

---

# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — NDAs

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

IT 3  
January 1999

99D-0054

GDL 1

---

# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — NDAs

*Additional copies are available from:*

*Office of Training and Communications  
Division of Communications Management  
Drug Information Branch, HFD-210*

*5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573*

*(Internet) <http://www.fda.gov/cder/guidance/index.htm>*

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

**IT 3  
January 1999**

## TABLE OF CONTENTS

I.	INTRODUCTION.....	4
II.	GENERAL ISSUES.....	4
	A. REFUSE TO FILE.....	5
	B. THE ARCHIVAL COPY.....	5
	C. PROVIDING A REVIEW COPY.....	5
	D. THE FIELD COPY.....	6
	E. SUPPLEMENTS AND AMENDMENTS.....	6
	F. ELECTRONIC SIGNATURES.....	6
	G. REVIEW AIDS.....	6
III.	ORGANIZING THE MAIN FOLDER.....	8
	A. FOLDERS.....	8
	B. COVER LETTER.....	9
	C. 356H FORM.....	9
	D. NDA TABLE OF CONTENTS.....	9
	E. FIGURE OF MAIN FOLDER.....	10
IV.	ORGANIZING THE ELECTRONIC SUBMISSION.....	11
	A. ITEM 1: TABLE OF CONTENTS (INDEX).....	11
	B. ITEM 2: LABELING.....	13
	C. ITEM 3: SUMMARY.....	18
	D. ITEM 4: CHEMISTRY, MANUFACTURING, AND CONTROL (CMC).....	19
	E. ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY.....	24
	F. ITEM 6: HUMAN PHARMACOLOGY AND BIOAVAILABILITY/BIOEQUIVALENCE.....	31
	G. ITEM 7: CLINICAL MICROBIOLOGY.....	35
	H. ITEM 8: CLINICAL.....	40
	I. ITEM 9: SAFETY UPDATE.....	43
	J. ITEM 10: STATISTICAL.....	43
	K. ITEM 11: CASE REPORT TABULATIONS (CRTs).....	44
	L. ITEM 12: CASE REPORT FORMS.....	53
	M. ITEM 13: PATENT INFORMATION.....	56
	N. ITEM 14: PATENT CERTIFICATION.....	56
	O. ITEM 15: ESTABLISHMENT DESCRIPTION (CBER ONLY).....	57
	P. ITEM 16: DEBARMENT CERTIFICATION.....	57
	Q. ITEM 17: FIELD COPY CERTIFICATION.....	57
	R. ITEM 18: USER FEE COVER SHEET.....	58
	S. ITEM 19: OTHER.....	58
	APPENDIX 1: EXAMPLE NONCLINICAL PHARMACOLOGY AND TOXICOLOGY DATASETS AND DATA ELEMENTS.....	60
	APPENDIX 2: EXAMPLE CONTENT OF SPECIFIC CLINICAL DATASETS.....	70

# Guidance for Industry<sup>1</sup>

## Providing Regulatory Submissions in Electronic Format — NDAs

### I. INTRODUCTION

This is one in a series of guidance documents intended to assist applicants making regulatory submissions in electronic format to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA). In some cases, guidance differs from CDER to CBER because of differences in the procedures and computer infrastructure in the centers. We will work to minimize these differences wherever possible. Agency guidance documents on electronic submissions will be updated regularly to reflect the evolving nature of the technology and the experience of those using this technology.

This specific guidance discusses issues related to the electronic submission of new drug applications (NDAs) and supplements and amendments to those applications to CDER. For a list of guidances that are under development on electronic submissions, see *Regulatory Submissions in Electronic Format — General Considerations* (January 1999). The General Considerations guidance also addresses issues, such as acceptable file formats, media, and submission procedures, that are common to all submission types.

### II. GENERAL ISSUES

Regulations in 21 CFR 314.50 provide general requirements for submitting marketing applications to CDER. Currently, FDA Form 356h outlines the components required in the submission of a new drug application. This form is available on the Internet at (<http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>). This section addresses briefly some general issues related to the electronic submission of NDAs.

---

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

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

## **A. Refuse to File**

We may refuse to file an application or supplement under 21 CFR 314.101, if either paper or electronic portions are illegible, uninterpretable, or otherwise clearly inadequate (e.g., a table of contents without hypertext links and bookmarks). Following this guidance document will help ensure that your electronic application meets the requirements in the regulations and can be easily archived, loaded on our network drives, and reviewed within specified time frames using our desktop tools.

## **B. The Archival Copy**

Once we have identified a submission type in public docket number 92S-0251 as one that we can accept in an electronic format, you have the option of providing all, or only a portion, of the archival copy of the submission 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 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. The paper portion of the archival copy should be submitted as described in other Agency guidance documents.

## **C. Providing a Review Copy**

For submissions to CDER, you are required to submit a review copy of the technical sections (i.e., chemistry, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, clinical, and statistical) of the application *in addition* to the copy for archive (21 CFR 314.50(l)). If you provide the archival copy in paper, you should provide the corresponding review copy in paper.

If you provide the archival copy in electronic format, you only need to provide a portion of the review copy in paper. The following portions of the review copy do not need to be submitted in paper:

- CMC section: methods validation reports
- Nonclinical pharmacology and toxicology sections: individual animal line listings
- Clinical sections: study report appendices 16.1.3 to 16.4 as defined by the ICH *E3 Structure and Content of Clinical Study Reports* (July 1996)

Check with the appropriate review division prior to putting together the review copy because some divisions may identify additional portions of the paper review copy that can be eliminated.

The following steps will help you assemble a paper review copy.

1. Use the archival PDF file to generate the paper review copy. This will ensure that the paper review copy is an accurate and complete copy of the archival document.
2. Arrange the documents in the same order as they appear in the section's table of contents.
3. Put each document in separate volumes. If the documents are small, you can combine many in one volume, separating each document by a tab identifying the document.
4. Include a copy of the section's table of contents at the beginning of the technical section so that each document can be located by volume number. The table of contents should include the document name, the location of review copy by volume(s), and the location of the archival copy. If the archival copy is electronic, provide the folder(s) and file name. If the archival copy is paper, provide the volume number.
5. You do not need to provide page numbers in addition to those already included in the individual documents. Separate pagination for the entire review copy is not needed.

#### **D. The Field Copy**

The field copy of the submission is not addressed in this guidance.

#### **E. Supplements and Amendments**

This guidance applies equally to the original submissions, supplements, and amendments to NDAs.

#### **F. Electronic Signatures**

The Agency is developing procedures for archiving documents with electronic signatures. Until those procedures are in place, documents for which regulations require an original signature, such as certifications, must be accompanied by a paper copy that includes the handwritten signature and the NDA number.

#### **G. Review Aids**

Review aids are electronic files provided *in addition* to those provided for archive as described in the guidance. Like the review copy of an application, a review aid would contain only the information found in the archival copy of the application, but in a different format.

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.

In CDER, procedures have been established for identifying and requesting potential review aids to ensure that the quality and usefulness of the review aid is worth the time and effort invested in its development. Therefore, a review aid should only be requested or agreed to if (1) it will add functionality not found in a submission provided in accordance with guidance and (2) we agree that the review aid will contribute significantly to the review of the application.

### 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. You should obtain the NDA number prior to submission.

**Figure: Main folder for NDA 123456**



#### 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. Each item has an assigned subfolder where documents and datasets that belong to the item are placed. See the following table for the items and folder organization.

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

## **B. Cover Letter**

You 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. 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.

## **C. 356h Form**

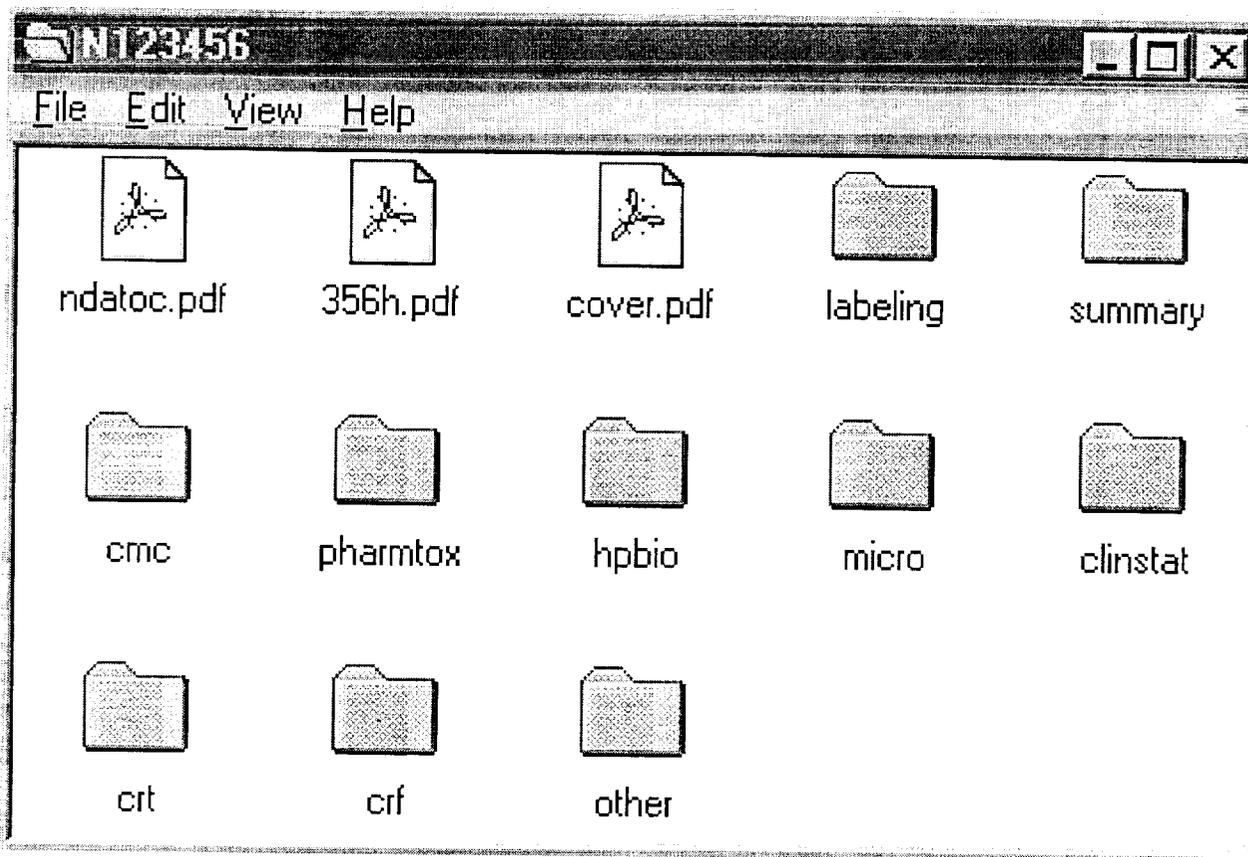
You should provide FDA form 356h as a PDF file named *356h.pdf* inside the main folder. On page 2 of the form, you should note next to each item if the documents for the item are in paper format, electronic format, or both paper and electronic format. The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, the *356h.pdf* file must be accompanied by a signed paper 356h form.

