Electronic Document Room

Conformance Review Checklist For NDAs

Appl_Type	Appl_No	Drug_Name	Sponsor_Applicant

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Conformance Review Checklist

I. INTRODUCTION

II. GENERAL ISSUES

A. Refuse to File

B. The Archival Copy

If portions of the NDA archival copy are submitted in paper and electronic format, the index (commonly referred to as the table of contents) for the submission must include the location of the paper documents by volume number and electronic files by file and folder name(s) so the index is comprehensive.

C. Providing a Review Copy

D. The Field Copy

E. Supplements and Amendments

F. 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 NDA number.

G. Review Aids

Provide all review aid files on floppy disks or CDROMs and secure them in a standard binder marked clearly on the outside REVIEW AIDS – NOT FOR ARCHIVE. Include the review aids in the appropriate technical section of the review copy.

III. ORGANIZING THE MAIN FOLDER

All documents and datasets for the electronic archival copy should be placed in a main folder using the NDA number (e.g., N123456) as the folder name.

A. Folders

Inside the main folder, all of the documents and datasets should be organized by the NDA items described on page 2 of FDA form 356h.

B. Cover Letter

You should provide a cover letter as a PDF file named *cover.pdf* inside the main folder. The cover letter should include the following:

- Description of the submission including appropriate regulatory information.
- Description of which portions of the submission are presented only in paper, only in electronic format, or in both paper and electronic format.

- Description of the electronic submission including the type and number of electronic media used (e.g., three CDROMs), and the approximate size of the submission (e.g., 2 gigabytes). Include the format used for DLT tapes.
- Statement that the submission is virus free with a description of the software (name, version, and company) used to check the files for viruses.
- The points of contact for the application.

Items Of An NDA As Described In Form 356h		
Item	**Description**	**Folder name**
1	Table of contents (Index)	main folder
2	Labeling	labeling
3	Summary	summary
4	Chemistry section	cmc
5	Nonclinical pharmacology and toxicology section	pharmtox
6	Human pharmacology and bioavailability/bioequivalence section	hpbio
7	Clinical microbiology section	micro
8	Clinical section	clinstat
9	Safety update report	update
10	Statistical section	clinstat
11	Case report tabulations	crt
12	Case report forms	crf
13	Patent information	other
14	Patent certification	other
15	Establishment description	other
16	Debarment certification	other
17	Field copy certification	other
18	User fee cover sheet	other
19	Other	other

C. 356h Form

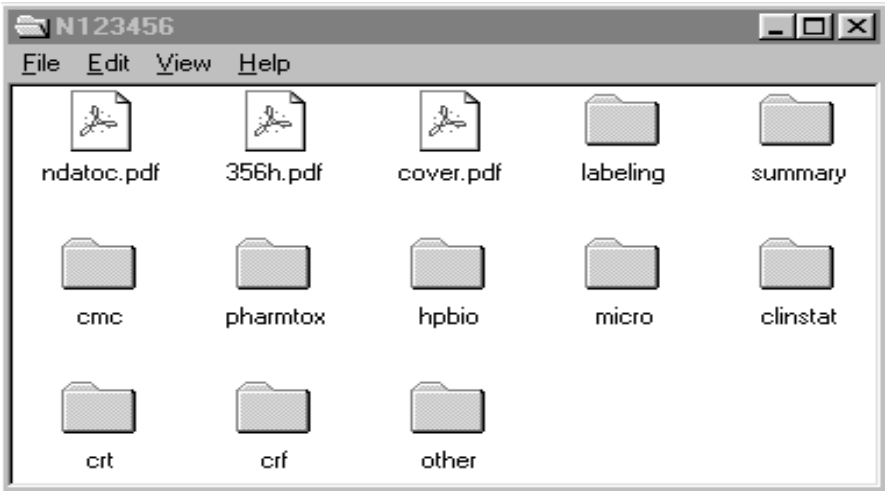
You should provide FDA form 356h as a PDF file named *356h.pdf* inside the main folder. On page 2 of the form, you should note next to each item if the documents for the item are in paper format, electronic format, or both paper and electronic format.

