

Guidance for Industry
Providing Regulatory Submissions to
the Center for Biologics Evaluation
and Research (CBER)
in Electronic Format —
Biologics Marketing Applications
[Biologics License Application (BLA), Product License
Application (PLA)/Establishment License Application
(ELA) and New Drug Applications (NDA)]

Additional copies are available from:

*Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448
<http://www.fda.gov/cber/guidelines.htm>
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
November 1999
REVISED

TABLE OF CONTENTS

Note: Page numbering may vary for documents distributed electronically

I.	INTRODUCTION	1
II.	GENERAL ISSUES	1
	A. Refuse to File	1
	B. Review and Archival Copies.....	2
	C. Supplements and Amendments.....	2
	D. Electronic Signatures.....	2
III.	ORGANIZING THE MAIN FOLDER	3
	A. Submission Structure.....	3
	B. Folders.....	6
	C. Cover Letter.....	7
	D. Form FDA 356h	7
	E. BLA Table of Contents.....	7
	F. Figure of Main Folder	8
	G. Submission Management	8
IV.	ORGANIZING THE ELECTRONIC SUBMISSION	9
	A. Item 1: Table of Contents (Index).....	9
	B. Item 2: Labeling.....	11
	C. Item 3: Summary.....	15
	D. Item 4: Chemistry, Manufacturing and Controls (CMC)	15
	E. Item 5: Nonclinical Pharmacology and Toxicology.....	21
	F. Item 6: Human Pharmacology and Bioavailability/Bioequivalence	28
	G. Item 7: Clinical Microbiology.....	32
	H. Item 8: Clinical	32
	I. Item 9: Safety Update.....	35
	J. Item 10: Statistical	36
	K. Item 11: Case Report Tabulations (CRTs)	36
	L. Item 12: Case Report Forms	42
	M. Item 13: Patent Information.....	44
	N. Item 14: Patent Certification.....	45
	O. Item 15: Establishment Description.....	45
	P. Item 16: Debarment Certification	48
	Q. Item 18: User Fee Cover Sheet.....	49
	R. Item 19: Other	49
V.	APPENDIXES	50
	Appendix 1: Example Nonclinical Pharmacology and Toxicology Datasets and Data Elements.....	50
	Appendix 2: Example Content of specific clinical datasets	59

Guidance for Industry¹

Providing Regulatory Submissions to the Center for Biologics Evaluation and Research in Electronic Format — Biologics Marketing Applications

I. INTRODUCTION

This is one in a series of guidance documents intended to assist applicants when making regulatory submissions in electronic format to the Center for Biologics Evaluation and Research (CBER). CBER will update guidance documents on electronic submissions periodically to reflect evolving technology and the experience of those using this technology.

This guidance discusses issues related to the electronic submission of license applications [e.g., Biologics License Applications (BLAs), Product License Applications/Establishment License Applications (PLAs/ELAs)], new drug applications (NDAs), and supplements and amendments to those applications to CBER. For a list of guidance documents that are under development regarding electronic submissions and guidance on general issues relevant to all electronic submissions refer to the companion guidance document, *Regulatory Submissions in Electronic Format — General Considerations* (January 1999) <http://www.fda.gov/cber/guidelines.htm>.

II. GENERAL ISSUES

Title 21, Code of Federal Regulations, Sections 601.2 and 314.50 provide the general requirements for submitting marketing applications to CBER. Currently, Form FDA 356h (<http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>) outlines the components required in the submission of a biologic or new drug application.

A. Refuse to File

CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). Therefore, CBER may RTF an application or supplement if the paper or electronic portions are illegible, uninterpretable, or otherwise clearly inadequate, including incompatible formats and inadequate organization. The absence of a complete

¹ This guidance has been prepared by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Center'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.

electronic database in an acceptable format to permit CBER review and statistical analyses may be considered to be inadequate, thereby resulting in a RTF decision. The intent of this guidance document is to provide information you need when constructing your electronic submission. Following this guidance document should help ensure that your electronic submission meets the requirements set forth in the regulations and can be easily archived, loaded on network drives, and reviewed within specified time frames using CBER desktop standards.

B. Review and Archival Copies

In the Federal Register of March 20, 1997 (62 FR 13467), the Agency announced the establishment of a docket, number 92S-0251, <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm> where it will publish those submissions it can accept in electronic format. Once CBER has identified in the docket number a submission type as one that can be reviewed and archived in an electronic only format, you may provide all, or only a portion of the archival and/or review copy of the submission in electronic format. Any portion of the application that is not provided in electronic format should be submitted in paper. If a submission contains both electronic and paper sections, the index (commonly referred to as the table of contents) for the submission should include the location of information submitted as a paper copy, and should identify the location of the electronic files by file and folder name. The location of information provided on paper only should be noted within the electronic submission through the use of a place holder. The place holder should direct the reviewer to the paper based submission and provide the volume and page number of the submission. Preferably, each item of the Form FDA 356h should be a complete electronic and/or paper document. The paper portion of a license application should be submitted in accordance with other Agency guidance documents.

C. Supplements and Amendments

This guidance document applies equally to the original submission of an application, and the subsequent supplements and amendments.

D. Electronic Signatures

The Agency is developing procedures to allow for the submission of electronic signatures. Until those procedures are in place; documents for which regulations require an original signature, such as forms and certifications, should be accompanied by a paper copy that includes the handwritten signature. When the Agency is prepared to accept electronic signatures, this will be posted in the above reference docket.

III. ORGANIZING THE MAIN FOLDER

All electronic documents and datasets that are intended to be part of the electronic license application should be placed in a main folder entitled *blamain*. Following the assignment of a reference number to a license application, the designated reference number should be used as the title of the main folder. When information is submitted to a preexisting electronic submission, the assigned reference number should be used as the title of the main folder.