## **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

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

### A. Item 1: Table of Contents (Index)

Regulations at 314.50(b) require a "comprehensive index by volume number and page number..." The comprehensive table of contents, hypertext links, and bookmarks in the electronic version play the same role as the comprehensive index by volume number and page number required in the paper copy. We find that bookmarks and hypertext links are essential for efficient navigation through an electronic submission. For electronic submissions, the comprehensive table of contents contains three levels of detail and the appropriate hypertext links and bookmarks. As noted above, CDER may refuse to file a submission that does not contain a comprehensive table of contents with 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. See the table of contents for NDA 123456, below, for an example of this level. 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. In general, this table of contents should consist of only a few pages.

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.

In the example of the table of contents for NDA 123456, below, a portion of the archival copy of the nonclinical pharmacology and toxicology sections is in paper and a portion is in 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 provided in only 4 paper volumes and starts in volume 1. The archival copies for items 14, 16, 17, and 18 are in volume 1, and the electronic copies are in a folder named *other*. The archival copy for all other items is provided only in electronic format. The table of contents shows the entire submission including the paper and the electronic portions.

If the archival copy of the item is in paper format, the volume numbers that hold the item should be listed in the table of contents. If the archival copy is in electronic format, the folder name containing the files should be listed in the table of contents. If portions of the item are in both paper and electronic format, the volume number and the folder name should be listed in the table of contents.

<b>Example: Table Of Contents For NDA 123456 (n/a = not available)</b>			
<b>Item</b>	<b>Description</b>	<b>Paper archive copy volume number</b>	<b>Electronic archive copy folder</b>
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

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.

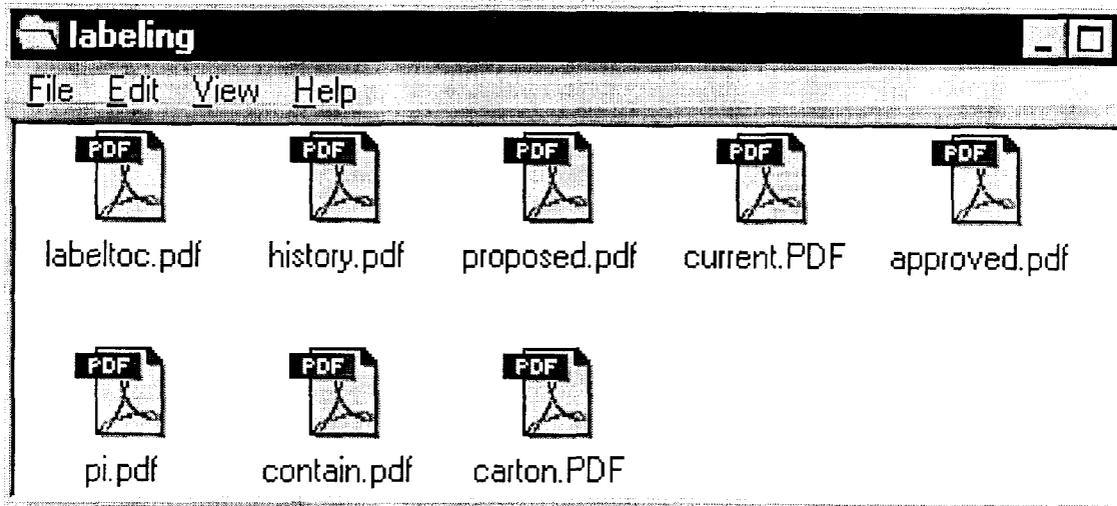
Some items, such as item 3 (the submission summary) and items 13 to 18, are single documents and do not have their own table of contents. In such cases, the hypertext link from the first level table of contents should go directly to the document.

## B. Item 2: Labeling

Labeling is item 2 on page 2 of FDA form 356h. The content and format of what is referred to in this item as *labeling text* is defined in 21 CFR 201.56 and 201.57 and includes all text, tables, and figures proposed for use in the package insert. The PDF files in this section should be generated from electronic source documents and not from scanned material.

### 1. Folder

You should place all documents for this item in a single folder named labeling. An example of the organization of the labeling folder is pictured below.



### 2. Table of contents

You must provide a table of contents listing all examples of labeling included in the submission and the history of labeling changes, if applicable, as a PDF file named *labeltoc.pdf*. This table of contents is considered part of the comprehensive table of contents required in 314.50(b). You should use the example headings below to organize the files in the table of contents. Include the location of the archive copy by folder and file name, if electronic, and by volume number if paper. As part of the comprehensive table of contents for the submission, 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 *labeltoc.pdf* file in the labeling folder.

<b>Labeling Table Of Contents</b>		
<b>Description</b>	<b>Review copy location volume number</b>	<b>Archive copy location folder/file name*</b>
I. Labeling history		
II. Labeling text		
a. Proposed labeling text		
b. Currently used labeling text		
c. Last approved labeling text		
III. Final printed package insert		
IV. Carton label		
V. Container label		

\*Use volume number if the archive copy is paper.

### 3. *Labeling history*

In each submission containing new labeling, you should supply a summary of all labeling changes, if applicable, in a PDF file named *history.pdf* and place it in the labeling folder. The labeling history helps us confirm changes made to the labeling and should contain the following information:

- A complete list of the labeling changes being proposed in the current submission and the explanation for the changes
- The date of the last approved labeling.
- A history of all changes since the last approved labeling. With each change, you should note the submission that originally described the change and the explanation for the change.
- A list of supplements pending approval that may affect the review of the labeling in the current submission.

#### 4. Labeling text

The labeling text is the content and format of labeling as defined in 21 CFR 201.56 and 201.57 and includes all text, tables, and figures used in the package insert. The labeling text should have the following characteristics:

- Print area should fit on an 8.5- by 11-inch sheet of paper with one inch margins
- Page orientation - Portrait
- No columns, headers, or footers
- Pagination starting with page 1
- Text font—Times New Roman 12 point
- Table font—Times New Roman 10 or preferably 12 point
- Header 1 font—Arial 12 point bold, capitalize all letters
- Header 2 font—Arial 12 point, bold, capitalize the initial letter for each word
- Header 3 font—Arial 12 point, regular, capitalize the initial letter for each word
- Header 4 font—Arial 12 point, italics, capitalize the initial letter for first word

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 ddmmyyyy. 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.

Title:	gooddrug
Subject:	good hydrochloride
Author:	good drug lab
Keywords:	123456,draft,02apr1998

a. Proposed labeling text

The proposed labeling text would be the draft labeling with an initial application or subsequent supplements, labeling provided with changes being effected submissions, or labeling changes submitted with the annual report. You should provide the proposed labeling text as a PDF file named *proposed.pdf*. Fill in the Document Information fields as described above.

In addition to the PDF file, you should provide all draft labeling text with an initial application or subsequent supplements in a word processing format as a review aid for editing purposes. You should consult the review division for the word processing format and version currently being used in the center.

b. Current labeling text

The current labeling text refers to the labeling text that is being used at the time of the submission. This labeling can be approved labeling as well as labeling that has not been approved such as changes being effected or changes with the annual report. You should provide the current labeling text as a PDF file named *current.pdf* and fill in the Document Information fields as described above.

c. Last approved labeling text

The last approved labeling text is the labeling most recently approved. You should provide the last approved labeling text as a PDF file named *approved.pdf*. Fill in the Document Information fields as described for labeling text.

5. *Package insert*

You should provide the final printed package insert as a single PDF file named *pi.pdf*. Fill in the Document Information fields as described with the labeling text.

6. *Carton labeling*

You should provide the carton labeling (all panels) as a PDF file(s). Fill in the Document Information fields as described with the labeling text.

7. *Container labeling*

You should provide the container labeling (all panels) as a PDF file(s).  
Fill in the Document Information fields as described with the labeling text.

8. *Other*

You should provide any other labeling that does not fall into the previous categories as PDF files with a view of each panel. Fill in the Document Information fields as described with the labeling text.

### C. Item 3: Summary

The summary of the submission is item 3 on page 2 of FDA form 356h.

#### 1. Folder

You should place the summary document in a single folder named *summary*.

#### 2. Table of contents

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

As part of the comprehensive table of contents required in 314.125(b), you must provide bookmarks for each item in the document's table of contents including all tables, figures, publications, and appendices.