D. NDA Table Of Contents

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.

E. Figure of Main Folder

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



IV. ORGANIZING THE ELECTRONIC SUBMISSION

A. Item 1: Table of Contents (Index)

Regulations at 314.50(b) require a "comprehensive index by volume number and page number….". For electronic submissions, the comprehensive table of contents contains three levels of detail and the appropriate hypertext links and bookmarks.

The first level of detail simply lists the items in the NDA as shown on page 2 of FDA form 356h. This level of the comprehensive table of contents should be a single page and should be provided as a single PDF file. The file containing the table of contents for the original NDA should be named *ndatoc.pdf*. The file containing the table of contents for an amendment should be named *amendtoc.pdf*. The file containing the table of contents for a supplement should be named *suppltoc.pdf*.

The second level of detail contains the table of contents for each item (e.g., labeling, CMC, CRTs; see specific item for details). Provide the appropriate bookmarks and hyperlinks for each document or dataset listed to the appropriate file.

The third level of detail is the table of contents for each document or dataset. For each document, provide bookmarks for each entry in the document's table of contents to the appropriate location. For datasets, provide a data definition table as a key to the elements being used in the datasets.

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

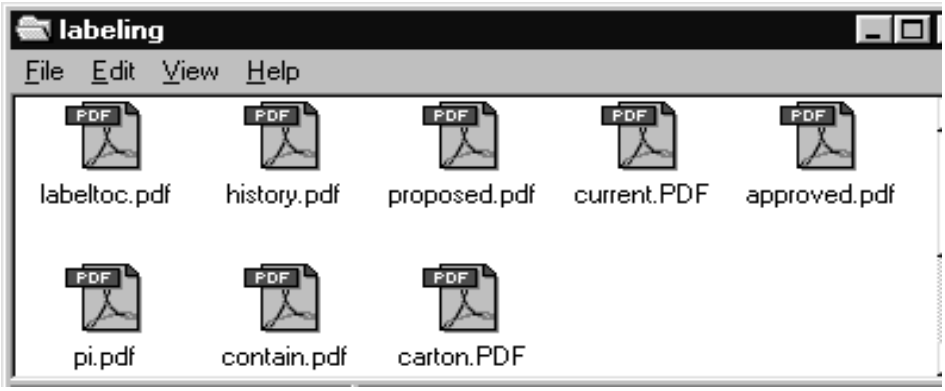
Some items, such as item 3 (the submission summary) and items 13 to 18, are single documents and do not have their own table of contents. In such cases, the hypertext link from the first level table of contents should go directly to the document.

Example: Table Of Contents For NDA 123456 (n/a = not available)			
Item	**Description**	**Paper archive copy volume number**	**Electronic archive copy folder**
1	Table of contents (Index)	1	main folder
2	Labeling	n/a	Labeling
3	Summary	n/a	Summary
4	Chemistry	1-4	n/a
5	Nonclinical pharmacology and toxicology	5-10	Pharmtox
6	Human pharmacokinetics and bioavailability/bioequivalence	n/a	Hpbio
7	Clinical microbiology	n/a	Micro
8	Clinical	n/a	Clinstat
9	Safety update report	n/a	n/a
10	Statistical	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	1	Other
15	Establishment description	n/a	n/a
16	Debarment certification	1	Other
17	Field copy certification	1	Other
18	User fee cover sheet	1	Other
19	Other	n/a	Other

B. Item 2: Labeling

1. Folder

You should place all documents for this item in a single folder named labeling.



2. Table of contents

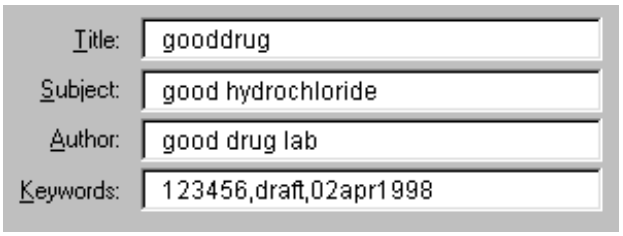
3. Labeling history

4. Labeling text

Document Information fields should contain the following information: (use only lower case letters).