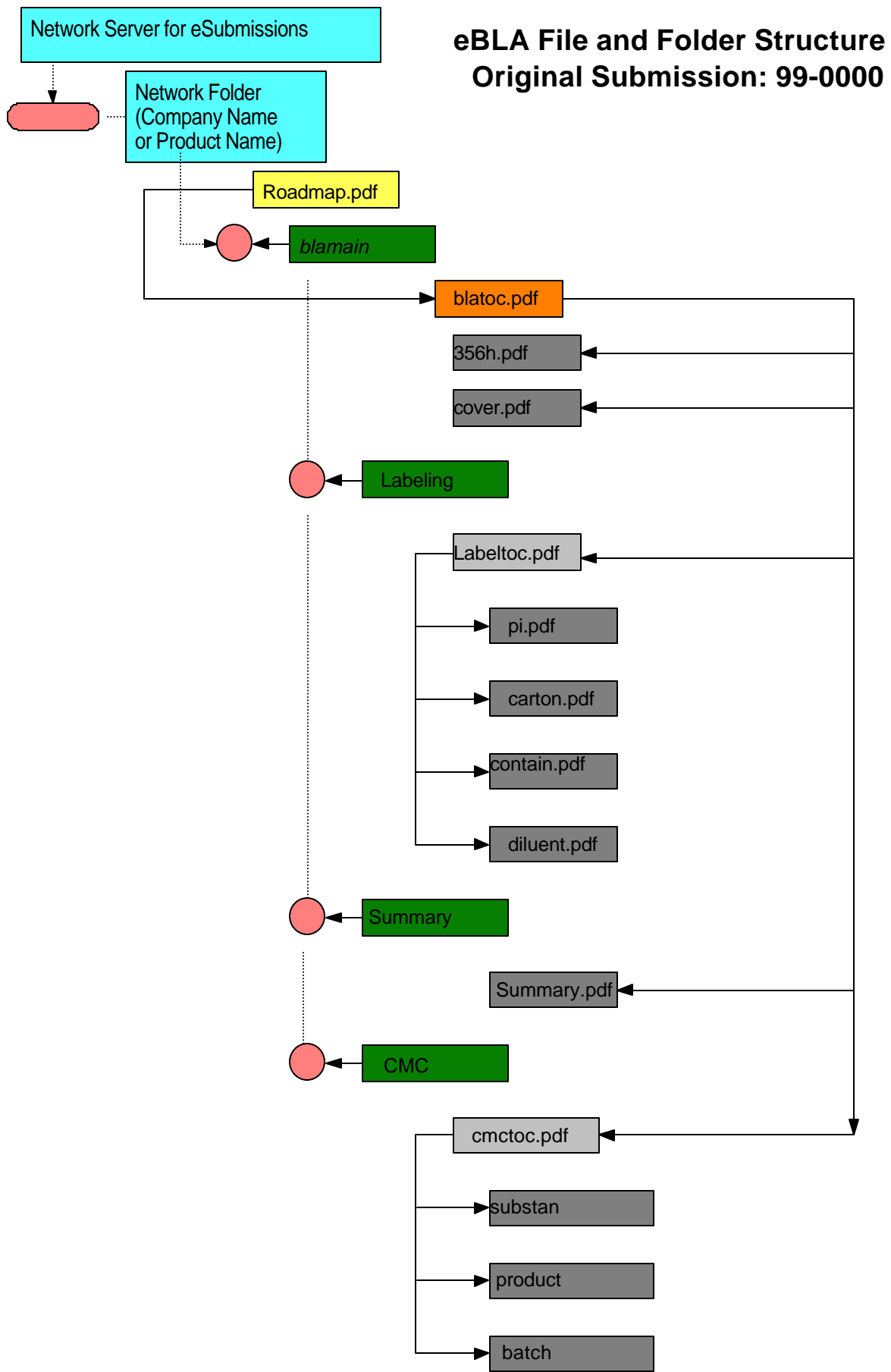
A. Submission Structure

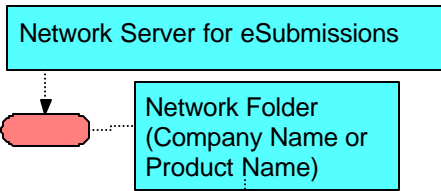
The structure and content of electronic submissions to CBER should be based on Form FDA 356h. Subsequent to the delivery of the original license application or supplement, any additional electronic and/or paper information will be added to the existing network base copy of the submission and distributed to appropriate reviewers. The root directory of an electronic application should contain a *roadmap.pdf* file to orient the review team to the original submission and to any and all subsequent information added to the application.

CBER suggests that a *roadmap.pdf* file be used to establish hypertext links to the application's main table of contents, and to the respective folders and files of the submission. This "roadmap" should be updated and resubmitted as additional information is added to the application. An example of one possible roadmap format is shown in the following illustrations.

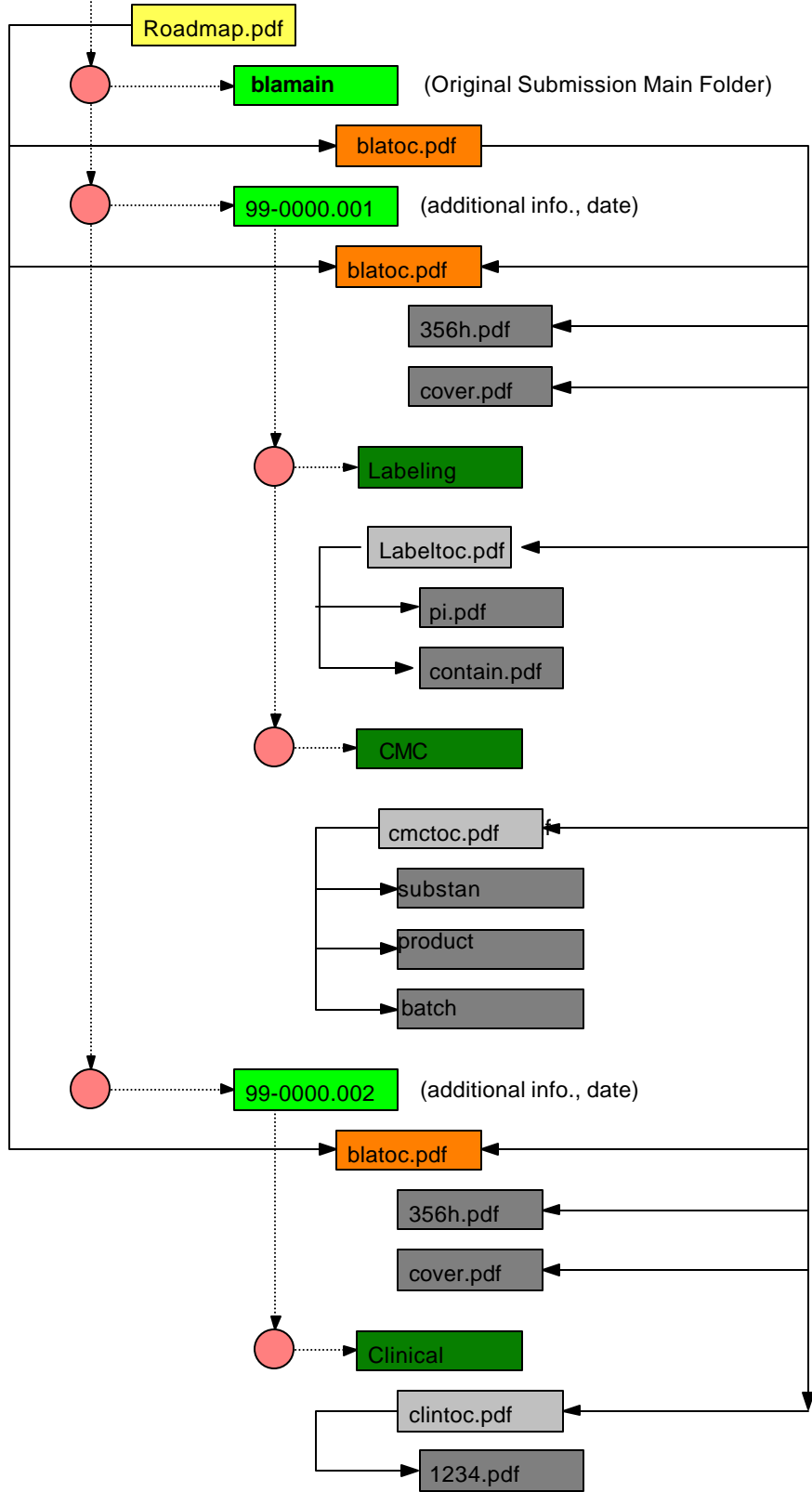
The roadmap file should not contribute in any way to the content of what is under review. It is a map, intended to facilitate navigation through the contents of the submission. The submission's *roadmap.pdf* file should be easily updated or modified using the "Replace file" command under the "Document"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

In addition to providing a navigable guide to the application, the *roadmap.pdf* file should include the sponsor's submission date in the DD-MM-YYYY format (e.g., 01-Jan-1999). The contents of the original submission and of subsequent amendments should be briefly described in a *roadmap.pdf* table. The location of these files and folders on the submitted CD-ROMs (Compact Disk – Read Only Memory) or DLT tapes (Digital Linear Tape) should be indicated in the *roadmap.pdf*. Where portions of the submission have been submitted only in paper, they should be included in the roadmap and table of contents and tagged as "paper only".





eBLA File and Folder Structure Original Submission and Amendments



Every electronic submission delivered to CBER should contain a list of 40 key words describing the submission. This list should be developed by the sponsor and contain a term that will identify the electronic document [e.g., sponsor name, reference number (if available), indication, product name, promotional name, USAN (United States Adopted Names) name, pivotal trial type (controlled, open label), types of data, etc.]. This summation should be located in the root directory on the CD-ROMs or DLT tape.

The file containing the 40 key words should be an ASCII (American Standard Code for Information Interchange) text file entitled *Summary.txt*. The ASCII test file will be utilized to retrieve electronic submissions from the CBER's electronic document room (EDR).

B. Folders

Inside the main folder, all of the documents and datasets should be organized in accordance with the items described on page 2 of Form FDA 356h. Each item should have an assigned subfolder where documents and datasets that belong to that item are placed. Table 1 lists these items and folder names.

Table 1. Items contained within a BLA as described in Form FDA 356h.

Items Contained Within A BLA As Described In Form FDA 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	Estab
16	Debarment certification	Other
17	Field copy certification	Other
18	User fee cover sheet	Other
19	Other	Other

C. Cover Letter

Inside the main folder, provide a cover letter as a PDF (Portable Document Format) file named *cover.pdf*. This cover letter should also be included with any paper portion of the archival copy. The cover letter should include the following items:

- A description of the submission including appropriate regulatory information.
- A listing of the sections of the submission filed as paper, only in electronic format, or in both paper and electronic formats.
- A description of the electronic submission including the type and number of electronic media used (e.g., two sets of three CD-ROMs), and the approximate size of the submission (e.g., 2 gigabytes), including the format used for DLT tapes
- A 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 regulatory and information technology (IT) points of contact for the application.