#### 3. Summary document

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

#### 4. Bookmarks and hypertext linking

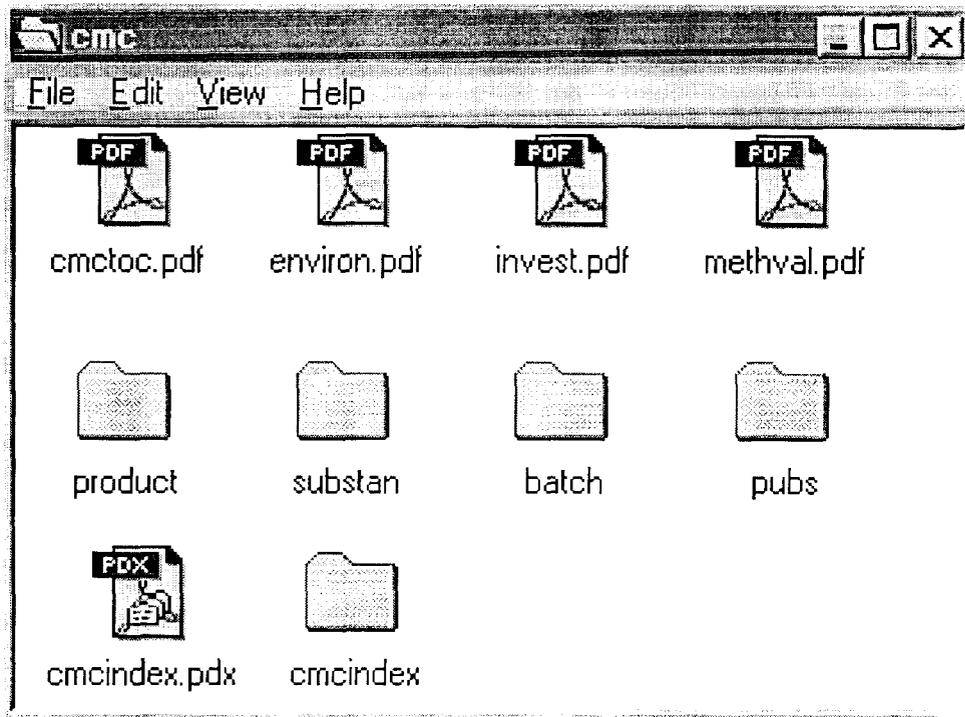
In the annotated label, you should provide hypertext links between all annotations and the appropriate sections of the summary or other items in the NDA.

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

The chemistry, manufacturing, and controls section is item 4 from page 2 of FDA form 356h.

*1. Folders*

You should create 4 folders, *substan*, *product*, *batch*, and *pubs* to organize the files in this section. Place these folders in a single folder named *cmc*. The file structure is pictured in the figure below (the file, *cmcindex.pdx* and additional subfolder, *cmcindex*, are for the full text index ).



*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). You should use the example headings below to organize the files in the table of contents. Provide the location of the paper review copy by volume number and the location of the archive copy by folder and file name, if electronic, and by volume number if paper. As part of the comprehensive table of contents for the submission, provide a hypertext link between the documents listed in the table of contents and the corresponding PDF file and bookmarks for the each item in the table of contents. Place the *cmctoc.pdf* file in the *cmc* folder.

<b>CMC Table Of Contents</b>		
<b>Description</b>	<b>Review copy location volume number</b>	<b>Archive copy location folder/file name*</b>
I. Drug Substance		
II. Drug Product		
III. Investigational Formulations		
IV. Environmental Assessment		
V. Methods Validation		
VI. Batch Records (list each batch record separately)		
VII. Publications (list each publication separately)		

\*Use volume number if the archive copy is paper.

### 3. *Drug substance*

Information regarding the drug substance should cover the following topics.

- Description & Characterization
- Manufacturer
- Synthesis/Method of Manufacture
- Process Controls
- Reference Standard
- Specifications/Analytical Procedures
- Microbiology
- Container/Closure System
- Stability

You can provide each one of these topics as separate PDF files or combine all topics for the drug substance into a single PDF file. If you provide the drug substance information as a single PDF file, organize the table of contents for this document using the topics listed above.

Place all files related to drug substance in the substan folder in the cmc folder. Identify each file in the Document Information Title field as *drug substance* and include the specific topic, if applicable.

#### 4. *Drug product*

Information regarding the drug product should cover the following topics.

- Components/Composition
- Specifications & Methods for Drug Product Ingredients
- Manufacturer
- Methods of Manufacturing and Packaging
- In-process Controls & Tests
- Specifications/Analytical Procedures
- Container/Closure System
- Microbiology
- Stability

You can provide each one of these topics as separate PDF files or combine all topics for the drug product into a single PDF file. If you provide the drug product information as a single PDF file, organize the table of contents for this document using the topics listed above.

Identify each file in the Document Information Title field as *drug product* and include the specific topic, if applicable.

#### 5. *Investigational formulations*

You should provide information about all of the investigational formulations in a single PDF file called *invest.pdf*. The table of contents for this document should list all investigational formulations separately with a bookmark and hypertext link to the appropriate formulation. Identify this file in the Document Information Title field as *investigational formulations*.

#### 6. *Environmental assessment*

You should provide the environmental assessment or a claim for categorical exclusion in a single PDF file called *environ.pdf*. Identify this file in the Document Information Title field as *environmental assessment*.

#### 7. *Methods validation*

You should provide all methods validations in a single PDF file called *methval.pdf*. This information should be identical to the information provided in the drug substance and drug product documents. Identify this file in the Document Information Title field as *methods validation*. The table of contents for this document should list each method with a bookmark and hypertext link to the appropriate procedure.

## 8. *Batch records*

You should provide each batch production record in a separate PDF file. Place all batch record PDF files into a single folder named *batch*. You should provide bookmarks to each section of the batch records. The batch folder should be placed in the *cmc* folder. Identify these files in the Document Information Title field with the batch record number. For example, batch record 105 is identified as *batch record 105*.

## 9. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. The *pubs* folder should be placed in the *cmc* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. The citation should include the first author's last name, the year of the publication, and the title of the article.

## 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).

Hypertext linking provided throughout the body of the document to supporting annotations, related sections, publications, appendices, tables, or figures that are not located on the same page helps reviewers navigate more efficiently through a document. For a reference list at the end of a document, you should provide a hypertext link from the item listed to the appropriate PDF publication file.

We have identified certain pieces of information that we frequently need to know and are often time consuming to locate in a particular submission. For example, for each clinical protocol, we need to identify the batch number of the drug substance used in the trial. If you provide a hypertext link from the clinical trial number to the batch number, this will improve our review efficiency. Suggested hypertext links for this information are summarized in the following list

- 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/degradants to their structures
- Chemical names to chemical abstract registry numbers

#### *11. Full text index*

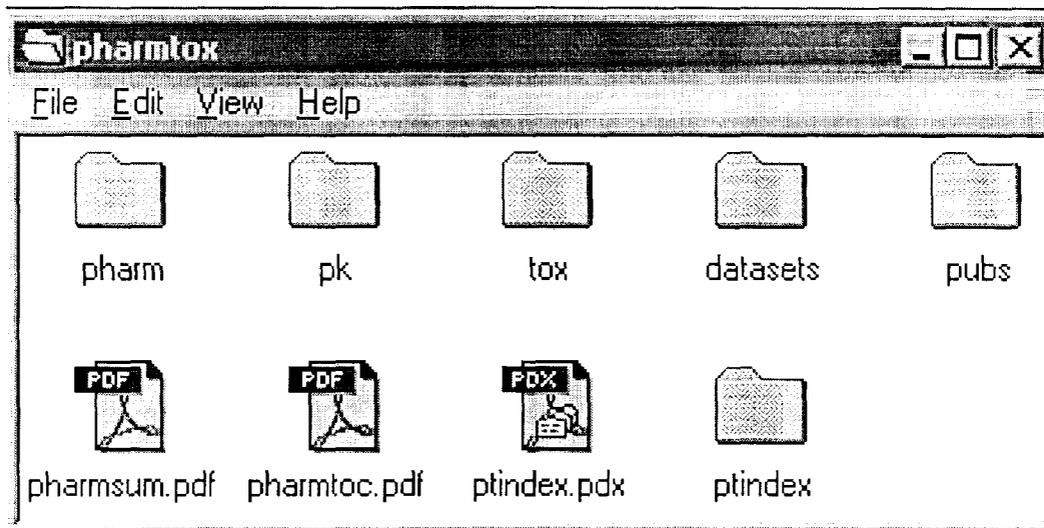
An index of the full text and the Document Information fields of all documents in this section should be provided. Name the index definition file *cmcindex.pdx*. Place all associated index files in a folder named *cmcindex*. Place the *cmcindex.pdx* definition file and the *cmcindex* subfolder in the 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

The nonclinical pharmacology and toxicology section is item 5 on page 2 of FDA form 356h.

### 1. Folders

You should create 5 folders, *pharm*, *pk*, *tox*, *datasets*, *pubs*, to organize the files in this section. The *pharm* folder contains pharmacology studies. The *pk* folder contains the pharmacokinetics studies, and the *tox* folder contains the toxicology studies. The *datasets* folder contain the datasets and the *pubs* folder contains the publications. Place these folders in a single folder named *pharmtox*. The file structure is pictured in the figure below (the file, *ptindex.pdx*, and additional subfolder, *ptindex*, are for the full text index).



### 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). You should use the example headings below to organize the files in the table of contents. Provide the location of the paper review copy by volume number and the location of the archive copy by folder and file name, if electronic, and by volume number if paper. As part of the comprehensive table of contents for the submission, provide a hypertext link between the documents listed in the table of contents and the corresponding PDF files and bookmarks for each item in the table of contents. If datasets were listed in the table of contents, provide a link to

the appropriate data definition file (define.pdf). This file is described below. Place the pharmtoc.pdf file in the pharmtox folder.

<b>Pharmtox Table Of Contents</b>		
<b>Description</b>	<b>Review copy volume number</b>	<b>Archive copy folder/file name*</b>
I. Summary		
II. Pharmacology studies		
a. Pharmacodynamics		
b. Safety pharmacology		
c. Other pharmacology studies		
III. Pharmacokinetics		
IV. Toxicology studies		
a. Single and repeat dose toxicity studies		
b. Genotoxicity studies		
c. Carcinogenicity studies		
d. Reproduction toxicity studies		
e. Supplemental toxicity studies		
V. Publications		

\*Use volume number if the archive copy is paper.

### 3. *Summary document*

You should provide a summary of the entire nonclinical pharmacology and toxicology section as a single PDF file named *pharmsum.pdf*. This document should include an overall summary of the nonclinical studies as well as more detailed summaries of each section (i.e., pharmacology, pharmacokinetics, and toxicology). The summary should be identified in the Document Information Title field as *pharmtox summary*. When supporting a conclusion by referring to a published article, data summary table or figure, providing a hypertext link to the corresponding published article, data table, or figure (whether located in a study report or elsewhere) will facilitate the review process.