- Title: brand name
- Subject: generic name
- Author: applicant, applicant's label code
- Keywords: NDA number (in form of 123456), approval status (*draft*, *approved*, *cbe* for changes being effected or *annual* for annual report), date of labeling in the form of ddmmmyyyy. For draft, changes being effected, and annual report changes, use the date of submission. For approved labeling, use the date of approval.

An example of the Document Information field for draft labeling text is provided below. Each item of the keyword field should be separated by a comma.



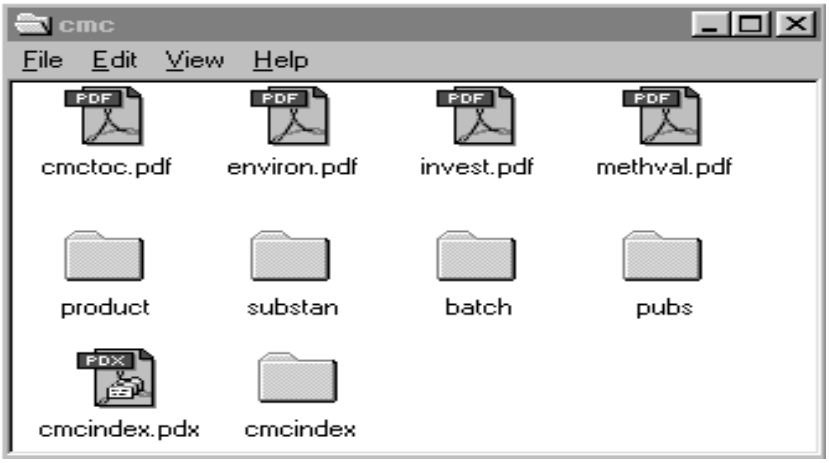
5. Package insert
6. Carton labeling
7. Container labeling
8. Other

C. Item 3: Summary

1. Folder
2. Table of contents
3. Summary document
4. Bookmarks and hypertext linking

D. Item 4: Chemistry, Manufacturing, and Control (CMC)

1. Folders



2. Table of contents

You must provide a table of contents listing all files provided in the CMC item as a PDF file named *cmctoc.pdf*. This table of contents is considered part of the comprehensive table of contents required in 314.50(b).

3. Drug substance
4. Drug product
5. Investigational formulations
6. Environmental assessment
7. Methods validation
8. Batch records
9. Publications
10. Bookmarks and hypertext links

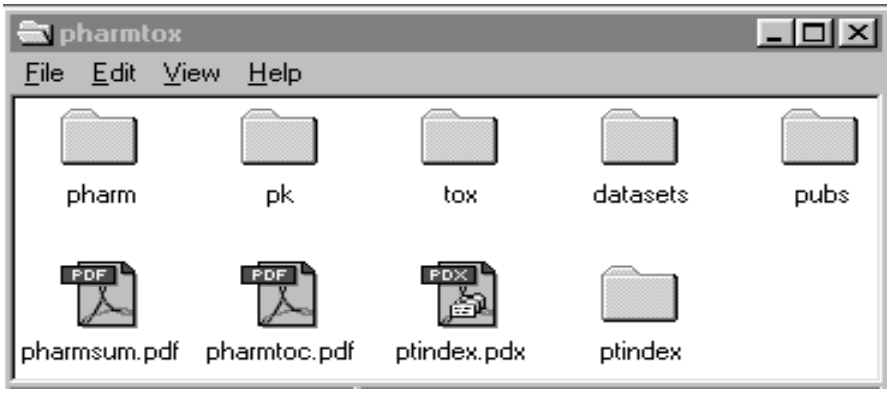
For all documents with a table of contents, you must provide bookmarks for each item in the document's table of contents including all tables, figures, publications, and appendices. These bookmarks serve as part of the comprehensive table of contents for the submission and, therefore, are required under 314.50(b).

11. Full text index

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 *cmcindex.pdx*. Place all associated index files in a folder named *cmcindex*. Place the cmcindex.pdx definition file and the cmcindex subfolder in the main 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.

