

Guidance for Industry

Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications (INDs)

Additional copies of this guidance document are available from:
Office of Communication, Training and Manufacturers Assistance (HFM-40)
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 1-800-835-4709 or 301-827-1800
(Internet) <http://www.fda.gov/cber/guidelines.htm>

For questions on the content of this document
contact Michael B. Fauntleroy at 301-827-5132

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
March 2002**

Table of Contents

I. INTRODUCTION	1
II. PURPOSE.....	2
III. GENERAL ISSUES	3
A. HARMONIZATION WITH GUIDANCE FOR MARKETING APPLICATIONS	3
B. SUBMISSIONS RELATED TO THE INITIAL IND.....	3
C. ACCEPTABILITY OF ELECTRONIC SUBMISSIONS	3
D. ELECTRONIC SIGNATURES	3
E. CROSS REFERENCES TO OTHER INDS.....	4
F. FOLDER AND FILE NAMES	4
G. BOOKMARKS AND HYPERTEXT LINKS	4
H. PUBLICATIONS.....	5
I. SUBMISSION MANAGEMENT.....	5
J. APPLICATION STRUCTURE	6
IV. ORGANIZING THE MAIN FOLDER	6
A. NAMING THE MAIN FOLDER.....	7
B. FOLDERS.....	7
C. COVER LETTER	8
D. FORM FDA 1571.....	8
E. IND TABLE OF CONTENTS.....	9
F. FULL TEXT INDEX FOR THE SUBMISSION	9
V. ORGANIZING THE SUBMISSION	10
A. ADMINISTRATIVE (ADMIN).....	10
B. CHEMISTRY, MANUFACTURING AND CONTROL (CMC).....	11
C. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY (PHARMTOX).....	12
D. CLINICAL.....	13
E. OTHER.....	16
VI. APPENDICES.....	17
APPENDIX A: ROADMAP FILE.....	17
APPENDIX B: IND TABLE OF CONTENTS.....	18
APPENDIX C: CBER ELECTRONIC SUBMISSION COORDINATORS	22

GUIDANCE FOR INDUSTRY

Providing Regulatory Submissions in Electronic Format — Investigational New Drug Applications

This guidance document represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This is one in a series of guidance documents intended to assist you, sponsors, in making regulatory submissions in electronic format to the Center for Biologics Evaluation and Research (CBER). We, FDA, intend to update guidance on electronic submissions regularly to reflect the evolving nature of the technology and the experience of those using this technology. As FDA develops guidance on electronic IND submissions in the Common Technical Document (CTD) format, we intend to harmonize this guidance with the CTD guidance.

In this guidance, we discuss specific issues unique to the electronic submission of Investigational New Drug applications (INDs) and their amendments. We have described general issues such as acceptable file formats, media, and submission procedures that are common to all submissions in the companion guidance, “Providing Regulatory Submissions in Electronic Format — General Considerations,” dated January 1999 (January 28, 1999, 64 FR 4433).

This guidance finalizes the draft guidance entitled “Guidance for Industry: Pilot Program for Electronic Investigational New Drug (eIND) Applications for Biological Products,” dated May 1998, that was announced in the Federal Register on June 1, 1998 (63 FR 104). We have incorporated into this guidance our experiences from the pilot program and comments received from the public, and from our electronic marketing applications guidance entitled, “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 Application (NDA)],” dated November 1999 (November 12, 1999; 64 FR 61647).

II. PURPOSE

This guidance is intended to facilitate the submission of INDs in electronic format as well as ensure quick and easy information access for the reviewer. The guidance features an IND main folder that is used throughout the life of the application. The IND main folder contains six subfolders, four of which are analogous to the review disciplines within CBER. They are described in section IV.B.

We have employed a table of contents (TOC) and bookmark driven navigational construct that is similar to the structure employed in CBER's electronic marketing application. You should include at the top of the bookmark hierarchy the following bookmarks: Roadmap, Main TOC, and Item TOC (i.e., for the item currently under review). When presenting a TOC in your electronic IND submission, analogous bookmarks should reside in the left hand margin.

Your submission should include individual PDF files that contain numeric prefixes. The numeric prefix should reflect the amendment number in which the file was submitted for review. The numeric prefix will facilitate the loading of new files into a pre-existing folder structure that features the IND main folder and its 6 subfolders (See IV.B.). However, the following PDF files should not contain numeric prefixes: *roadmap.pdf* (see Appendix A), *protocoltoc.pdf* (see V.D.1 and Appendix A, Figure VI-4), and *adverse_eventstoc.pdf* (see V.D.2 and Appendix A, Figure VI-5). These files are cumulative and will be replaced in subsequent submissions.

The electronic IND also features the use of the *roadmap.pdf* file. This is the recommended entry point for the electronic submission. The *roadmap.pdf* file should contain functional hypertext links to the original submission's main TOC and to each subsequent submission's TOC. You should include the submission serial number found in the prefix of each file for that submission (see Appendix A). You should update and resubmit this file with each amending submission. As a result, the *roadmap.pdf* file always will contain a current comprehensive submission history that will enable a reviewer easily to access the original IND and its subsequent amendments through their main TOC's.

When amending your IND, you should utilize the same IND main folder and subfolder names (that you used) in your original IND submission. The amending submissions' IND main folder should include the appropriate subfolders for the content of that submission (see IV.B.). The files should be identified through the use of the amending submissions serial number in their file name prefix (see III.F.). We will load the individual files of the new amendment, which reflect a new submission serial number in their prefix, into the preexisting content subfolders on our server. If the amendment contains a content subfolder not previously submitted to the IND, we will load the entire subfolder into the IND main folder on our server. You should submit an updated overall submission index and an updated subfolder specific index with every amendment to the IND. We will load these indexes into the preexisting folder structure.