### 4. *Study reports*

You should provide each study report with all appendices as a separate PDF file. Including the study number in the name of the file helps us locate files. For example, study 1234 can be named *1234.pdf*. Place the file in the appropriate subfolder of the pharmtox folder. 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. If the animal line listings are provided as a separate file, include the study

number in the name of the animal line listings file and add *d* (for data) to the file name. For example, the file containing the animal line listings for study 1234 can be named *1234d.pdf*. Place the two PDF files (e.g., full study report and individual animal line listings) into a folder whose name includes the study number. Place these folders in the appropriate subfolder of the pharmtox folder.

The Title portion of the Document Information field of each study report should be designated as *study* and followed by the study report number and the study type. For example, study 2001, a 12-month toxicity study, should be identified as: *study 2001, repeat dose, toxicity study*. For the file that has the animal line listing alone, the word *data* should be added to the Title field. For the above example, the animal line listing file would be identified as: *study 2001, data, repeat dose, toxicity study*.

#### 5. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. The *pubs* folder should be placed in the pharmtox folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. The citation should include the first author's last name, the year of the publication, and the title of the article.

#### 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).

Hypertext links provided throughout the body of the document to supporting annotations, related sections, publications, appendices, tables, or figures that are not located on the same page help us navigate more efficiently through a document. For a reference list at the end of a document, you should provide a hypertext link from the item listed to the appropriate PDF publication file. Hypertext links can also be used to locate studies used to justify dose selection for toxicity studies such as carcinogenicity and reproduction toxicity studies.

## 7. *Full text index*

An index of the full text and the Document Information fields of all documents in the pharmtox section should be provided. The index definition file should be named *ptindex.pdx*. Place all associated index files in a folder named *ptindex*. Place the *ptindex.pdx* definition file and the *ptindex* subfolder in the main 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.

## 8. *Animal line listings as datasets*

Animal line listings that you would provide on paper or in PDF format may be provided as datasets. Just as you provide data for each domain (e.g., body weights, clinical signs) as a table in a paper or PDF submission, with electronic datasets, each domain should be provided as a single dataset.

***The decision to submit the individual line listings as electronic datasets, instead of on paper or in PDF format, should be made on a study-by-study basis with the prior agreement of the review division.*** For example, in CDER, statisticians perform analyses on the tumor data from each carcinogenicity study, and they need this information provided as an electronic dataset. See Appendix 1 on datasets and data elements for the dataset recommended by these reviewers (*tumor.xpt*).

### a. *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). We import the data into various software tools. The most commonly used tools include: database programs, spreadsheet programs, and statistical analysis programs.

Many of the software tools used by the reviewers require datasets to be loaded into random access memory (RAM) prior to opening the file. Therefore, dataset files should be organized so their size is less than 25 MB per file. The files should not be compressed. Each dataset should be saved as an individual file.

Data variable names should be no more than 8 characters. A more descriptive data variable label, up to 32 characters in length, should also be provided.

b. Organization of data

Prior to the submission, you should discuss with the review division the datasets to be provided and the data elements that should be included in each dataset. Examples of the datasets and data elements to consider are provided in Appendix 1 on example datasets and data elements. These examples are meant to serve as a starting point for discussion between you and the review division on the content and organization of the datasets and, therefore, are not all inclusive. We plan on refining these data elements as we gain more experience.

Datasets can be divided further to achieve a size smaller than 25 MB. For example, clinical chemistry data may be further divided by specific lab tests. Don't divide a dataset type unless the size is greater than 25 MB, and when you divide a dataset type, do so with the fewest number of overall datasets. File names should include the three-character extension *xpt* to be compatible with our desktop set up and training.

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

For the datasets to be useable, the data elements should be defined. You should document all of the data elements in data definition tables. There should be one set of data definition tables for each study.

The first table should include a listing of all datasets provided for the study with a description of the dataset and the location of the dataset file. Provide a hypertext link from the description of the dataset to the appropriate data definition table. Provide a hypertext link from the listing of the file to the SAS transport file. The reviewer can use the first hypertext link to view the data definition table and the second to open the SAS transport dataset file. In the following table, the dataset for weights is described as body weights of the animals and the dataset file is located in folder 1234 in the datasets folder, which is in the *pharmtox* folder.

<b>Datasets For Study 1234</b>		
<b>Dataset</b>	<b>Description of dataset</b>	<b>Location</b>
Weights	Body weights of the animals	Pharmtox/datasets/1234/weights.xpt
....	...	...

Subsequent pages should contain a table for each dataset that includes an organized listing of all variable names used in the dataset, a 32-character descriptive variable label, data types, codes (and decodes), and comments. The comments field is for further description of the variables. For derived variables, the method for calculating the variable should be included in the comments field. Example data definition tables are provided in Appendix 1 on example datasets and data elements.

This collection of data definition tables should be provided as a single PDF file named *define.pdf* and placed in the appropriate study folder in the datasets folder. The Title portion of the Document Information field of each data definition file should include the appropriate study report number and data definitions. For example, the data definition file for study 2001 would be identified as: *study 2001, data definitions*. This file is considered part of the comprehensive table of contents and, therefore, must be provided as required under 314.50(b).

d. Dataset table of contents

The dataset table of contents is also part of the comprehensive table of contents and must list all studies 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.

e. General considerations for datasets

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

- Each animal should be identified with a single, unique number for all the datasets in the entire application. This unique number should be provided in each dataset. This is essential when we join different datasets to collect and evaluate responses associated with each animal.
- 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.
- The variable names and codes should be consistent across studies. This is necessary when combining datasets and reduces the time for learning the datasets. For example, if glucose is checked in a number of studies, use the same name to describe this variable in

all of the studies. Conversely, do not use the same name for different variables.

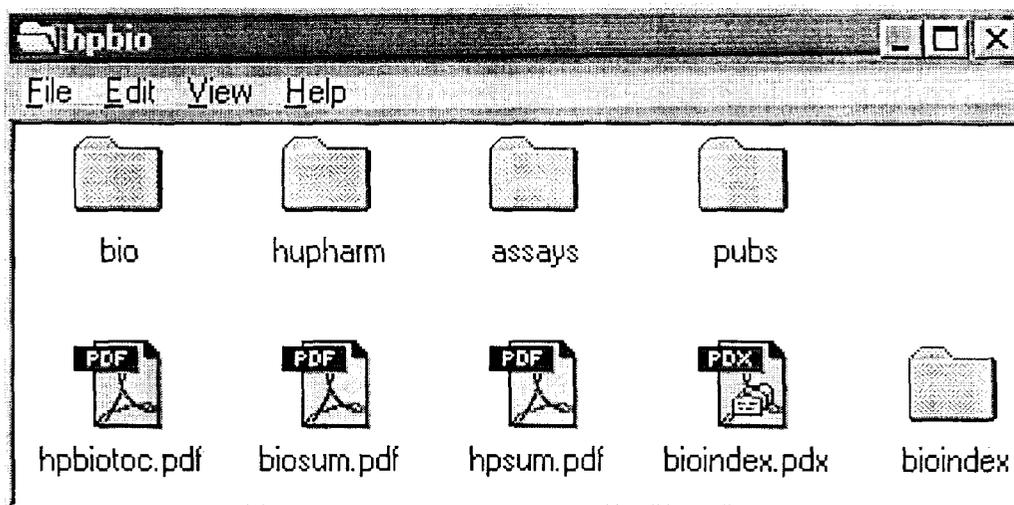
- Duration is frequently part of an analysis. To facilitate the review, you should provide the duration of treatment based on the start of study treatment and expressed in minutes, hours, or days, whichever is appropriate. When expressed in days, the following formula should be used to calculate study day ((sampling date)-(date of first dose) + 1).
- Since results are usually analyzed based on treatment group and sex of the animals, each dataset should include these variables to save time.
- Data variable names should be limited to 8 characters with a more descriptive name, up to 32 characters, provided as a data variable label.
- Text should be used instead of, or in addition to, arbitrary number codes. For example, for the variable organ, if there is a number code for each organ type, a separate column should be included that has the text name of the organ.
- For the dose data element, use numeric values rather than control, LD (low dose), MD (mid dose), or HD (high dose).

## F. Item 6: Human Pharmacology and Bioavailability/Bioequivalence

The human pharmacology and bioavailability/bioequivalence section is item 6 on page 2 of FDA form 356h.

### 1. Folders

You should create 4 folders, *bio*, *hupharm*, *assays*, and *pubs* to organize the files in this section. The *bio* folder contains studies related to bioavailability, bioequivalence, food effects, dissolution, and in vitro/in vivo correlations. This folder also contains formulation information. The *hupharm* folder contain studies using human biomaterials, pharmacokinetics studies, and pharmacodynamics studies. The *assays* folder contains assay descriptions and their validation reports including cross validation assays. The *pubs* folder contains publications. Place these folders in a single folder named *hpbio*. The file structure is pictured in the figure below (the additional file, *bioindex.pdx* and subfolder *bioindex* are for the full text index).



### 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). You should use the example headings below to organize the files in the table of contents. Provide the location of the paper review copy by volume number and the location of the archive copy by folder and file name, if electronic, and by volume number if paper. As part of the comprehensive table of contents

for the submission, 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. If datasets were listed in the table of contents, provide a link to the appropriate data definition file (define.pdf). This file is described in item 11, case report tabulations (crt).