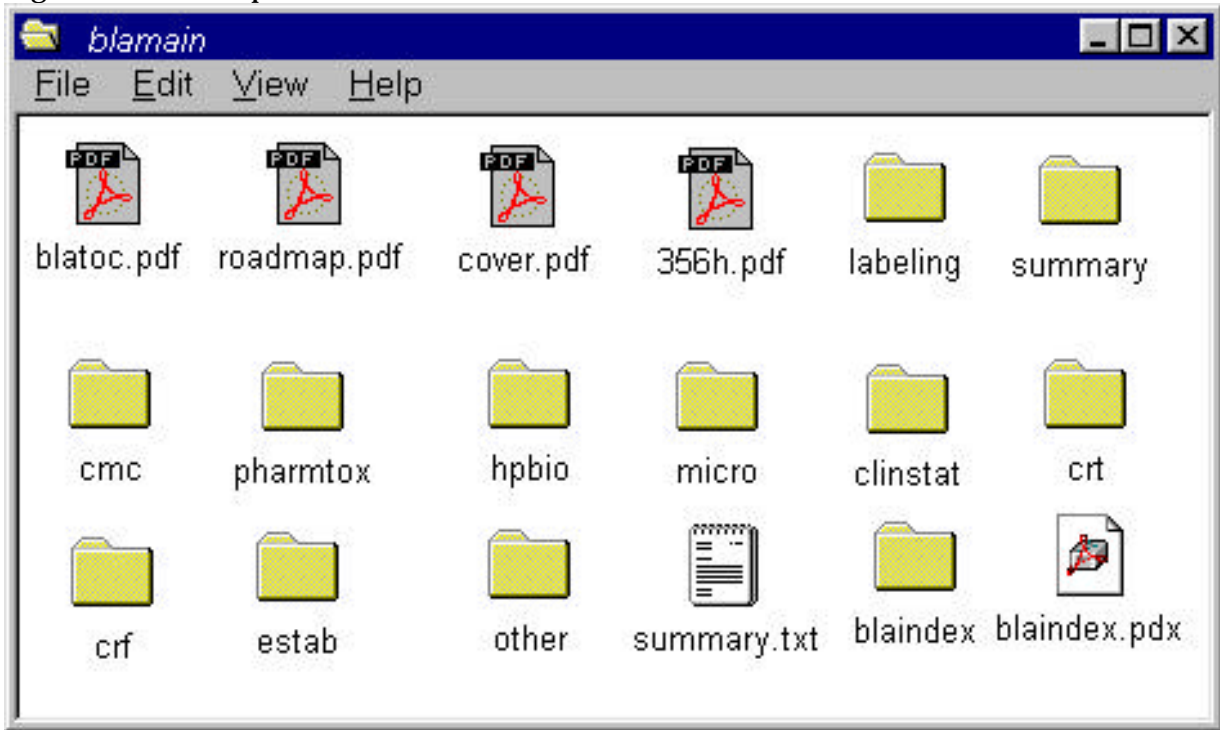
D. Form FDA 356h

Provide Form FDA 356h as a PDF file named *356h.pdf* inside the main folder. On page 2 of the form, the applicant should note, next to each item, if the documents 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 submission should be accompanied by a signed paper Form FDA 356h.

E. BLA Table of Contents

Inside the main folder, the applicant should provide a table of contents for the submission named *blatoc.pdf*. See Item 1 for additional information.

Figure 1: An example of the *blamain* folder



F. Figure of Main Folder

Figure 1 is an example of the contents of the main folder for sample BLA 123456. Each item from Table 1 appears as a separate folder.

G. Submission Management

Timely communications with the appropriate office prior to submitting an electronic document are essential to facilitate its management. CBER should receive written notification of your intent to submit an electronic document at least six to eight months prior to the target arrival date for the submission. Within that timeframe, sponsors seeking to submit electronic documents to CBER should provide a completed copy of the computer assisted license application (CALA) questionnaire (<http://www.fda.gov/cber/guidelines.htm>). Subsequent to the receipt of the CALA questionnaire [fax or email submission followed by a regulatory submission to the appropriate Investigational New Drug application (IND)], a teleconference will be scheduled with the appropriate Center staff. During this teleconference information relating to the proposed electronic submission will be discussed. During these discussions, CBER will notify the sponsor of any issues specific to the submission that may not be covered in the current electronic submission's guidance. CBER will also discuss administrative and management issues relating to the submission of electronic documents.

IV. ORGANIZING THE ELECTRONIC SUBMISSION

An electronic copy of the application should contain the documents and datasets corresponding to the items listed on Form FDA 356h.

A. Item 1: Table of Contents (Index)

For every electronic submission, a comprehensive table of contents should be submitted containing three or four levels of detail, with the appropriate hypertext links and bookmarks. The first level of detail simply lists the items in the BLA as shown on page 2 of Form FDA 356h (Table 2). At this level, the comprehensive table of contents should be a single page and provided as a single PDF file. The file containing the table of contents for an original BLA or an amendment to that submission should be named *blatoc.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, Chemistry, Manufacturing and Controls (CMC), Case Report Tabulations (CRTs)]. The table of contents for a particular item should appear within that item's folder. Within the item's table of contents, include a bookmark for the item and a bookmark for the submission's master table of contents. 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 and fourth levels of detail consist of the subheadings in the table of contents for each document or dataset. For each document, provide bookmarks and hypertext links from each entry in the document's table of contents to the appropriate location in the submission. 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 BLA 123456 (Table 2), a portion 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 "chemistry" section is provided in only 4 paper volumes, starting with Volume 1, and there is no electronic version. The table of contents shows the entire submission including the paper and the electronic portions.

If an item is in paper format, the volume numbers that hold the item should be listed in the table of contents. If an item 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, both the volume number and the folder name should be listed in the table of contents.

Table 2: An example of the main table of contents

Example: Table Of Contents For BLA 123456 (n/a = not available)			
Item	Description	Paper copy Volume number	Electronic copy folder
1	Table of contents (Index)	1	Main folder
2	Labeling	n/a	Labeling
3	Summary	n/a	Summary
4	Chemistry	4.1-4.4	n/a
5	Nonclinical pharmacology and toxicology section	5.5-5.10	Pharmtox
6	Human pharmacokinetics and bioavailability	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	n/a	Other
15	Establishment description	n/a	Estab
16	Debarment certification	n/a	Other
17	Field copy certification	n/a	Other
18	User fee cover sheet	n/a	Other
19	Other	n/a	Other

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 in Table 2, such as items 3, 13, 14, and 16-19, 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.

An index of the full text and the Document Information fields of all items in the application or supplement should be provided. Name the index definition file *blaindex.pdx*. Place all associated index files in a folder named blaindex. Place the blaindex.pdx definition file and the blaindex file subfolders in the main folder. Associate the blatoc.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.

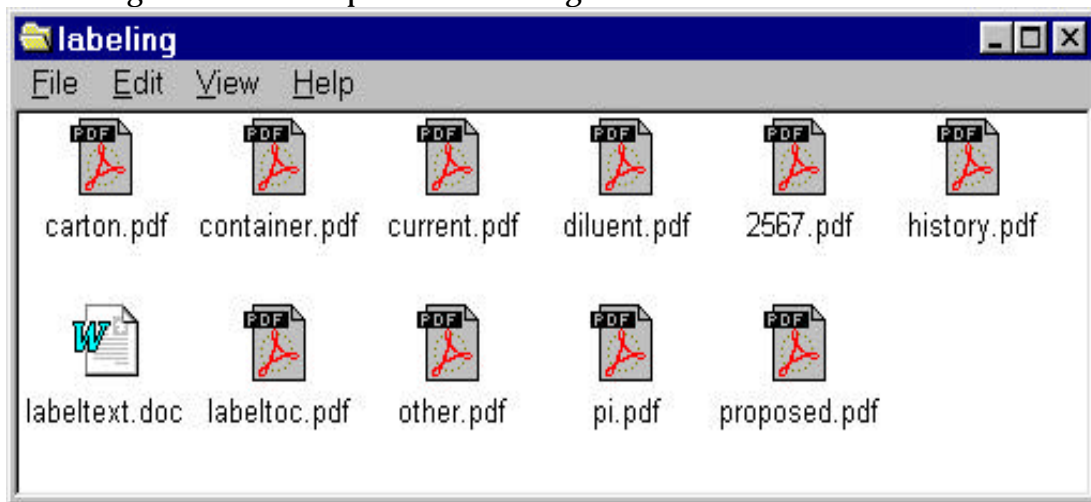
B. Item 2: Labeling

Labeling is item 2 on page 2 of Form FDA 356h. Form FDA 2567, available at <http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>, should be provided as a PDF file with all labeling. This file should be named *2567.pdf*. The content and format of what is referred to in this section is defined in 21 CFR 201.56, 201.57, 606.120 - .122, 610.60 - .65, and 660.28 - .55 and includes all text, tables, and figures proposed for use in the package insert. The PDF text files in this section should be generated from electronic source documents and not from scanned material.