E. Item 5: Nonclinical Pharmacology and Toxicology

1. Folders



2. Table of contents

You must provide a table of contents listing all study reports (including study report numbers), publications, and the summary provided in the pharmtox section as a PDF file named *pharmtoc.pdf*. If datasets are provided for a study, you should note this in the table of contents. This table of contents is considered part of the comprehensive table of contents required in 314.50(b).

3. Summary document
4. Study reports

Because files 50 MB or larger are technically more difficult to handle, study reports that are larger than 50 MB should be divided into two PDF files with the individual animal line listings for the study provided as a separate file.

5. Publications

6. Bookmarks and hypertext links

For all documents with a table of contents, you must provide bookmarks for each item in the document's table of contents including all tables, figures, publication, and appendices including datasets, if applicable. If datasets are provided with the study, you should include a bookmark to the appropriate data definition file (define.pdf). These bookmarks and hypertext links serve as part of the comprehensive table of contents for the submission and, therefore, are required under 314.50(b).

7. Full text index

8. Animal line listings as datasets

a. Format of the datasets

You should provide each dataset as a SAS transport file. Dataset files should be organized so their size is less than 25 MB per file. The files should not be compressed. Each dataset should be saved as an individual file.

b. Organization of data

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

c. Documentation of the datasets

d. Dataset table of contents

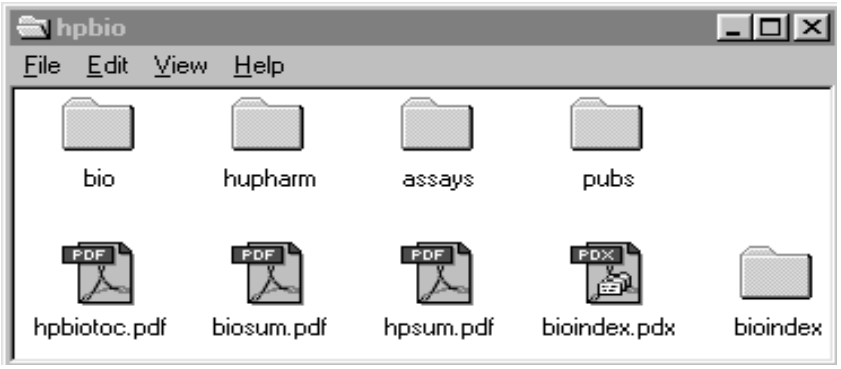
e. General considerations for datasets

F. Item 6: Human Pharmacology and Bioavailability/Bioequivalence

1. Folders

2. Table of contents

You must provide a table of contents listing all study reports (including study report numbers), publications, and the summaries provided for the hpbio section as a PDF file named *hpbiotoc.pdf* and place it in the hpbio folder. If datasets are provided for a study, you should note this in the table of contents. This table of contents is considered part of the comprehensive table of contents required in 314.50(b



3. Summary

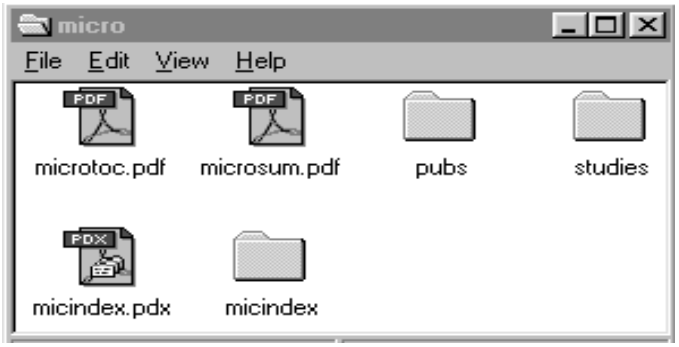
4. Study reports
5. Datasets
6. Publications
7. Bookmarks and hypertext links

For all documents with a table of contents, you must provide bookmarks for each item in the document's table of contents including all tables, figures, publications, and appendices including datasets, if applicable. These bookmarks serve as part of the comprehensive table of contents for the submission and, therefore, are required under 314.50(b). If datasets are provided with the study, you should include a bookmark to the appropriate data definition file (define.pdf).