<b>Human Pharmacology and Bioavailability/Bioequivalence Table Of Contents</b>		
<b>Description</b>	<b>Review copy Volume number</b>	<b>Archive copy Folder/file name*</b>
I. Summaries		Hpbio
a. Bioavailability/Bioequivalence Summary		
b. Human Pharmacology Summary		
II. Reports for Bioavailability and Bioequivalence Studies		Hpbio/bio
a. Bioavailability Study Reports		
b. Bioequivalence Study Reports		
c. IVIVC		
III. Reports for Studies Using Human Biomaterials		Hpbio/hupharm
a. Plasma Protein Binding Studies		
b. Metabolism Studies Using Hepatocytes, Microsomes etc.		
IV. Human pharmacokinetics (PK) Study Reports		Hpbio/hupharm
a. Baseline PK Study Reports, Initial Safety and Tolerability		
1. Healthy Volunteers		
2. Patients		
b. PK Study Reports in Population Subsets To Evaluate Effects of Intrinsic Factors (e.g., age, ethnic groups, organ dysfunction, gender, body size and weight)		
c. PK Study Reports in Population Subsets To Evaluate Effects of Extrinsic Factors (e.g., dietary factors, smoking, drug-drug interactions)		
d. Population PK Study Reports		
V. Human Pharmacodynamics (PD) Study Reports		Hpbio/hupharm
a. Study Reports in Healthy Volunteers		
1. Dose-Response		
2. PK-PD Relationships		
b. Studies Reports in Patients		
1. Dose-Response		
2. PK-PD Relationships		
VI. Assays		Hpbio/assays
VII. Publications		Hpbio/pubs

\*Use volume number if the archive copy is paper.

### 3. Summary

You should provide summary documents for the human pharmacology and bioavailability/bioequivalence sections as PDF files named *hpsum.pdf* and *biosum.pdf*, respectively. Place these files in the *hpbio* folder. You should include a hypertext link between each reference in the summary 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 summaries should be identified in the Document Information Title field as *human pharmacology summary* and *bioavailability/bioequivalence summary*, respectively.

### 4. Study reports

You should provide each study report with all appendices (except case report tabulations (crt) and case report forms, which are described in item 11 and 12, respectively) as an individual PDF file. Including the study number in the name of the file helps us locate files. For example, study 1234 can be named *1234.pdf*. Using the table of contents as a guide, place the file in the appropriate subfolder in the *hpbio* folder.

The Document Information Title field for the studies should include the type of study and the study number. For example, the report for study 201, a drug interaction study, should be designated as *study 201, drug interaction*.

### 5. Datasets

We are developing specifications for data elements for human pharmacology and biopharmaceutics data and plan on providing detailed guidance for structured datasets in the future. Until that guidance is available, you should provide datasets as SAS transport files. Confer with the appropriate reviewers on the datasets to be provided and the data elements to be included in the datasets.

Place all dataset files into folders named for the study report or type of data/analysis (e.g., *popPK* for population PK study data). Put these folders in the datasets subfolder of the crt folder.

If datasets are included, note this with their respective study reports in the *hpbio* table of contents. Include the file location and a link to open the appropriate data definition file (*define.pdf*).

## 6. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. The *pubs* folder should be placed in the *hpbio* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. The citation should include the first author's last name, the year of the publication, and the title of the article.

## 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*).

Hypertext linking provided throughout the body of the document to supporting annotations, datasets, related sections, publications, appendices, tables, or figures that are not located on the same page will help the reviewer navigate more efficiently through a document. For a reference list at the end of a document, you should provide a hypertext link from the item listed to the appropriate PDF publication file.

## 8. *Full text index*

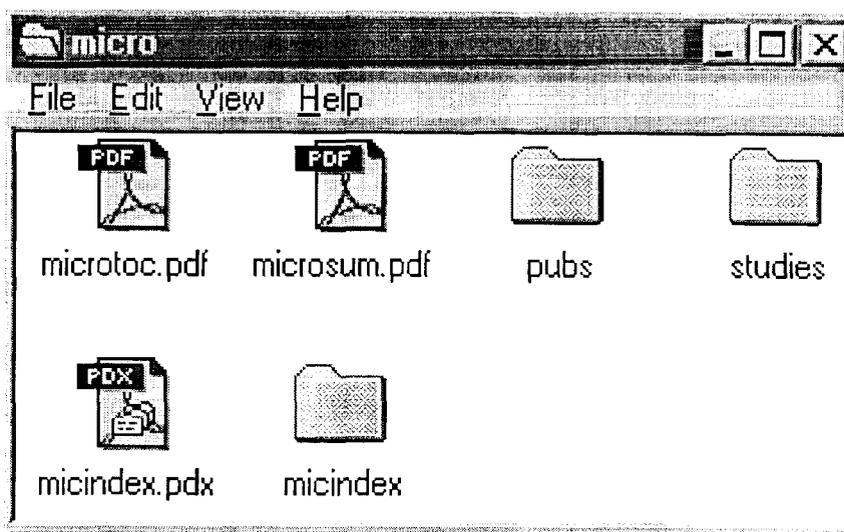
An index of the full text and the Document Information fields of all documents in this section should be provided. The index definition file should be named *hpbio.pdx*. Place all associated index files in a folder named *hpbio*. Place the *hpbio.pdx* definition file and the *hpbio* index file subfolder in the main *hpbio* folder. Associate the *hpbio.toc.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.

## G. Item 7: Clinical Microbiology

The clinical microbiology section is item 7 on page 2 of FDA form 356h and includes information for anti-infective, anti-viral, and immunomodulator products submitted to CDER. Files and organization may differ depending on the type of product.

### 1. Folders

You should create 2 folders, *studies* and *pubs*, to organize the files in this section. Place these folders in a single folder named *micro*. The file structure is pictured in the figure below (the additional file, *micindex.pdx* and subfolder *micindex* are for the full text index).



### 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)). You should use the example headings below to organize the files in the table of contents. Provide the location of the paper review copy by volume number and the location of the archive copy by folder and file name, if electronic, and by volume number if paper. As part of the comprehensive table of contents for the submission, provide a hypertext link between the documents listed in the table of contents and the corresponding PDF file and bookmarks for the each item in the table of contents. If datasets were listed in the table of contents, provide a link to the appropriate data definition file (*define.pdf*). This file is described in item 11, case report tabulations (*crt*). Place the *microtoc.pdf* file in the *micro* folder.

<b>Microbiology Table Of Contents—Anti Infective Product</b>		
<b>Description</b>	<b>Review copy Volume number</b>	<b>Archive copy folder/file name*</b>
I. Summary		
II. General In vitro Clinical Information to Characterize the Antimicrobial		
Antimicrobial spectrum of activity		
Mechanism(s) of action		
Mechanism(s) of resistance		
Time-kill kinetics		
Intracellular antimicrobial concentration assessment		
Relevant published literature		
III. Human and Animal Data for the Establishment of Provisional Breakpoints		
Pharmacokinetics		
Pharmacodynamics		
Bioavailability		
Prophylactic and therapeutic animal studies		
Relevant published literature		
IV. Susceptibility Test Method Analysis		
Factors affecting in vitro susceptibility test methods		
Quality control parameters		
In vitro dilution (MIC) methods		
Disk diffusion (zone diameter) methods		
Verification to support modification of standardized methods		
V. Derivation of the Provisional Breakpoints for Use in Investigational Clinical Trials		
Justification of proposed breakpoints		
VI. Establishment of Final Breakpoints for the Package Insert		
Organism relevance to pending indications		
Susceptibility trial quality control data		
Dilution disc diffusion correlation		
Bacteriological efficacy studies		
Clinical efficacy		

\*Use volume number if the archive copy is paper.

**Microbiology Table Of Contents—Anti Viral Product**

Description	Review copy Volume number	Archive copy folder/file name*
I. Summary		
II. In vitro/in vivo (animal model) preclinical data and related laboratory protocols and methodologies		
A. Mechanism of Drug Action		
B. Antiviral Spectrum of Activity		
1. Range of susceptible virus/cell combinations#		
2. Dose/response curves for activity/cytotoxicity		
3. Impact of model system variables on drug activity (e.g., multiplicity of infection, timing of drug treatment, serum effects)		
C. Drug resistance		
1. Mechanisms of Drug Resistance		
2. Drug susceptibility profile		
3. Cross-resistance		
D. Combination Drug Interactions		
E. Immunologic effects (where applicable)		
III. In vivo (human) data and supporting laboratory methodology		
A. Viral load assay specifications		
1. Assay performance characteristics (e.g., quantitative lower limit, qualitative lower limit, specificity, sensitivity, precision, accuracy, stability, effects of interfering substances).		
2. Assay design/methodology, rationale (e.g., suitability of the assay for the target population and protocol design).		
B. Viral load data		
C. Resistance/cross-resistance data from clinical trial specimens		
D. Additional virologic/immunologic measurements		
1. Assay performance characteristics		
2. Clinical data		
IV. Miscellaneous microbiologic information		

\* Use volume number if the archive copy is paper.

# This information should focus on virus types relevant to the indication(s) under consideration.

### 3. *Summary document*

The summary document for this section should be named *microsum.pdf* and placed in the micro folder. You should include a hypertext link between each reference in the summary 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).

### 4. *Study reports*

You should provide each study report as an individual PDF file. Including the study number in the name of the file helps us locate files. For example, study 1234 can be named *1234.pdf*. Using the table of contents as a guide, place the file in the appropriate subfolder in the *micro* folder.

The Document Information Title field for the studies should include the type of study and the study number.

### 5. *Datasets*

You should provide a single SAS transport file for each dataset. Confer with the appropriate reviewers on the datasets to be provided and the data elements to be included in the datasets. Place all dataset files into folders named for the study report or type of data/analysis. Put these folders in the datasets subfolder of the crt folder.

If datasets are included, note this with their respective reports in the micro table of contents. Include the file location and a link to open the appropriate data definition file (*define.pdf*).

### 6. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. The *pubs* folder should be placed in the micro folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. The citation should include the first author's last name, the year of the publication, and the title of the article.

### 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*).

Hypertext linking provided throughout the body of the document to supporting annotations, datasets, related sections, publications, appendices, tables, or figures that are not located on the same page will help the reviewer navigate more efficiently through a document. For a reference list at the end of a document, you should provide a hypertext link from the item listed to the appropriate PDF publication file.