1. Folder

All documents for this section should be placed in a single folder named *labeling*. An example of the organization of the *labeling* folder is pictured below. When multiple products are submitted under the same BLA or PLA/ELA, separate product subfolders should be created for each product's labeling.

Figure 2. An example of the *labeling* folder



2. Table of contents

Provide a table of contents listing all labeling included in the submission and the history of labeling changes, if applicable, as a PDF file named *labeltoc.pdf*. The example headings in Table 3 may be used to organize the files in the table of contents. Include the location of the file by folder and file name, if electronic, and by volume number if paper. As part of the 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 *labeltoc.pdf* file in the labeling folder.

Table 3: An example of the labeling table of contents

Labeling Table Of Contents	
	LOCATION*
I. Labeling history	
II. Package Insert (Circular)	
a. Proposed labeling text	
b. Currently used labeling text	
c. Last approved labeling text	
III. Container label	
IV. Carton label/Package label	
V. Diluent	
VI. Other	

(*Use the file name if the information is presented as an electronic document or volume number if the document is a paper copy.)

3. *Labeling history*

In each submission containing new labeling, 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 CBER identify 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 reference to 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. *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 - (appropriate)
- No columns
- 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
- Sequential line numbers in the left margin of draft text

When presenting tables of information, it is critically important that the reviewer be able to view this information on a single computer screen. The use of 10 or 12 point fonts may further complicate this presentation, however, in these instances, utilize the largest font that will allow for the presentation of the table on the computer screen of Center’s standard desktop workstation.

Document information fields should contain the following information:

- Title: USAN or other established name
 - Subject: Product name
 - Author: applicant, applicant's label code
 - Keywords: BLA, PLA/ELA, NDA number (in form of 123456), Document name, Labeling review number, if known, 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.
- a. Proposed labeling text

The “proposed labeling text” is either the draft labeling with an initial application or subsequent prior approval supplements. When labeling revisions or changes are submitted, provide a copy of the annotated version (i.e., redlined) as a pdf file. The purpose of this file is to readily show the changes to the proposed labeling or currently approved labeling.

The “proposed labeling text” should be provided as a PDF file named *proposed.pdf*. The annotated version of the proposed labeling should be provided as a PDF file named *redline.pdf*. Fill in the document information fields as described above.

In addition to the PDF file, provide all the draft labeling text within an initial application, its subsequent supplements and amendments as an MS Word document in a file folder named *labeltext.doc* for editing purposes.

b. Current labeling text

The “current labeling text” is 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. Final labeling

The final package insert should be provided as a PDF file(s). The document should be captured at its actual size or to scale, with the scale visually represented. In addition, the PDF files should reflect the actual color of the text, tables and figures within the document.

5. *Container labeling*

Container labeling (all panels) should be provided as a PDF file(s). Container labeling (all panels) should be captured at their actual size or to scale, with the scale visually represented. In addition, these PDF files should reflect the actual color of the container labeling (all panels). Fill in the document information fields as described with the labeling text.

6. *Carton labeling/Package Label*

Carton labeling (all panels) should be provided as a PDF file(s). Carton labels (all panels) should be captured at their actual size or to scale with the scale visually represented. In addition, these PDF files should reflect the actual color of the carton labeling (all panels). Fill in the document information fields as described with the labeling text.

7. *Diluent*

Diluent labeling (all panels) should be provided as a PDF file(s). Diluent labels (all panels) should be captured at their actual size or to scale with the scale visually represented. In addition, these PDF files should reflect the actual color of the diluent labeling (all panels). Fill in the document information fields as described with the labeling text.

8. *Other*

Provide any other labeling that does fall into the previous categories as a PDF file(s), with a view of each panel. These labels (all panels) should be captured at their actual size or to scale with the scale visually represented. In addition, these PDF files should reflect the actual color of the labeling (all panels). Fill in the document information fields as described for the labeling text [e.g., dispensing pack, patient package insert, demonstration labeling (placebo)].

C. Item 3: Summary

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

1. *Folder*

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.

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*. It should also be identified in the Document Information Title field as *submission summary*.

4. *Bookmarks and hypertext linking*

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

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

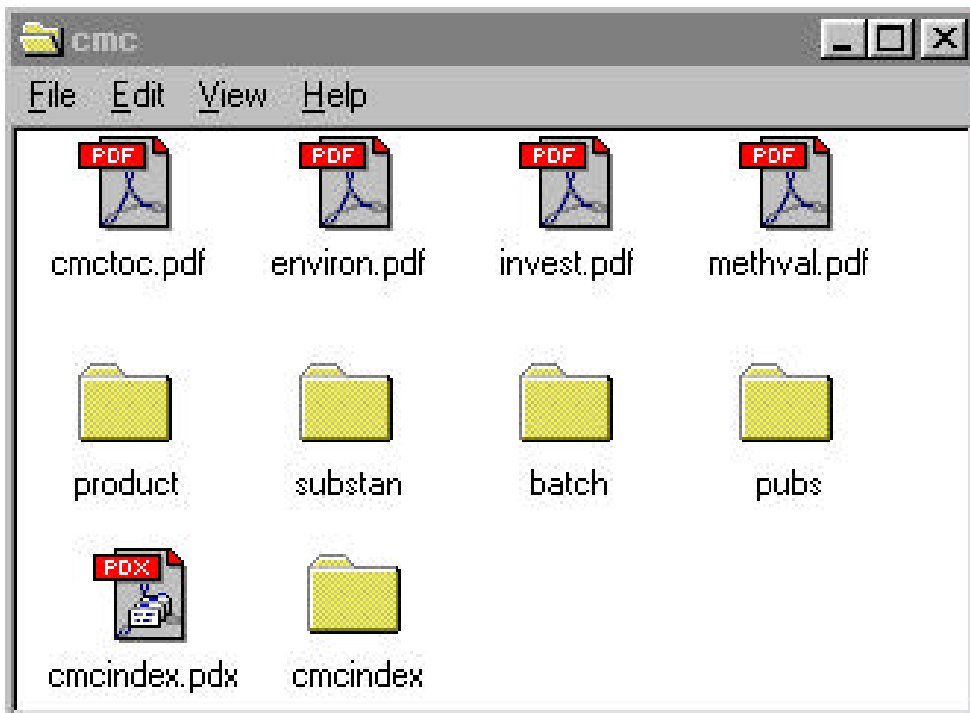
The chemistry, manufacturing and controls section is item 4 from page 2 of Form FDA 356h.

1. *Folders*

The information for this section should be placed into a folder named *cmc*. CBER recommends the creation of 4 subfolders, *substan*, *product*,

batch, and *pubs* to organize the files in this section. The file structure is pictured in Figure 3 (the file, *cmcindex.pdf* and additional subfolder, *cmcindex* are for the full text index).

Figure 3: An example of the *cmc* folder



2. *Table of contents*

A table of contents should be provided, that lists all files provided in the CMC section, as a PDF file named *cmctoc.pdf*. To organize the files in the table of contents use the example headings in Table 4. The headings will vary with products and you should consult the appropriate guidance documents for the correct headings. 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.

Table 4: An example of the CMC Table of Contents

CMC Table Of Contents	
	Location*
I. Biological Drug Substance	
II. Biological 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 the file name if the information is presented as an electronic document or volume number if the document is a paper copy.)

3. *Biological Substance*

Information regarding the drug substance should be divided into the following topics:

- Description & Characterization
- Manufacturer(s)
- Method(s) of Manufacture
- Process Controls
- Reference Standard(s)
- Specifications/Analytical Methods
- Microbiology
- Container/Closure System
- Stability

CBER recommends that each of the topics listed within the biological substance folder be provided as a separate PDF file or that they be combined (all topics) into a single PDF file. If you provide the biological substance information as a single PDF file, organize the table of contents for this document using the topics listed above.

Place all files relating to biological substance in the substan folder in the CMC folder. Identify each file in the document information Title field as *biological substance* and include the specific topic, if applicable.

4. *Biological Product*

Information regarding the biological product should be divided into the following topics:

- Components/Composition
- Specifications and Methods for Biological Product Ingredients
- Manufacturer(s)
- Methods of Manufacturing and Packaging
- Specifications/Test Methods
- Container/Closure System
- Microbiology
- Stability

CBER recommends that each one of the topics listed within the biological product folder be provided as a separate PDF file or that they be combined (all topics) into a single PDF file. If you provide the biological 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 *biological product* and include the specific topic, if applicable.

