf
Item 15	Establishment description	estab.pdf
Item 16	Debarment certification	debar.pdf
Item 17	Field copy certification	fieldcer.pdf
Item 18	User fee cover sheet	userfee.pdf

IV. ARCHIVAL COPY IN PAPER FORMAT

Once CDER identifies in public docket number 92S-0251 a submission type as one that can be archived in an electronic format, the applicant has the option of providing all, or only a portion of, the archival copy of the submission type in electronic format. Any portion of the archival copy of a submission not provided in electronic format must be submitted in paper.

If portions of the archival copy are submitted in paper and electronic format, the index (commonly referred to as the table of contents) for the submission should include the location of the electronic files by file and folder name so the index is comprehensive. See section III for the appropriate folder names.

The paper portion of the archival copy should be submitted as described in the guidance entitled *Formatting, Assembling, and Submitting New Drug and Antibiotic Applications*.

V. REVIEW COPY

The regulations require the applicant to submit both an archival and review copy of the submission. An archival copy provided in electronic format can also serve as the source, or a partial source for the primary review of the submission. Reviewers are able to use electronic submissions of CRTs, CRFs and many other parts of the application. However, at this time, many reviewers prefer to use a paper copy when reading text and other heavily used parts of the application. Therefore, even when a submission is provided in electronic format, applicants must continue to provide paper review copies of parts of the technical sections (i.e., chemistry, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, clinical and statistical) [21 CFR 314.50(d)]. The portions of the review copy for which a paper copy need not be submitted when the archival copy is submitted in electronic format are described in table 7.

Paper review copies for each section must be separately bound [21 CFR 314.50]. Each review copy should include a table of contents for the section, a copy of the application form (FDA 356h), a copy of the cover letter, any letter of reference or authorization, a copy of the index for the entire application, and a copy of the application summary of the submission (item 2 on page 2 of FDA form 356h). See *Formatting, Assembling, and Submitting New Drug and Antibiotic Applications* for additional information.

When the review copy accompanies an electronic archival copy, the following also should be considered:

- The review division may elect to identify additional portions of the review copy for which a paper submission may be eliminated.
- The paper review copy must be an accurate and complete copy of the archival document (or portion of a document). This can be accomplished by using the archival PDF file to generate the paper review copy.
- Each document (or portion of a document) provided in the review copy should be physically separated by volumes (or tab dividers within volumes) just as each document is provided as a separate PDF file in the archival copy.
- The documents in the review copy should be arranged in the same order as listed in the table of contents provided with the archival copy. The table of contents for the review copy should include the location of the review copy of each document by volume number(s) and the location of the corresponding archival PDF file by folder.

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Table 7: Portions of the paper review copy that need not be submitted if the corresponding archival copy is submitted in electronic format	
CMC	<ul style="list-style-type: none"> • assay validation reports
Nonclinical pharmacology and toxicology	<ul style="list-style-type: none"> • individual animal line listings
Clinical sections <ul style="list-style-type: none"> • Human pharmacokinetics and bioavailability • Microbiology • Clinical • Statistical 	<p>study report appendices 16.1.3 to 16.4 as defined by the E3 <i>Structure and Content of Clinical Study Reports</i> (See this document for additional details on the following appendices)</p> <ul style="list-style-type: none"> • 16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority)- Representative written information for patient and sample consent forms • 16.1.4 List and description of investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study • 16.1.5 Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority's requirement • 16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used • 16.1.7 Randomization scheme and codes (patient identification and treatment assigned) • 16.1.8 Audit certificates • 16.1.9 Documentation of statistical methods • 16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used • 16.1.11 Publications based on the study • 16.1.12 Important publications referenced in the report • 16.2 Patient data listings • 16.3 Case report forms • 16.4 Individual patient data listings

VI. SUPPLEMENTS AND AMENDMENTS

The submission format for an amendment to a pending application or supplement to an approved application should be the same as that used for an original application. Each submission should consist of two copies, a complete archival copy and an appropriately segmented review copy. See sections III, IV, and V for guidance.

VII. REVIEW AIDS

Applicants can supply review aids in addition to the archival and review copy of the submission to help in the review of the application. Examples of review aids that applicants can provide include the following.

- Portions of the submission in a word processor format. Such files are helpful for reviewers who frequently copy and edit an applicant's tables. The files can also be used for editing labeling and comparing different versions of labeling.
- Data in electronic format to be used with a specific review tool (e.g., database, spreadsheet, and/or statistical analysis programs). The format and content of this kind of material should be discussed with the review division prior to submission.
- Customized systems that contain documents and/or data sets in proprietary electronic formats with specialized tools for handling documents and analyzing data. The format and content of this material should be discussed with the review division prior to submission.

The decision to provide review aids should be made on a case-by-case basis after consulting with that review division. Review aids should be supplied as desk copies and are not considered part of the archival submission.

The review division and applicant should consult with CDER's Office of Information Technology (OIT) concerning any review aid that requires connection to CDER's network or may require OIT resources.

The media to be used for electronic review aids should be based on the type of media that can be handled by the specific review division. Possibilities include 3.5 inch floppy disks, CD ROM, and other removable media. After the initial NDA submission, all review aids should be sent directly to the review division document room. See section VIII for more information.

VIII. SENDING SUBMISSIONS TO CDER

A. Where to Send the Submission

One copy of all electronic files being provided to serve as the archival copy of a submission should be sent to the CDER Central Document Room (CDR). The paper portion of any submission and all review aids should be sent to the appropriate document room (e.g., original NDAs are sent to the CDR while amendments and supplements are sent to the appropriate divisional document room). Electronic submissions serving as the archival copy of a submission should be separated from any review aid provided in electronic format. A summary of where to send submissions is in table 8.

Type of Submission	Central Document Room	Divisional Document Room
Original NDA	<ul style="list-style-type: none">• Electronic Archival copy• Paper Archival copy• Review copy• Review aids	
Amendment to a pending NDA	Electronic Archival copy	<ul style="list-style-type: none">• Paper Archival copy• Review copy• Review aids
Supplement to an approved NDA	Electronic Archival copy	<ul style="list-style-type: none">• Paper Archival copy• Review copy• Review aids

Addresses for the document rooms can be found in the guidance *Formatting, Assembling, and Submitting New Drug and Antibiotic Applications*.

B. Type of Media Used for Transmitting Electronic Submissions

The CDR is prepared to accept electronic submissions provided on the media listed in table 9, below. To optimize processing efficiency, the CDR recommends 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.

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Size of Submission	Media and format	Maximum Units
Less than 10MB	3.5 inch DOS Formatted Floppy Disks	10
Less than 3.25GB	CD-ROM ISO 9660	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 maximum

C. Preparing the Media for Submission

All electronic media should arrive adequately secured in a standard binder. The first electronic media binder should only include a paper copy of the cover letter described in section III, the appropriate regulatory forms, and the electronic media for archive. The applicant should include a paper copy of FDA form 356h. On page 2 of the form, the applicant should note by each item if the documents for the item are in paper format, electronic format, or both paper and electronic format.

Label the media with the following information:

- NDA number preceded by an N.
- 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 #)

D. Processing the Electronic Submission

The CDR personnel will copy the electronic files to tape to create a permanent archival copy of the submission and to a server to create a read-only review copy.

IX. TECHNICAL SUPPORT

Questions regarding the preparation of all submissions in electronic format should be directed to the Electronic Submissions Coordinator, Office of Information Technology, email ESUB@CDER.fda.gov.