8. *Full text index:*

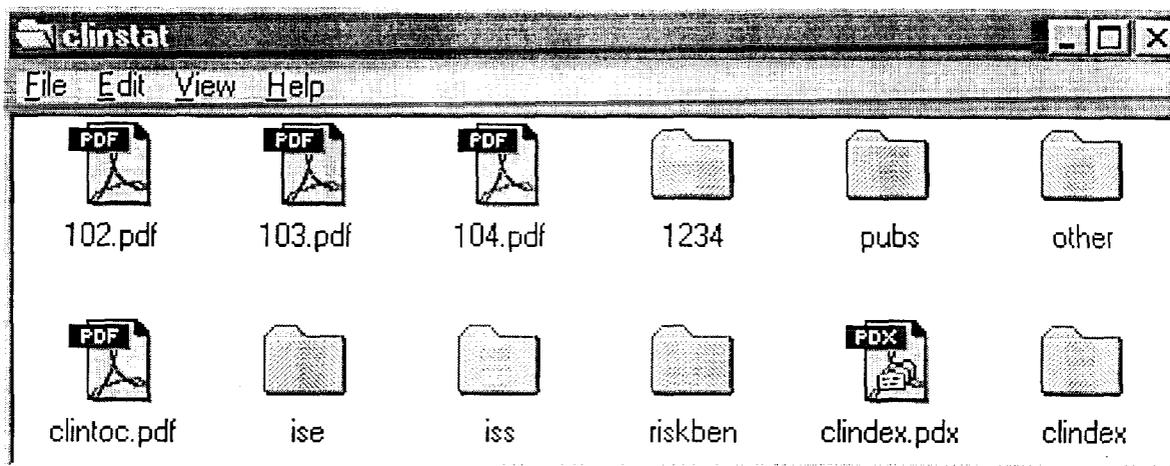
An index of the full text and the Document Information fields of all documents in this section should be provided. The index definition file should be named *micindex.pdx*. Place all associated index files in a folder named *micindex*. Place the *micindex.pdx* definition file and the *micindex* subfolder in the main 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.

## H. Item 8: Clinical

The clinical section is item 8 on page 2 of FDA form 356h. Additional information on the content of this section can be found in the *ICH E3 Structure and Content of Clinical Study Reports* (July 1996).

### 1. Folders

You should create a folder for each indication and for each integrated summary. In some cases, you may also need to create folders for individual studies and place them inside the appropriate indications folder. Using the indication or study numbers as the folder name and naming the integrated summary of safety, the integrated summary of efficacy, and integrated summary of risk and benefit, *iss*, *ise* and *riskben*, respectively, will facilitate the review. You should also create two folders, *pubs* and *other*, for publications and additional information, respectively. Place all folders in a single folder named *clinstat*. An example of the file structure is pictured below (the additional file, *clindex.pdx* and subfolder *clindex* are for the full text index).



### 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)). The *clinstat* table of contents should list all study reports (including study report numbers) by type of study (e.g., controlled clinical studies, uncontrolled studies), as appropriate. If datasets are provided for a study or summary, you should note this in the table of contents. All other documents in the clinical section, including publications, should also be listed. Provide the location of the paper review copy by volume number and the location of the archive copy by folder and file name if electronic, and by volume number

if paper. As part of the comprehensive table of contents, provide hypertext links between the documents listed in the table of contents and the corresponding PDF file and bookmarks for each item in the table of contents. If datasets were listed in the table of contents, provide a link to the appropriate data definition file (define.pdf). This file is described in item 11, case report tabulations (crt).

In some applications, more than one indication is studied. If this is the case, you should also organize the listing of files by indication as appropriate. See the table below for an example.

<b>Clinstat Table Of Contents</b>		
<b>Description</b>	<b>Review copy volume number</b>	<b>Archive copy folder/file name*</b>
Indication <sup>1</sup>		
Controlled study reports		
Uncontrolled study reports		
Integrated summary of efficacy		
Integrated summary of safety		
Integrated summary of benefits and risks		
Other studies and information		
Publications		

\* Use volume number if the archive copy is paper.

<sup>1</sup> Repeat for each indication

### 3. Study reports

You should provide each study report as a separate PDF file. The file should include all appendices as defined in the ICH *E3 Structure and Content of Clinical Study Reports* (July 1996), except for case report forms (CRF) and individual patient data listings (case report tabulations (CRT)). Including the study number in the name of the file helps us locate files. For example, study 1234 can be named *1234.pdf*.

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. The first file should include the body of the study report, the reference list, the tables and figures that follow the study report, the protocol, all amendments, and a sample CRF. This includes sections 1 to 16.1.2 of the clinical study report as defined in ICH *E3 Structure and Content of Clinical Study Reports* (July 1996). The second file should include all of the remaining appendices except for the CRFs and CRTs. Add the letter *a* to the end of the file name to distinguish the file with the appendices from the main file. You should place both files in a folder with the study number as a name. This folder should be placed in the

clinstat folder. Guidance for the CRTs and CRFs are found under item 11 and 12, respectively.

The title portion of the Document Information field of each study should include the study number.

#### 4. *Integrated summaries*

You should handle the integrated summaries in the same manner as the study reports. Name the integrated summary of safety and the integrated summary of efficacy and risk/benefit *iss.pdf*, *ise.pdf*, and *riskben.pdf*, respectively. Include integrated summary of safety, integrated summary of efficacy, or risk benefit in the Title portion of the Document Information field.

#### 5. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. The *pubs* folder should be placed in the *clinstat* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. The citation should include the first author's last name, the year of the publication, and the title of the article.

#### 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).

Hypertext links 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 facilitate the review. For a reference list at the end of a document, you should provide a hypertext link from the item listed to the appropriate PDF publication file.

#### 7. *Full text index*

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

subfolder in the main 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.

## **I. Item 9: Safety Update**

The safety update is item 9 on page 2 of FDA form 356h. In general, you should follow the guidance provided in item 8 for study reports, publications, and summaries.

### *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*

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

## **J. Item 10: Statistical**

For electronic submissions, item 8 and item 10 are identical. Documents describing statistical methods and the like should be included in item 8. Therefore, for this item, you only need to link the submission table of contents to the *clintoc.pdf*.

## **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. Just as you provide each CRF domain (e.g., demographics, vital signs, adverse events) as a table in a paper submission, in an electronic submission, each CRF domain should be provided as a single dataset. In addition, datasets suitable for reproducing and confirming analyses may also be needed. Prior to the submission, you should discuss with the review division the datasets to be provided and the data elements that should be included in each dataset.

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). We import the data into various software tools. The most commonly used tools include database programs, spreadsheet programs, and statistical analysis programs.

Because many of the software tools used by reviewers require datasets to be loaded into random access memory (RAM) prior to opening the file, 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*

The data organization varies from indication to indication. Prior to the submission, you should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset, and the organization of the data within the file. The type of individual datasets that are generally provided to support each study and integrated summaries are included in the following list.

- Demographics
- Inclusion criteria
- Exclusion criteria
- Concomitant medication
- Medical history
- Drug exposure
- Disposition
- Efficacy results
- Human pharmacology and bioavailability/bioequivalence data
- Microbiology data
- Adverse Events
- Lab – chemistry
- Lab – hematology
- Lab – urinalysis
- ECG
- Vital signs
- Physical examination

Examples of the variables to include in the individual datasets are included in Appendix 2 on content of specific clinical datasets. These examples are intended as a starting point for discussion between you and the reviewing division about the data elements that you should provide in the submission. The data elements and organization may vary depending on the reviewing division and indication.

Divide datasets that are larger than 25 MB into smaller datasets. For example, clinical chemistry data may be further divided by specific lab tests. A dataset type should not be divided unless the size is greater than 25 MB and, when dividing a dataset type, it should be done with the fewest number of overall datasets. You should discuss the organization of the datasets with the appropriate review division. File names should include the three character extension *xpt* to be compatible with our desktop set up and training.

All datasets for an individual study, specific data analysis (e.g., population PK), or integrated summary should be placed in a folder identified by the study name, type of data/analysis, or integrated summary name and placed in a single folder called *datasets*. The datasets folder should be placed in the *crt* folder.

### 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.

For the datasets to be useable, the definitions of the variables should be provided. You should document all of the variables in the datasets in data definition tables. There should be one set of data definition tables for each study, specific data analysis (e.g., population PK) and integrated summary.

The first table should include a listing of all datasets provided for the study with a description of the dataset and the location of the dataset file. Provide a hypertext link from the description of the dataset to the appropriate data definition table. Provide a hypertext link from the location listing of the file to the SAS transport file. The reviewer can use the first hypertext link to view the data definition table and the second to open the SAS transport dataset file. You should also provide a link to the appropriate annotated case report form file (blankcrf.pdf).

In the following table, the dataset for AE is described as adverse events, and the dataset file is located in folder 1234 in the datasets folder, which is in the crt folder.

<b>Datasets For Study 1234</b>		
<b>Dataset</b>	<b>Description of dataset</b>	<b>Location</b>
AE	Adverse events	Crt/datasets/1234/ae.xpt
...	...	...

Subsequent pages should contain a table for each dataset that includes an organized listing of all variable names (up to 8 characters) used in the dataset, a descriptive variable label (up to 32 characters), data types, codes (and decodes), and comments. The comments field is for further description of the variables. For derived variables, the method for calculating the variable should be included in the comments field. For raw variables, the location of the variable on the annotated CRF should be provided as well as the CRF field name if different from the variable name in the dataset. Providing a hypertext link from each raw data variable in the data definition table to the appropriate location of the blankcrf.pdf also helps the review process. An example of part of a data definition table for the demographics dataset for study 1234 is provided below.

Study 1234 – Demographics Dataset Variables				
Variable	Label	Type	Codes	Comments <sup>1</sup>
PATID	Unique patient ID number	char		Demographics page 3
SEX	Sex of subject	char	f = female m = male	Demographics page 3
BDATE	Birth date	date		Demographics page 3
DUR	Duration of Treatment	num		Derived STOP DATE – START DATE
TRT	Assigned treatment group	num	0= placebo 5= 5mg/day	

<sup>1</sup> Use footnotes for longer comments.

The data definition tables should be provided as a single PDF file named *define.pdf* and placed in the appropriate study, specific analysis type or integrated summary folder in the datasets folder. The Title portion of the Document Information field of each data definition file should include the appropriate study report number, specific analysis type or integrated summary name and *data definitions*. For example, the data definition file for study 2001 would be identified as: *study 2001, data definitions*. This file is considered part of the comprehensive table of contents.