5. *Investigational formulations/Comparability*

Information focusing on investigational formulations should be provided 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*

The environmental assessment or a claim for categorical exclusion should be provided, in a single PDF file called *environ.pdf*. Identify this file in the Document Information Title Field as *environmental assessment*.

7. *Methods validation*

All method validations should be provided in a single PDF file called *methval.pdf*. This information should be identical to the information provided in the biological substance and biological 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 method.

8. *Batch records*

Provide each executed batch record in a separate PDF file. Place all executed batch record PDF files into a single folder named *batch*. Each section of a batch record should contain a bookmark. The batch folder should be placed in the cmc folder. Identify this file in the Document Information Title field with the batch record number. For example, batch record 105 should be identified as *batch record number 105*.

9. *Publications*

Each publication should be provided as a separate PDF file. Place all publications, in alphabetical order, into a single folder named *pubs*. Establish a hyperlink between the citation and the publication in the pubs folder. 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 should provide bookmarks and hypertext links for each item in the document's table of contents including all tables, figures, publication, and appendices.

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.

CBER have identified certain pieces of information that is frequently needed to know and are sometimes time consuming to locate in a particular submission. The suggested hypertext links for this information are summarized in the following list:

- Biological substance and biological products batch numbers to stability data,

- Biological substance and biological products batch numbers to formulation composition,
- Clinical protocol numbers to the appropriate biological substance and biological products batch numbers,
- Stability studies to description of container/closure systems,
- Impurity profile to forced degradation data,
- Impurity profile to source of impurity,
- Specifications to validation reports to test methods,
- Names of biological or chemical substances/degradants to their structures,
- Removal of impurities to validation studies,
- In process control parameters to validation studies,
- Letters of cross-reference to Master File's.

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 *cmc*. Place the *cmc.pdx* definition file and the *cmc* index file 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.

For license applications with blood and blood products, information should be organized as presented in the following guidance documents available at <http://www.fda.gov/cber/guidelines.htm>:

Guidance for Industry For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human and Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the FDA Form 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use", May 1999.

Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product, March 1999.

Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products or Animal Plasma or Serum-Derived Products, February 1999.

License applications for vaccines and allergenic products should be organized as presented in the following guidance documents:

Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999.

Guidance for Industry On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test (Draft), April 1999.

License applications for therapeutic products should be organized as presented in the following guidance documents:

Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products, January 1997:

Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use, August 1996.

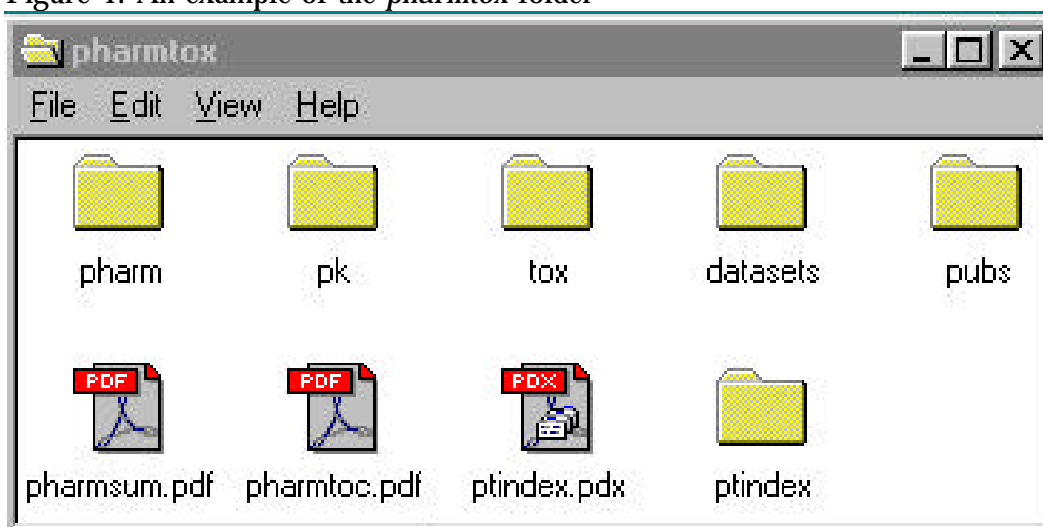
E. Item 5: Nonclinical Pharmacology and Toxicology

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

1. Folders

All information for this section should be placed in a folder named *pharmtox*. CBER recommends the creation of 5 subfolders, *pharm*, *pk*, *tox*, *datasets*, and *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 contains the datasets and the *pubs* folder contains the publications. The file structure is pictured in Figure 4 (the file, *ptindex.pdx* and additional subfolder, *pindex* are for the full text index).

Figure 4: An example of the *pharmtox* folder



2. *Table of contents*

A table of contents listing all study reports (including study report numbers), publications, and the summary should be provided in the *pharmtox* section as a PDF file named *pharmtoc.pdf*. If datasets are provided for a study, note this in the table of contents. To organize the files in the table of contents use the example headings in Table 4. 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 are listed in the table of contents, provide a hyperlink to the appropriate data definition file (*define.pdf*). This file is described below. Place the *pharmtoc.pdf* file in the *pharmtox* folder.

Table 4: An example of the pharmtox table of contents

Pharmtox Table Of Contents	
	Location *
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. Datasets	
VI. Publications	

(* Use the file name if the information is presented as an electronic document or volume number if the document is a paper copy.)

3. *Summary document*

A summary of the entire nonclinical pharmacology and toxicology section should be provided as a single PDF file named *pharmsum.pdf*. This document should include an overall summary of the preclinical 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, a hypertext link should be provided to the corresponding published article, data table, or figure (whether located in a study report or elsewhere).

4. *Study reports*

Study reports with all appendices should be provided as a separate PDF file. The study number should be included in the name of the file. For example, study 1234 can be named *1234.pdf*. Place the file in the appropriate subfolder of the pharmtox folder. Files 25 MB or larger are technically more difficult to handle, so study reports that are larger than 25 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 in beagle dogs, should be identified as: *study 2001, 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 listings file would be identified as: *study 2001, data, toxicity study*.

5. *Publications*

Each publication should be provided as a separate PDF file. Place all publications into a single folder named *pubs*. Establish a hyperlink between the citation and the publication in the *pubs* folder. The *pubs* folder should be placed in the pharmtox folder. The citation for the publication should be included 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 should provide bookmarks and hypertext links for each item in the document's table of contents including all tables, figures, publication, and appendices.

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 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 reproductive toxicology 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.pdx* 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. 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. See Appendix 1 for recommended datasets and data elements.

a. *Format of the datasets*

Provide each dataset as a SAS transport file as described in the companion guidance, *Regulatory Submissions in Electronic Format — General Considerations*, to facilitate its use in a variety of software tools.

Dataset files should be organized so that each file is less than 25 MB. 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. These examples are meant to serve as a starting point for discussions with the review division on the content and

organization of the datasets and, therefore, are not all inclusive. CBER plans 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.

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 usable, 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. In Table 5, 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.

Table 5: An Example of the Dataset Documentation

Datasets For Study 1234		
Dataset	Description of dataset	Location
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.

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 definitions should be designated as the study, followed by the study number and the contents. For example, the data definition file for study 2001 would be identified as: study 2001, data definitions.

d. Dataset table of contents

The dataset table of contents is also part of the comprehensive table of contents and should list all studies that have datasets. You should provide a hypertext link to the appropriate data definition table file. 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, so that the results for each animal can be evaluated across studies. This unique number should be provided in each dataset.
- 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 and should be unique to a particular attribute. 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 express it consistently 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.
- 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 or inexplicit 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 descriptors, such as control, LD (low dose), MD (mid dose), or HD (high dose).