8. Full text index

G. Item 7: Clinical Microbiology

1. Folders



2. Table of contents

You must provide a table of contents listing all reports and publications for this section as a PDF file named *microtoc.pdf*. If datasets are provided for a study, you should note this in the table of contents. Place this file in the micro folder. This table of contents is considered part of the comprehensive table of contents (314.50(b)).

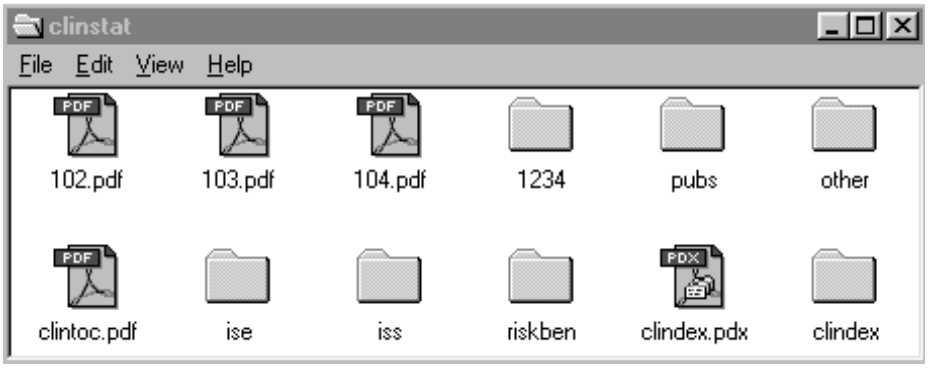
3. Summary document
4. Study reports
5. Datasets
6. Publications
7. Bookmarks and hypertext links

As part of a comprehensive table of contents for the submission, you must provide bookmarks for each item in the document's table of contents including all tables, figures, and appendices including datasets, if applicable (314.125(b)). If datasets are provided with a report, you should include a bookmark to the appropriate data definition file (define.pdf).

8. Full text index:

H. Item 8: Clinical

1. Folders



2. Table of contents

You must provide a table of contents listing all files in this section. Provide the table of contents as a PDF file; name this file *clintoc.pdf* and place it in the clinstat folder. We consider the table of contents to be part of the comprehensive table of contents (314.50(b)).

3. Study reports

Because files 50 MB or larger are technically more difficult to handle, study reports that are larger than 50 MB should be divided into two PDF files.

4. Integrated summaries

5. Publications

6. Bookmarks and hypertext links

For all documents with a table of contents, you must provide bookmarks for each item in the document's table of contents including all tables, figures, publications, and appendices including datasets. For datasets, you should include a bookmark to the appropriate data definition file (define.pdf). These bookmarks serve as part of the comprehensive table of contents for the submission and, therefore, are required under 314.50(b).

7. Full text index

I. Item 9: Safety Update

1. Folders

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

2. Table of contents

A table of contents for all files in this section must be provided in the form of a PDF file as part of the comprehensive table of contents (314.125(b)). The organization of the table of contents should follow the guidance provided in item 8. Name the PDF file *updattoc.pdf* and place it in the update folder.

3. Full text index

J. Item 10: Statistical For electronic submissions, item 8 and item 10 are identical.

K. Item 11: Case Report Tabulations (CRTs)

CRTs are item 11 on page 2 of FDA form 356h.

You should provide CRTs in datasets allowing the reviewers to use their own software for analysis. Each dataset is a single file and, in general, includes a combination of raw and derived data.

In addition to electronic datasets, study data collected for individual patients, organized by time, can be provided in PDF files. We call this collection of data a patient profile, and it serves as an adjunct to the electronic datasets. Patient profiles are not meant to be a replacement for electronic datasets.

1. Format of the datasets

You should provide each dataset as a SAS transport file as described in the companion guidance, *Regulatory Submissions in Electronic Format — General Considerations* (January 1999

Dataset files should be organized so that their size is generally less than 25 MB per file. The files should not be compressed. Each dataset should be saved as an individual file.

The data variable names should be no more than 8 characters in length because of restrictions in our data format. We recommend that you provide a more descriptive data variable label, up to 32 characters in length.