The annotated CRF is a blank CRF including treatment assignment forms that maps each blank on the CRF to the corresponding element in the database. The annotated CRF should provide the variable names and coding. Each page and each blank of the CRF should be represented. The sponsor should write *not entered in database* in all sections where this applies. The annotated CRF should be provided as a PDF file. Name the file *blankcrf.pdf* and place it in the appropriate subfolder in the datasets folder. The Title portion of the Document Information field of each annotated crf file should include the appropriate study report number and *annotated crf*. For example, the annotated crf for study 2001 would be identified as: *study 2001, annotated crf*.

#### 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*

An index of the full text and the Document Information field of all documents in the dataset folder should be provided. The index definition file should be named *datindex.pdx*. Place all associated index files in a folder named *datindex*. Place the *datindex.pdx* definition file and the *datindex* subfolder in the main dataset folder. Associate *datatoc.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.

## 6. *General considerations for datasets*

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

- Each subject should be identified with a single, unique number for the entire application. The unique number needs to be provided in each dataset. This is essential for joining different datasets.
- For a data table, each variable should be represented as a single field in the dataset or column heading. Each row should contain a single observation or result for an individual patient. In some datasets, this will result in multiple rows per patient.
- The variable names and codes should be consistent across studies. This is necessary when combining datasets and reduces the time for learning the datasets. For example, if glucose is checked in a number of studies, use the same name to describe this variable in all of the studies. Conversely, do not use the same name for different variables.
- The format of variables for similar types of data should also be consistent within and across studies. For example, all variables that are a calendar date (e.g., birthdate, screening visit date, randomization date, date of death) should use the same format for representing the date.
- Duration is frequently part of an analysis. 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 dataset should include these variables.

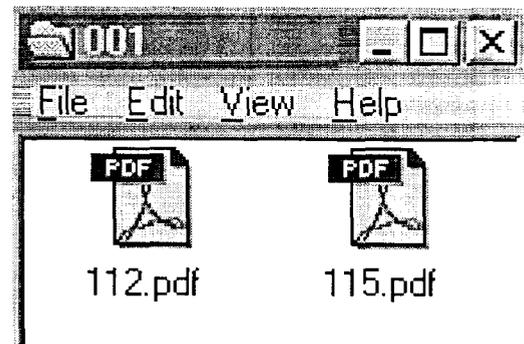
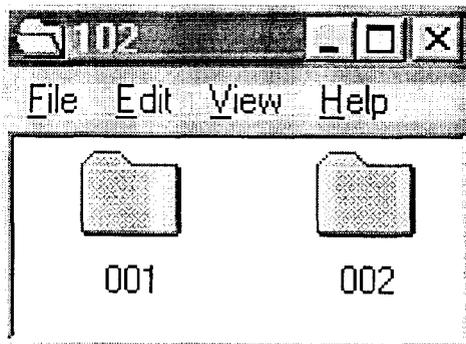
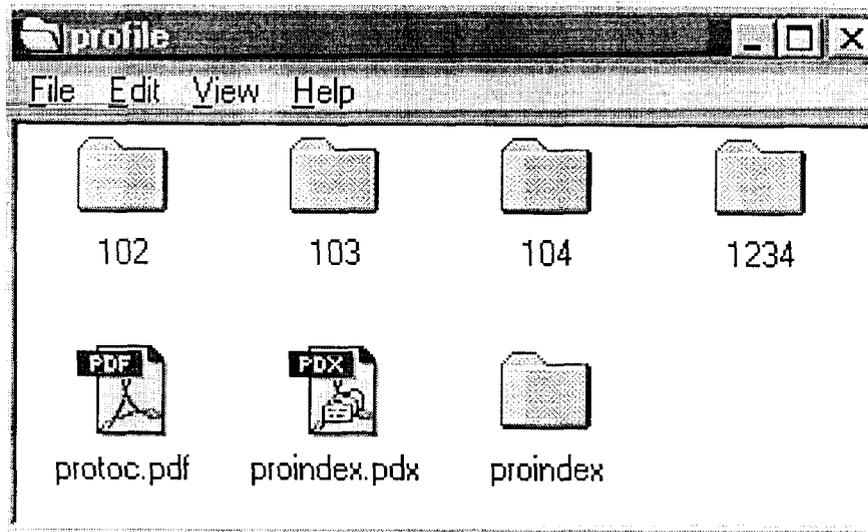
- For treatment assignment, all placebo subjects should be 0, and in fixed dose studies, the treatment assignment variable should be the prescribed dose.
- Data variable names should be limited to 8 characters with a more descriptive name, up to 32 characters, provided as a data variable label.
- Text should be used instead of, or in addition to, arbitrary number codes. For example, for the variable *concomitant medications*, if there is a number code for each type of medication, a separate column should be included that has the actual name of the concomitant medication.

## 7. Patient profiles as PDF files

Patient profiles are PDF files that include all study data collected for an individual patient organized by time. This presentation of the data serves as a complement to the electronic datasets and should not be considered a satisfactory substitute for the electronic datasets. Check with the review division regarding patient profiles. The need for patient profiles depends on the indication. Sometimes they are not needed at all, or are needed only for patients who discontinued or had a serious adverse event.

### a. Folders

You should create a folder for each study to organize the patient profiles. In each study folder, you may need to provide a folder for each study site. Use the study numbers and site numbers when naming the respective folder. Place the study folders in a single folder named *profiles* and place it in the crt folder. The file structure is pictured below (the additional file, proindex.pdx and subfolder proindex are for the full text index).



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. Place the PDF files in the appropriate study site folder. For example, all patient profiles for site 03 for study 301 would be placed into a folder named 03, which then would be placed in a folder named 301.

Alternatively, you can provide all patient profiles for an entire study in one file if the size of each individual patient profile is small and there are not a large number of patient profiles needed for the study. Including the study number in the file name will help identify the file. Place these PDF files in the appropriate study folder.

The Document Information Title field for each file should include *profile*, 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: *profile, study 2001, site 003, PID 2001-003-001*.

When all patient profiles for a study are placed in a single file, the Document Information Title field should contain *profile* and the study number.

d. Bookmarks and hypertext links

You should provide bookmarks to help the reviewer navigate the patient profiles. For larger patient profiles, a bookmark should be provided to each CRF domain. If all patient profiles for a study are included in one file, the bookmark hierarchy should include each patient by study site.

e. Full text index

An index of the full text and the Document Information field of all documents in the profile folder should be provided. The index definition file should be named *proindex.pdx*. Place all associated index files in a folder named *proindex*. Place the *proindex.pdx* definition file and the *proindex* subfolder in the main profile folder. Associate *protoc.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.

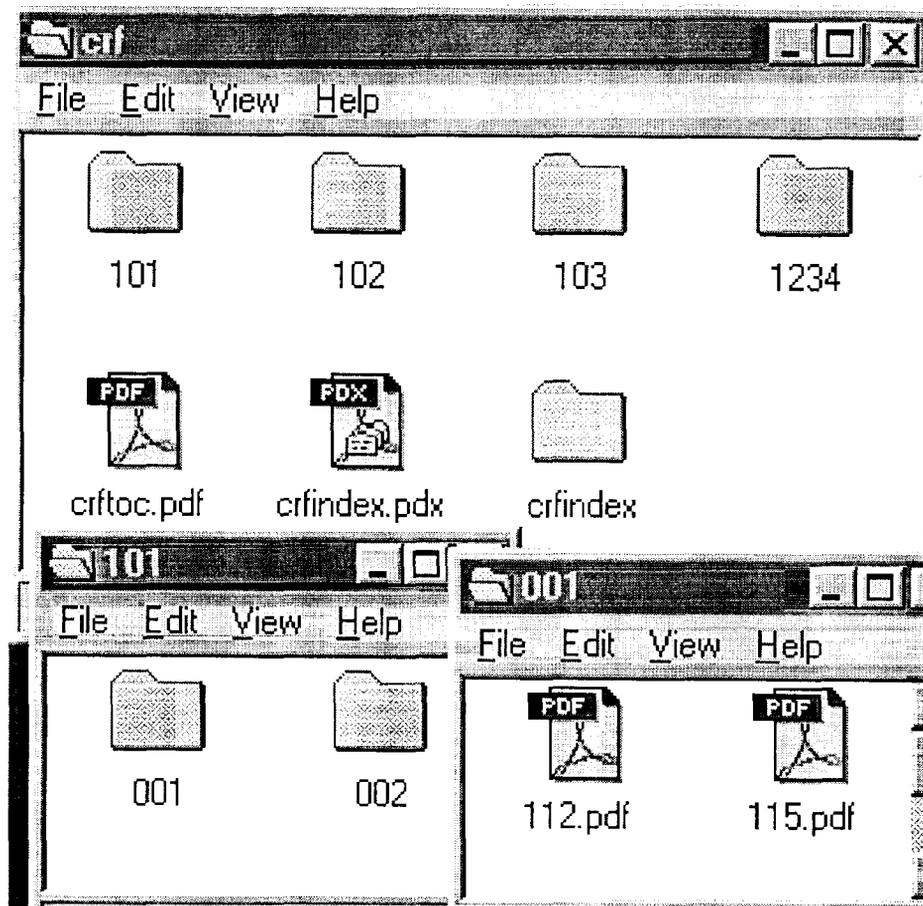
## L. Item 12: Case Report Forms

Case report forms (CRFs) are item 12 on page 2 in FDA form 356h.

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. In each study folder, you should include a folder for each study site. Use the study numbers and site numbers when naming the respective folder. Place the study folders in a single folder named *crf*. An example of the file structure is pictured below (the additional file, *crfindex.pdx* and subfolder *crfindex* are for the full text index).



## 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). We recommend bookmarks for each CRF domain and study visit to help the reviewer navigate the CRFs.

For addendum and corrections, making a hypertext link from the amended item to the corrected page or addendum is a useful way to avoid confusion.

## 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**

This is item 13 on page 2 of FDA form 356h.