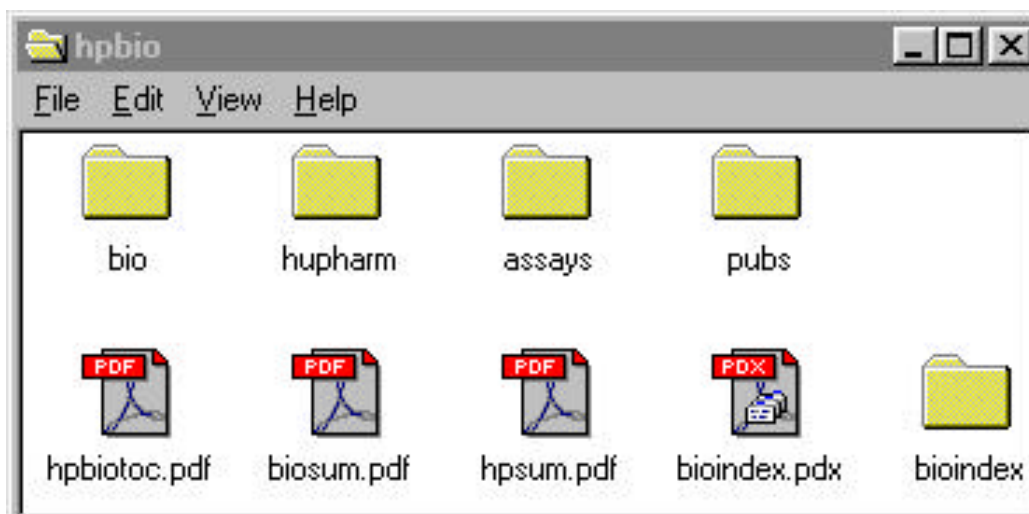
F. Item 6: Human Pharmacology and Bioavailability/Bioequivalence

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

1. Folders

All information required in this section should be placed in the *hpbio* folder. CBER recommends the creation of 4 folders, *bio*, *hupharm*, *assays* and *pubs* to organize the files in this section. The *bio* folder contains studies related to bioavailability, bioequivalence and formulation. The *hupharm* folder contain studies using human biomaterials, pharmacokinetics studies and pharmacodynamics studies. The *assay* folder contains assay descriptions and their validation reports including cross validation assays. The *pubs* folder contains publications. The file structure is pictured in Figure 5 (the additional file, *bioindex.pdx* and subfolder *bioindex* are for the full text index).

Figure 5: An example of the *hpbio* folder



2. *Table of contents*

A table of contents listing all study reports (including study report numbers), publications, and the summaries provided for the *hpbio* section should be provided as a PDF file named *hpbiotoc.pdf* and placed in the *hpbio* folder. If datasets are provided for a study, you should note this in the table of contents. The example headings in Table 6 should be used to organize the files in the table of contents. 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 are 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*).

Table 6: An example of the Hpbio Table of Contents

	Location*
I. Summaries	
a. Bioavailability/Bioequivalence Summary	
b. Human Pharmacology Summary	
II. Reports for Bioavailability and Bioequivalence Studies	
a. Bioavailability Study Reports	
b. Bioequivalence Study Reports	
c. IVIVC	
III. Reports for Studies Using Human Biomaterials	
a. Plasma Protein Binding Studies	
b. Metabolism Studies Using Hepatocytes, Microsomes etc.	
IV. Human pharmacokinetics (PK) Study Reports	
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	
a. Study Reports in Healthy Volunteers	
b. Studies Reports in Patients	
VI. Assays	
VII. Publications	

(*Use the file name if the information is presented as an electronic document or volume number if the document is a paper copy).

3. Summary

Summary documents for the human pharmacology and bioavailability/bioequivalence sections should be provided as PDF files named *hpsum.pdf* and *biosum.pdf*, respectively. Place these files in the hpbio folder. In addition, include hypertext links from 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*

All study reports with appendices (except case report tabulations and case report forms which are described in items 11 and 12, respectively) should be provided as individual PDF file. Include the study number in the name of the file. 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*

CBER is developing specifications for data elements for human pharmacology and biopharmaceutics data and plan on providing detailed guidance for structured datasets in the future. Until this guidance is available, you should provide datasets as SAS transport files. Confer with the appropriate reviewers on the types of 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 pharmacokinetics (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*. Establish a hyperlink between the citation and the publication in the *pubs* folder. 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, bookmarks and hypertext links should be provided for each item in the document's table of contents including all tables, figures, publication, and appendices. 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. A reference list at the end of a document should contain hypertext links 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 *bioindex.pdx*. Place all associated index files in a folder named bioindex. Place the bioindex.pdx definition file and the bio index file subfolder in the main hpbio folder. Associate the hpbiotoc.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

Item 7 on page 2 of Form FDA 356h applies only to submissions to CDER.

H. Item 8: Clinical

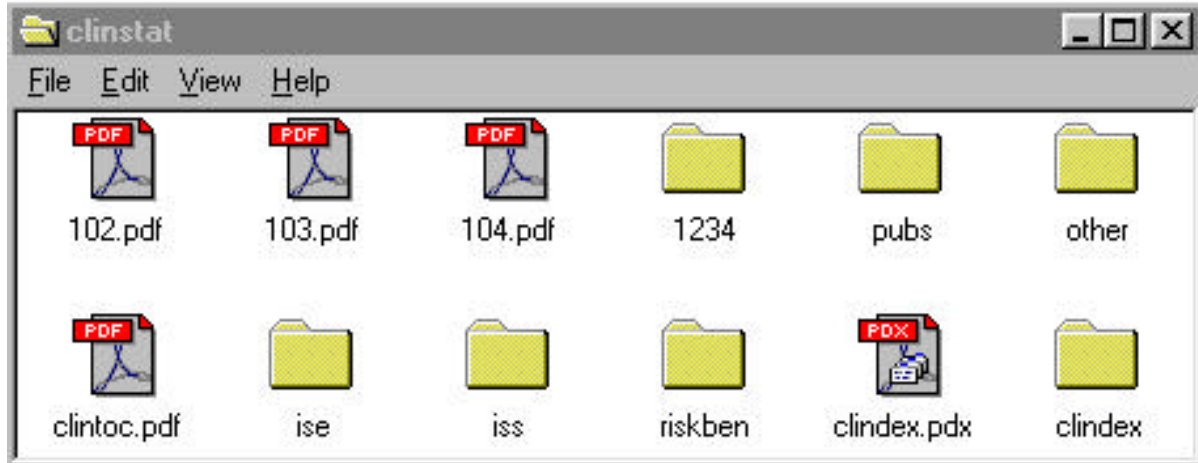
The clinical section is item 8 on page 2 of Form FDA 356h. Additional information on the content of this section can be found in the ICH E3 document *Structure and Content of Clinical Study Reports*, July 1996, available at <http://www.ifpma.org/ich5e.html> and the Guidance for Industry Submission of Abbreviated Reports and Synopses in Support of Marketing Applications, September 21, 1999, available at <http://www.fda.gov/cber/guidelines.htm>

1. *Folders*

All information in this section should be placed into a folder named *clinstat*. CBER recommends the creation of a folder for each indication and for each indication's integrated summary of efficacy. 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. An example of the file structure is pictured in Figure 6 (the additional file *clindex.pdx* and the subfolder *clindex* are for the full text index).

Figure 6: An example of the *clinstat* folder



2. Table of Contents

Provide a table of contents which lists all of the files in this section. The table of contents should be provided as a PDF file named *clintoc.pdf*. This file should be placed in the *clinstat* folder. 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, as well as each indications integrated summary of efficacy. 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 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 definitions file (*define.pdf*). This file is described in item 11, case report tabulations.

In some applications, more than one indication and/or therapeutic product is studied. If this is the case, you should also organize the listing of files by indication and therapeutic product as appropriate. See Table 7.

Table 7: An example of the *clinstat* table of contents

Clinstat Table Of Contents	
	Location*
Indication ¹	
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 the file name if the information is presented as an electronic document or volume number if the document is a paper copy).

¹ Repeat for each indication and therapeutic product

3. *Study reports*

Each study report should be provided as a separate PDF file. The file should include all appendices as defined in the ICH E3 document *Structure and Content of Clinical Study Reports* (July 1996), except for case report forms (CRF) and individual patient data listings [case report tabulations (CRT)]. Include the study number in the name of the file. For example, study 1234 can be named *1234.pdf*.

Because files 25 MB or larger are technically more difficult to handle, study reports that are larger than 25 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.

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

4. *Integrated summaries*

Handle the integrated summaries in the same manner as the study reports. Name the integrated summary of safety, the integrated summary of efficacy and risk/benefit *iss.pdf*, *ise.pdf*, and, *riskben.pdf*, respectively.

Include integrated summary of safety, the summary of efficacy and 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*. Establish a hyperlink between the citation and the publication in the *pubs* folder. 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 listed within the table of contents, you should provide bookmarks and hypertext links for each item in the document's table of contents including all tables, figures, publication, and appendices even if included in a separate file. For datasets, you should include a bookmark to the appropriate data definition file (*define.pdf*).

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 Form FDA 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 should be provided in the form of a PDF file. 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 *update*. Place the *upindex.pdx* definition file and the update 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 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)

Case report tabulations are item 11 on page 2 of Form FDA 356h.

CRTs should be provided as either SAS datasets allowing the review divisions to use their own software for analysis or as a PDF printout of the SAS dataset. Each CRT dataset should be a single file and, in general, will include a combination of raw and derived data. Prior to the submission, a sponsor should discuss with the review division the datasets to be provided and the data elements that should be included in each dataset.