2. Organization of data

3. Documentation of the datasets

You should include two PDF files, one of the data definition tables (*define.pdf*) and one of the annotated case report forms (*blankcrf.pdf*) to describe the datasets for each study, specific data analysis (e.g., population PK), and integrated summaries.

4. Dataset table of contents

The dataset table of contents is also part of the comprehensive table of contents and must list all studies and integrated summaries that have datasets. You must provide a hypertext link to the appropriate data definition table file (314.50(b)). The table of contents should be provided as a PDF file named *datatoc.pdf* and placed in the datasets folder.

5. *Full text index*

6. General considerations for datasets

7. Patient profiles as PDF files

a. Folders

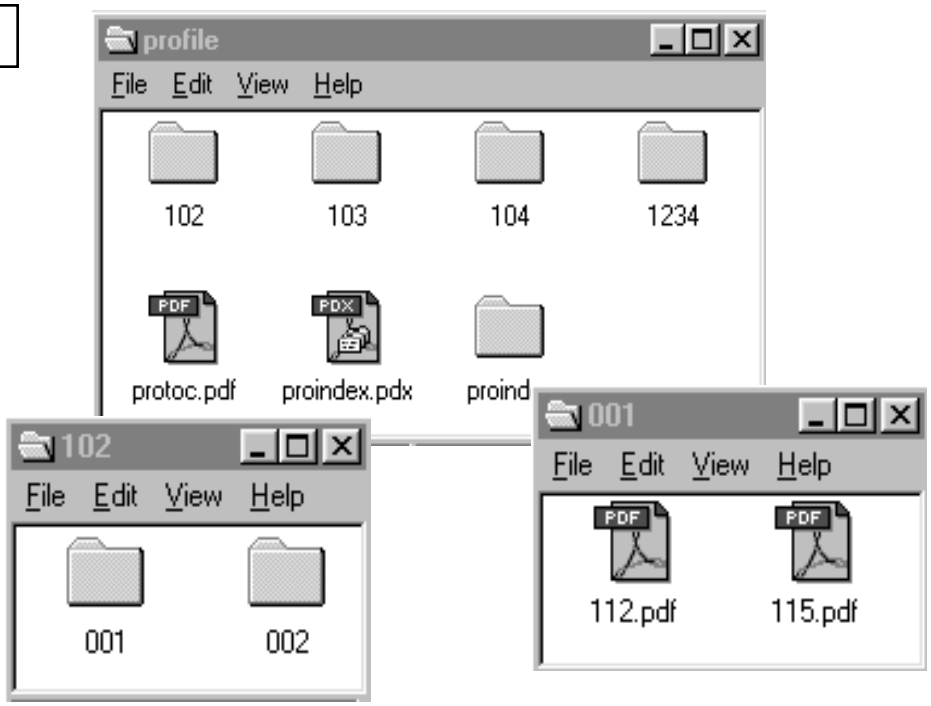
b. Table of contents

You must provide in a PDF file a table of contents listing all patient profiles by study. Name this file *protoc.pdf*. This table of contents is considered part of the comprehensive table of contents (314.50(b)). List the patient identification numbers by study, site, and treatment assignment and describe the location of the patient profile with the file name and folder(s). Provide a hypertext link between the documents listed in the table of contents and the corresponding PDF file and bookmarks for each item in the table of contents. Place the protoc.pdf file in the profile folder.

c. Patient profiles

You should 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.

d. Bookmarks and hypertext links
e. Full text index



L. Item 12: Case Report Forms

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. For data collected electronically, all data collected for an individual patient should be organized by domain and time and provided as a PDF file. This presentation is the same as a patient profile described in item 11 (CRTs). This file should subsequently be handled the same as an imaged CRFs.