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*.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification or declaration must be accompanied by a signed paper certification or declaration.

**N. Item 14: Patent Certification**

This is item 14 on page 2 of FDA form 356h.

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*.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification or declaration must be accompanied by a signed paper certification or declaration.

**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**

This is item 16 on page 2 of FDA form 356h.

*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*.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

**Q. Item 17: Field Copy Certification**

This is item 17 on page 2 of FDA form 356h.

*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*.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

**R. Item 18: User Fee Cover Sheet**

This is item 18 on page 2 of FDA form 356h.

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*.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

**S. Item 19: Other**

This is item 19 on page 2 of FDA form 356h. Information that is not included in item 1 to 18 is included in this item. For example, certifications for financial disclosure by clinical investigators are included in this item.

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. For example, provide certification for financial disclosure by clinical

investigators as a single PDF file named *financial.pdf* and place it in the other folder. List this file in the submission table of contents and provide a hypertext link from the table of contents to the file.

The Agency is developing procedures to allow the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

## APPENDIX 1: EXAMPLE NONCLINICAL PHARMACOLOGY AND TOXICOLOGY DATASETS AND DATA ELEMENTS

The following examples of datasets and data elements are intended to serve as a starting point for discussion between you and the review division on the content and organization of the datasets and, therefore, are not all inclusive. We plan on refining these datasets and data elements and adding more datasets as we gain more experience.

<b>Data Definition Tables (place the study subfolder name in the space with the ***)</b>		
<b>Dataset</b>	<b>Description of dataset</b>	<b>Location of dataset</b>
Tumor	Tumor frequency for statistical analysis	Pharmtox/datasets/***/Tumor.xpt
Weights	Body weights	Pharmtox/datasets/***/Weights.xpt
Food	Food consumption	Pharmtox/datasets/***/Food.xpt
Water	Water consumption	Pharmtox/datasets/***/Water.xpt
Signs	Clinical signs	Pharmtox/datasets/***/Signs.xpt
Chem	Plasma clinical chemistry	Pharmtox/datasets/***/Chem.xpt
Hemat	Hematology	Pharmtox/datasets/***/Hemat.xpt
Urine	Urinalysis	Pharmtox/datasets/***/Urine.xpt
Drug	Plasma drug and metabolite levels	Pharmtox/datasets/***/Drug.xpt
Mortal	Mortality information	Pharmtox/datasets/***/Mortal.xpt
Organ	Organ weights	Pharmtox/datasets/***/organ.xpt
Macro	Macroscopic examination of tissues	Pharmtox/datasets/***/Macro.xpt
Micro	Microscopic examination (histopathology)	Pharmtox/datasets/***/Histo.xpt
Other	Other datasets as needed	..

<b>Tumor Dataset For Statistical Analysis<sup>1,2</sup> (tumor.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
STUDYNUM	Study number	char		<sup>3</sup>
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R= rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0 = No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2 = Benign 3 = Undetermined	<sup>4</sup>
DEATHCAU	Cause of death	num	1 = Tumor caused death 2 = Tumor did not cause death 3 = Undetermined	<sup>4</sup>
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2 = Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

<sup>1</sup> Each animal in the study should have at least one record even if it does not have a tumor.

<sup>2</sup> Additional variables, as appropriate, can be added to the bottom of this dataset.

<sup>3</sup> ANIMLNUM limit to no more than 12 characters; ORGANCOD and TUMORCOD limited to no more than 8 characters; ORGAN and TUMOR should be as concise as possible.

<sup>4</sup> A missing value should be given for the variable MALIGNST, DEATHCAU, TUMOR and TUMORCOD when the organ is unuseable or not examined.

<sup>5</sup> Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

<b>Body Weights For Each Animal (weights.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	num		
SPECIES	Animal species	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
BASELINE	Weight at baseline	num		
DAYS	Days on drug at observation	num		
WEIGHT	Body weight	num		
CHANGE	Change in weight compared to baseline	num		WEIGHT-BASELINE
UNIT	Unit of weight measurements	num		
OTHER	...	...	...	...

<b>Food Consumption For Each Animal (food.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at observation	num		
FOOD	Food consumption	num		
UNIT	Unit of measurement	num		
OTHER	...	...	...	...

<b>Water Consumption For Each Animal (water.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at observation	num		
WATER	Water consumption	num		
UNIT	Unit of measurement	num		
OTHER	...	...	...	...

<b>Clinical signs For Each Animal (signs.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
SIGN	Clinical sign	char		<sup>1</sup>
START	Days on drug sign first seen	num		
DURATION	Duration of sign	num		
COURSE	Course of sign	char	Intermittent or continuous	
TERMINAL	Flag if sign present at death	char	y= yes n= no na = not applicable	<sup>2</sup>
OTHER	...	...	...	...

<sup>1</sup>One clinical sign per row. Record "normal" if no abnormal clinical signs were reported.

<sup>2</sup>"Not applicable" used for animals without clinical signs

<b>Plasma Clinical Chemistry For Each Animal (chem.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at time of test	num		
LABTEST	Lab test name	char		
BASELINE	Baseline lab value	num		
RESULT	Test result value	num		
CHANGE	Change from baseline	num		RESULT - BASELINE
UNIT	Unit of lab test	char		
OTHER	...	...	...	...

<b>Hematology Results For Each Animal (hemat.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at observation	num		
LABTEST	Name of lab test	char		
UNIT	Unit of lab test	char		
BASELINE	Baseline lab value	num		
RESULT	Test result value	num		
CHANGE	Change from baseline	num		RESULT - BASELINE
OTHER	...	...	...	...

<b>Urinalysis Results For Each Animal (urine.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at observation	num		
LABTEST	Name of lab test	char		
UNIT	Unit of lab test	char		
BASELINE	Baseline lab value	num		
RESULT	Test result value	num		
CHANGE	Change from baseline	num		RESULT - BASELINE
OTHER	...	...	...	...

<b>Plasma Drug Levels For Each Animal (drug.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at observation	num		
DRUG	Name of drug	char		Include levels for drug and major metabolites
UNIT	Unit of measurement	char		
RESULT	Drug level	num		
OTHER	...	...	...	...

<b>Mortality Data For Each Animal (mortal.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, ... in ascending order from control. Provide the dosing for each group.	
TYPE	Type of death	char	Scheduled or Unscheduled	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death	
WEIGHT	Terminal body weight	num		
UNIT	Unit of measurement	num		
OTHER	...	...	...	...

Organ Weight For Every Organ For Each Animal <sup>1</sup> (organwt.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
FNLBDYWT	Final body weight	num		
DAYS	Days on drug at observation	num		
ORGANNAM	Organ name	char		
ORGANWT	Weight of organ in grams	num		
UNIT	Unit of measurement	num		
RATIO	Organ to body weight ratio	num		ORGANWT/ FNLBDYWT
BILATERL	Bilateral organ code	num	1= organ is not bilateral or weight is for one of the two bilateral organs 2= organ is bilateral and weight is expressed for combined weight of the two bilateral	
OTHER	...	...	...	...

<sup>1</sup> All organs should be accounted for all animals. Each organ should be listed under ORGANNAM for each animal. If an organ was not weighed, the ORGANWT and BILATERL should be indicated as missing.

<b>Macroscopic Findings For Each Animal (macro.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death	
ORGANNAM	Name of organ	char		
ABNORMAL	Abnormal flag	char	Abnormal or normal	
MACRO	Macroscopic findings	char		Limit to 256 characters <sup>1</sup>
MICROABN	Microscopic findings	char	Abnormal or Normal	
GRADE	Grade or severity of abnormality	char		
TUMOR	Tumor flag	char	None, Benign, Malignant, or Undeterminate	
FNLBDYWT	Final body weight	num		
OTHER	...	...	...	...

<sup>1</sup> Limit to 256 characters. Full details for abnormal findings should be described in study report

<b>Microscopic Findings (histopathology) For Each Animal (micro.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
ANIMLNUM	Animal number	char		
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4 = Accidental death	
ORGANNAM	Name of organ	char		Include blood
ABNORMAL	Abnormal flag	char	Abnormal or normal	
MICRO	Microscopic findings	char		<sup>1</sup>
MACROABN	Macroscopic findings	char	Abnormal or normal	
GRADE	Grade or severity of abnormality	char		
TUMOR	Tumor flag	char	None, Benign, Malignant, or Undeterminate	
FNLBDYWT	Final body weight	num		
OTHER	...	...	...	...

<sup>1</sup> Limit to 256 characters. Full details for abnormal findings should be described in study report.

## **APPENDIX 2: EXAMPLE CONTENT OF SPECIFIC CLINICAL DATASETS**

The following lists contain suggested data elements for the individual datasets. This listing is meant to serve as a starting point for discussion between you and the review division on the content and organization of the datasets and, therefore, is not all inclusive. We plan on refining these data elements as we gain more experience. The extent of the data needed for each indication varies, 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.

If you are submitting programs that you used in your statistical analysis software to arrive at the final analysis for principal efficacy and safety data, those programs should be placed in the appropriate subfolder of the crt folder. The programs should contain sufficient detail to allow the reviewer to follow the logical flow of the program.

**Demographics**

- Age
- Sex
- Race
- Weight
- Height
- Country
- (Consult the review division regarding additional variables)

**Inclusion criteria**

- Vary by protocol – consult with the review division

**Exclusion criteria**

- Vary by protocol – consult with the review division

**Concomitant medications**

- Drug name
- Drug start date
- Drug stop date
- Drug started before study (yes/no)
- Drug type
- Dose
- Reason for medication
- (Consult the review division regarding additional variables)

**Medical history**

- Medical condition
- Past condition (yes/no)
- Current condition (yes/no)
- Body system
- Date of diagnosis
- (Consult the review division regarding additional variables)

**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
- (Consult the review division regarding additional variables)

**Drug 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
- (Consult the review division regarding additional variables)

**Efficacy results**

- Consult the appropriate reviewers

**Human pharmacology and bioavailability/bioequivalence data**

- Consult with the appropriate reviewers

**Microbiology data**

- Consult with the appropriate reviewers

**Physical examination**

- 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)

**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)

## **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)