The electronic functional CRT datasets may not be adequate to eliminate the need for the submission of data files suitable for reproducing and confirming the study analyses submitted by the applicant. Submission of these SAS datasets should be discussed with the appropriate review division.

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*.

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. CBER recommends 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 as follows:

- 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. These examples are intended as a starting point

for discussions with the reviewing division regarding the data elements that should be provided in the submission. The data elements and organization may vary depending on the reviewing division and indication.

The layout of the data in the rows and columns in the dataset should be done so as to emulate the arrangement that would normally have been used in the printed CRT's in a paper submission. Applicants should use as a conceptual model – the opening of the dataset in a reader-only (viewer-only) program that solely allows scrolling through a dataset file. Doing so should bring up screens of rows and columns of values and/or text information that is very similar in organization to what has been traditionally presented on paper.

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. 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 standards 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*

Provide two PDF files, one should contain the data definition tables (define.pdf) and the other should house 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.

In Table 8, 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.

Table 8: An example of the case report tabulations dataset documentation

Datasets For Study 1234		
Dataset	Description of dataset	Location
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 case report should be provided, along with 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 in Table 9.

Table 9: An example case report tabulation demographics dataset variables

Study 1234 – Demographics Dataset Variables				
Variable	Label	Type	Codes	Comments¹
PATID	Unique patient ID number	Char		Demographics page 1
SEX	Sex of subject	Char	f = female m = male	Demographics page 1
BDATE	Birth date	Date		Demographics page 1
DUR	Duration of Treatment	Num		Derived STOP DATE – START DATE
TRT	Assigned treatment group	Num	0= placebo 5= 5mg/day	

¹ 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 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.

A final data definition table should be provided that lists, in a single table, all variables in all datasets for that study. This table should be arranged in alphabetical order by variable name. This table should also include the name of each dataset where each of the listed variables is included.

The annotated CRF is a blank CRF including treatment assignment forms that map 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 should list all studies and integrated summaries that have datasets. A hypertext link should be provided to the appropriate data definition table file. 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 the 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. This unique number needs to be provided in each dataset. This is essential for joining different datasets.
- The variable names and codes should be consistent across studies and should be unique. 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 representation of variables within and across the datasets should be consistent for similar types of data. For example, all variables that are a calendar date (e.g., birthdate, screening visit date, randomization date, date of death, etc.) should use the same format for representing the date. Similarly, data indicating time within study or duration of an event within study should use the same format throughout (e.g., days, weeks, or months) unless noncomparable timescales are being addressed.
- Duration is frequently part of an analysis. Start and stop times and dates should also be provided as duration of treatment based on the start of study treatment and expressed consistently in minutes, hours, or days, whichever is appropriate. When expressed in days, the following formula should be used to calculate study day: $((\text{test date}) - (\text{date of first dose}) + 1)$.
- Results are frequently analyzed based on the study, center/site, treatment assignment, sex, age, and/or race of the subjects. 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 or inexplicit 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.
- Provide a file named *sites.pdf*. This file should contain a comprehensive list of investigators and study sites (*sites*). The reference list should contain the following four columns: name of investigator; investigator ID (site number); investigator's address (study site); and the number of subjects enrolled at the site. If the site number changes, note this in the appropriate column in addition to providing an accurate accounting of the number of individuals enrolled under the specific site number(s).

L. Item 12: Case Report Forms

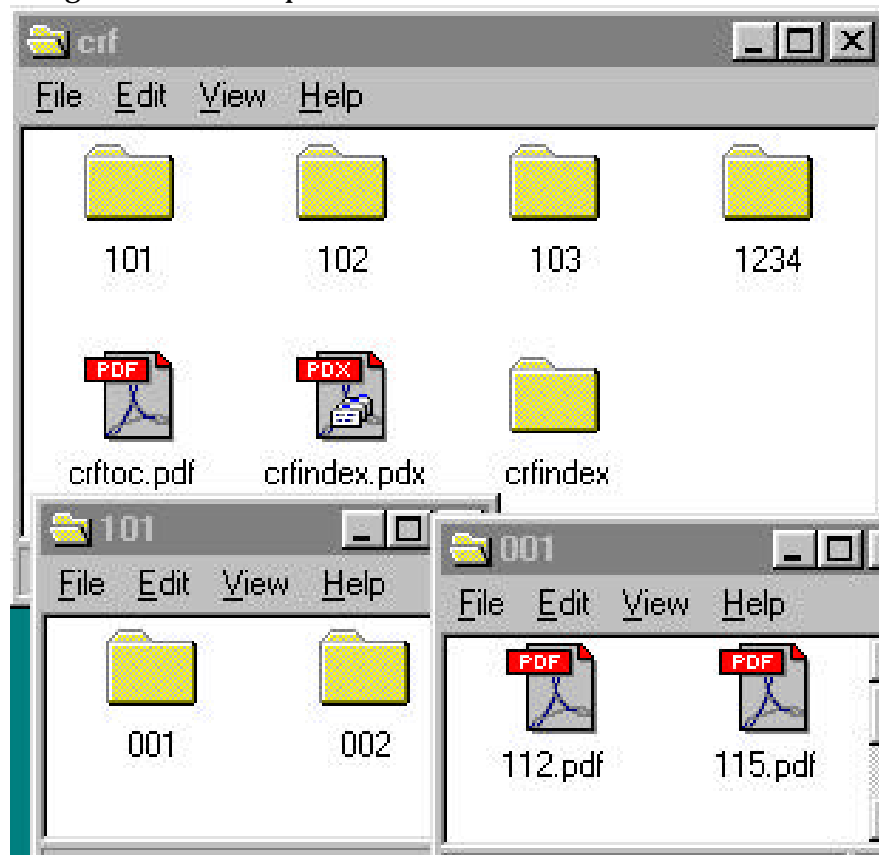
Case report forms are item 12 on page 2 in Form FDA 356h.

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 electronic data collection, CBER recommends the use of PDF generated forms. Prior to the submission of CRFs captured using remote data entry, a sponsor should discuss their submission with the effected review division and consult the Guidance for Industry: Computerized Systems used in Clinical Trials, May 10, 1999, available at <http://www.fda.gov/cber/guidelines.htm>.

1. Folders

All information for this section should be placed in a folder named *crf*. Create a folder for each study to organize the CRFs. In each study folder, there should be a folder for each study site. Use the study numbers and site numbers when naming the respective folder. An example of the file structure is pictured in Figure 7 (the additional file, *crfindex.pdx* and subfolder *crfindex* are for the full text index).

Figure 7: An example of the *crf* folders



2. *Table of contents*

A table of contents should be supplied that lists all CRFs provided by their study, site and treatment assignment, as a PDF file named *crftoc.pdf*. List the patient identification numbers by study, site and treatment assignment and describe the location of the CRFs with the file name and folder(s). 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 should be provided. Place the *crftoc.pdf* file in the *crf* folder.

3. *Case report forms*

Each individual patient's complete case report form should be provided as a single PDF file. Include the patient ID in the file name. Place the PDF files in the appropriate study site folder. For example, all CRFs for site 003 for study 301 would be placed into a folder named *003*, which then would be placed in a folder named *301*.

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*

CBER recommends bookmarks for each CRF domain and study visit to help the reviewer navigate the CRFs. These bookmarks can be considered as part of the comprehensive table of contents.

For addenda and corrections, provide a hypertext link from the amended item to the corrected page or addendum.

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 Form FDA 356h.

1. *Folder*

Place all 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*

Information pertaining to the patent information should be provided in a single PDF file named *patinfo.pdf*.

The Agency is developing procedures to allow for 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 Form FDA 356h.

1. *Folder*

Place all 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 *patcert.pdf* file.

3. *Patent certification*

Information pertaining to the patent certification should be provided in a single PDF file named *patcert.pdf*.

The Agency is developing procedures to allow for 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.