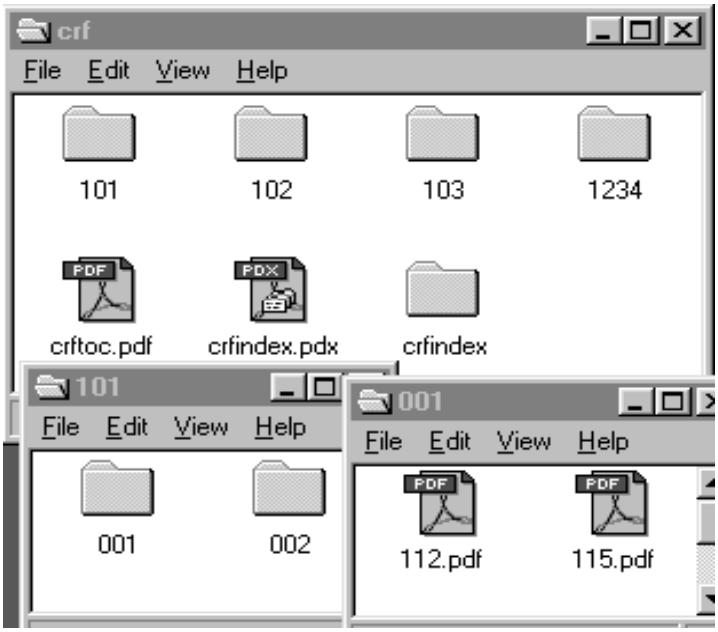
1. Folders - You should create a folder for each study to organize the CRFs.

2. Table of contents

You must provide a table of contents listing all case report forms provided by study, site and treatment assignment as a PDF file. Name this file *crftoc.pdf*. This table of contents is considered part of the comprehensive table of contents (314.50(b)). List the patient identification numbers by study, site and treatment assignment and describe the location of the case report forms with the file name and folder(s). Provide a hypertext link between the documents listed in the table of contents and the corresponding PDF file and bookmarks for each item in the table of contents. Place the crftoc.pdf file in the crf folder.

3. Case report forms

You should provide each individual patient's complete CRF as a single PDF file. Including the patient ID in the file name will help identify the file. Place the PDF files in the appropriate study site folder. For example, all CRFs for site 001 for



study 101 would be placed into a folder named *001*, which then would be placed in a folder named *101*.

The Document Information Title field for each file should include the letters *crf*, 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 CRF 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.

4. Bookmarks and hypertext links

Each CRF must have bookmarks as part of the comprehensive table of contents required under 314.50(b).

5. Full text index

An index of the full text and the Document Information field of all documents in the crf folder should be provided. Even if all of the CRFs are images, the text in the Document Information field should be indexed. The index definition file should be named *crfindex.pdx*. Place all associated index files in a folder named *crfindex*. Place the crfindex.pdx definition file and the crfindex subfolder in the main 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.

M. Item 13: Patent Information

1. Folder

You should place documents for this section in the folder named *other*.

2. Table of contents

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

3. Patent information

You should provide the information pertaining to the patent information in a single PDF file named *patinfo.pdf*.

N. Item 14: Patent Certification

1. Folder

You should place the document for this section in the folder named *other*.

2. Table of contents

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

3. Patent certification

You should provide the information pertaining to the patent certification in a single PDF file named *patcert.pdf*.

O. Item 15: Establishment Description (CBER only)

Item 15 on page 2 of FDA form 356h applies only to submissions to CBER.

P. Item 16: Debarment Certification

1. Folder

You should place the debarment certification in the folder named *other.*

2. Table of contents

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

3. Debarment certification

The debarment statement should be provided in a single PDF file named *debar.pdf.*

Q. Item 17: Field Copy Certification

1. Folder

You should place the field copy certification in the folder named *other.*

2. Table of contents

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

3. Field copy certification

The field copy certification should be provided in a single PDF file named *fieldcer.pdf* .

R. Item 18: User Fee Cover Sheet

1. Folder

You should place the User Fee Cover Sheet in the folder named *other.*

2. Table of contents

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

3. User fee cover sheet (FDA form 3397)

The user fee cover sheet should be provided as a single PDF file named *userfee.pdf*.

S. Item 19: Other

1. Folder

You should place all additional information for this item in the folder named *other*.

2. Table of contents

There should be a hypertext link from the submission table of contents directly to each file in this item.

3. Other items

You should provide each additional item as a separate PDF file