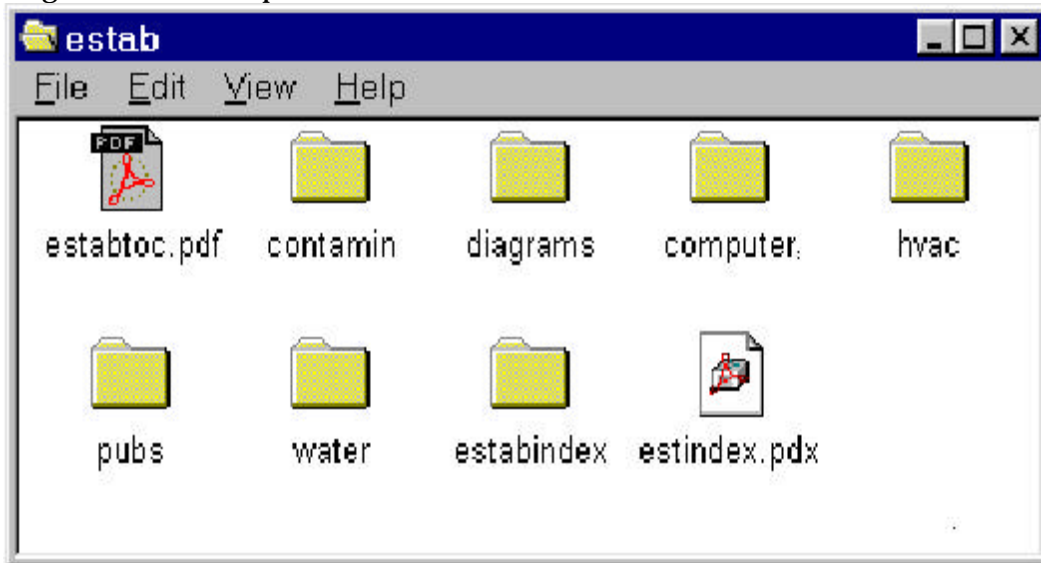
O. Item 15: Establishment Description

The establishment description section is item 15 on page 2 of Form FDA 356h.

1. *Folder*

The submission should contain a folder named *estab*. Within the *estab* folder, the following individual folders should be created: *water*, *HVAC*, *contamin*, *computer*, *diagrams* and *pubs*. An example of the file structure is pictured in Figure 8 (the file, *estindex.pdx* and additional subfolder, *estabindex* are for the full text index).

Figure 8: An example of the estab folder



2. Table of contents

A table of contents should be provided that lists all files provided in the establishment section, as a PDF file named *estabtoc.pdf*. To organize the files in the table of contents use the example headings in Table 10. The headings may vary from product to product and you should consult the appropriate guidance documents for correct headings. As part of the comprehensive table of contents for the submission, provide hypertext links between the documents listed in the table of contents and the corresponding PDF files, in addition to, bookmarks for each item in the table of contents. Place the *estabtoc.pdf* file in the *estab* folder.

Table 10: An example of the estab table of contents

Estab Table Of Contents	
	Location*
I. Water system	
II. Heat, ventilation and air conditioning systems (HVAC)	
III. Contamination and cross contamination	
IV. Computer systems	
V. Lyophilization	
VI. Diagrams	
VII. Publications (list each publication separately)	

(*Use the file name if the information is presented as an electronic document or volume number if the document is a paper copy.)

Consider the use of computer aided design (CAD) to produce facility floor plans, and/or blueprints. These files can be embedded in adobe acrobat (PDF) and presented as graphics. This will facilitate the presentation of establishment information.

3. *Publications*

Each publication should be provided as a separate PDF file. Place all publications, in alphabetical order, into a single folder named *pubs*. Establish a hyperlink between the citation and the publication in the *pubs* folder. The *pubs* folder should be placed in the *estab* folder. Note 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 and first name initial, the year of the publication and the title of the article.

4. *Bookmarks and hypertext links*

For all documents within the table of contents, including all tables publications, and appendices, you should provide bookmarks and hypertext links. 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.

5. *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 *estabindex.pdx*. Place all associated index files in the folder named *estab*. Place the *estab.pdx* definition file and the *estab* index file subfolder in the main *estab* folder. Associate the *estabtoc.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.

For more detailed descriptions of the appropriate establishment content in item 15 refer to the following documents available at <http://www.fda.gov/cber/guidelines.htm>:

Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products or Animal Plasma or Serum-Derived Products, February 1999.

Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls information and Establishment Description for Autologous Somatic Cell Therapy Products, January 1997.

Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological in Vitro Diagnostic Product, March 1999.

Guidance for Industry On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test, April 1999.

Guidance for Industry For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human and Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use", May 1999.

Guidance for Industry Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999.

Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use, August 1996.

P. Item 16: Debarment Certification

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

1. *Folder*

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 for the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

Q. Item 18: User Fee Cover Sheet

This is item 18 on page 2 of Form FDA 356h

1. *Folder*

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 for the submission of electronic signatures. Until those procedures are in place, any certification must be accompanied by a signed paper certification.

R. Item 19: Other

This is item 19 on page 2 of Form FDA 356h. Information that is not included in item 1 to 18 is included under 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.

V. APPENDIXES

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. CBER plan on refining these datasets and data elements and adding more datasets as we gain more experience.

Data Definition Tables (place the study subfolder name in the space with the ***)		
Dataset	Description of dataset	Location of dataset
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 chemistry levels	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	..

Tumor Dataset For Statistical Analysis^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Footnotes
STUDYNUM	Study number	Char		3
ANIMLNUM	Animal number	Char		
SPECIE	Animal specie	Char	M= mouse R= rat	
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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	Char		
DTHSACST	Death or sacrifice status	Num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Intermittent sacrifice 4 = Accidental death	
ANIMLEXM	Animal microscopic examination code	Num	1 = At least one tissue was examined 2 = No tissues were examined	
TUMORCOD	Tumor type code	Num		3,4
TUMOR	Tumor name	Char		3,4
ORGNCODE	Organ/tissue code	Num		3,5
ORGAN	Organ/tissue name	Char		3,5
DETECTTM	Time in days of detection	Num		
MALIGNST	Malignancy status	Num	1 = Malignant 2 = Benign 3 = Undetermined	
DEATHCAU	Cause of death	Num	1 = Tumor caused death 2 = Tumor did not cause death 3 = Undetermined	
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	

¹ Each animal in the study should have at least one record even if they do not have a tumor.

² Additional variables or categories of a variable, as appropriate, can be added to this dataset.

³ ANIMLNUM limit to less than 12 characters; ORGNCODE and TUMORCOD limited to less than 8 characters; ORGAN and TUMOR should be as concise as possible.

⁴ A missing value should be given for the variable TUMOR and TUMORCOD when the organ is unusable or not examined.

⁵ 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.

Body Weights For Each Animal Over Time (weights.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Num		
SPECIE	Animal specie	Char		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

Food Consumption Over Time For Each Animal (food.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Num		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

Water Consumption Over Time For Each Animal (water.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Num		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

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

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

²"Not applicable" used for animals without clinical signs

Plasma Clinical Chemistry Over Time For Each Animal (chem.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Char		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

Hematology Results For Each Animal (hemat.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number			
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

Urinalysis Dataset (urine.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number			
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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

Plasma Drug Levels (drug.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number			
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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 metabolites
UNIT	Unit of measurement	Char		
RESULT	Drug level	Num		
OTHER

Mortality Dataset (mortal.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Char		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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	
DEATH	Description of death	Char	Final sacrifice, Sacrificed moribund, or Found dead	
DAYS	Days on drug at time of death	Num		
WEIGHT	Terminal body weight	Num		
UNIT	Unit of measurement	Num		
OTHER

Organ Weight For Every Organ For Each Animal¹ (organwt.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	Num		
SEX	Sex	Char	M= male F= female	
DOSEGP	Dose group	Char	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		
ORGAN	Organ name	Char		
ORGANWT	Weight of organ in grams	Num		
UNIT	Unit of measurement	Num		
RATIO	Organ to body weight ratio	Num		ORGAN WT/ FNLBDY WT
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

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

Macroscopic Findings For Each Animal (macro.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	char		
SEX	Sex	char	M= male F= female	
DOSEGP	Dose group	char	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at sacrifice	num		
DEATH	Description of death	char	Final sacrifice, Sacrificed moribund, or Found dead	
ORGNAME	Name of organ	char		
ABNORMAL	Abnormal flag	char	Abnormal or Normal	
MACRO	Macroscopic findings	char		Limit to 256 characters ¹
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

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

Microscopic Findings (histopathology) For Each Animal (micro.xpt)				
Variable	Label	Type	Codes	Comments
ANIMLNUM	Animal number	char		
SEX	Sex	char	M= male F= female	
DOSEGP	Dose group	char	Use 0, 1, 2, 3, 4, . . . in ascending order from control. Provide the dosing for each group.	
DAYS	Days on drug at sacrifice	num		
DEATH	Description of death	char	Final sacrifice, Sacrificed moribund, or Found dead	
ORGNAME	Name of organ	char		Include blood
ABNORMAL	Abnormal flag	char	Abnormal or Normal	
MICRO	Microscopic findings	char		¹
MACROABN	Macroscopic findings	char	Abnormal or Normal	
GRADE	Grade or severity of abnormality	char		
TUMOR	Tumor flag	char	None, Benign, Malignant, or Indeterminate	
FNLBDYWT	Final body weight	num		
OTHER

¹ 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. CBER plans to refine 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)