III. GENERAL ISSUES

Regulations in 21 CFR part 312 provide the general requirements for submitting INDs to CBER. Currently, Form FDA 1571 (<http://www.fda.gov/opacom/morechoices/fdaforms/cber.html>) outlines the components required in the submission of an IND.

A. Harmonization with Guidance for Marketing Applications

We have tried to harmonize the guidance for providing INDs and marketing applications in electronic format whenever possible. You should refer to the “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 Application (NDA)],” November 1999, Revised, as a reference, (<http://www.fda.gov/cber/guidelines.htm>).

B. Submissions related to the initial IND

This guidance applies equally to the original submission of an IND and to the subsequent submissions amending the original application. We have described IND submission types on the Form FDA 1571 under item 11. If you decide to provide an IND in electronic format, you should provide the entire submission in electronic format. You also should provide all amendments to the original submission in electronic format.

C. Acceptability of Electronic Submissions

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 the submissions it will accept in electronic format. Once a Center has identified in the docket a submission type as one that can be processed, reviewed and archived in an electronic only format, you may provide the submission utilizing electronic media without any paper copies (21 CFR 11.1(d) and 11.2).

D. Electronic Signatures

We are developing procedures for archiving documents with electronic signatures. Until those procedures are in place, you should include with the electronic document the following:

- Documents for which the regulations require an original signature.
- A paper copy that includes the handwritten signature of the sponsor’s authorized representative; and the IND number to identify the electronic document and attachments.

E. Cross References to other INDs

At times, IND submissions are supported by a cross-reference to another IND [21 CFR 312.23(b)]. The utility of the electronic IND submission will be further increased if all reference materials are supplied with the IND submission. You should handle these files in the same manner as other electronic files submitted to the IND. For example, you should generate the files from electronic source files rather than from scanned paper documents if at all possible. If the electronic source file is not available, we will accept a scanned copy. You should describe the file format and organization of these files as described in this guidance.

If an electronic IND or other form of documentation already exists in CBER, and the appropriate letters of authorization are supplied, the IND review team will be granted access to those documents. If the files you choose to reference have been provided in electronic format, you should include the main folder name in which the document resides in place of the volume number required under 21 CFR 312.23(b). You should provide copies of the appropriate letters of authorization in the *admin* folder of the submission.

F. Folder and File Names

We have provided specific names for the folders (see Table 1) and subfolders of the submission as well as the table of contents files including the roadmap file. Using these names will minimize confusion among the Center's reviewers.

For file names not specifically described, we ask that you use the following naming conventions.

- Include the submission serial number for the file in the initial 4 numbers of the file.
- Use a descriptive name for the file up to a total of 28 characters. This is a total of 32 characters including the 4-digit serial number.
- Use the appropriate 3 - character extension for the file (e.g., pdf, xpt).
- Be consistent with the file names. For example, if you use the protocol number as part of the name of the original protocol, you should include the same name for the protocol revision.

For example, protocol 1234 provided in amendment number six could be named *0006_1234.pdf*. The revised protocol submitted as part of amendment 125 would be named *0125_1234.pdf*.

G. 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, publications, and appendices even if included in a separate file, to serve as part of the table of contents for the submission.

To facilitate the review, you should provide hypertext links to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page throughout the body of the 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. In order to provide reviewers maximal flexibility in using electronic documents, please avoid linking items across submission folders. We intend to review the information according to discipline and thus you should present your information in a modular fashion. For example, if you intend to use a reference to support a point in the CMC folder, you should not place the reference in the Clinical folder.

You should also include a bookmark to the roadmap, the submission's main table of contents, and the folder's table of contents at the highest level of the bookmark hierarchy for documents that you supplied as part of the submission.

H. Publications

You should provide each publication as a separate PDF file. Establish a hypertext link between the reference to the publication in the application and the publication. You should include the citation for the publication in the title portion of the Document Information field for each publication file.

I. Submission Management

Timely communications with the appropriate center and office staff prior to the submission of an electronic document are essential. You should contact us when questions arise.

You should notify us in writing of your intent to submit an electronic IND at least three months prior to the target arrival date for the application. Upon receipt and review of the written notification, our staff will schedule a teleconference to discuss the proposed electronic dossier. You should submit a CD-ROM, containing mock-up text and data, conveying your interpretation of the guidance for review by Center staff 45 days before the submission target date. As individual sponsors or product teams gain experience in utilizing this submission type, we may find the CD-ROM demonstration to be unnecessary.

Because the review of an initial IND submission must be completed in 30 days, it is essential that the electronic IND submission function smoothly. The CD-ROM demonstration is a critical part of ensuring that smooth function. The CD-ROM demonstration should facilitate discussions of the planned regulatory submission through the presentations of mock-up text, tables, graphics, and data to CBER from the sponsor. The CD-ROM demonstration will: (1) present us with an opportunity to ensure that documents are presented in a standard format across all electronic IND applications; (2) present an opportunity for feedback from the review team on the presentation of regulatory information (e.g. dataset structures, hypertext links,

bookmarking, and document quality); and (3) present an opportunity for our technical staff to provide feedback on how well the proposed submission structure is consistent with our guidance. Effective use of the demonstration and timely communication with our staff should enhance your understanding of this guidance document and its intent. We have listed the appropriate staff contacts for your submissions in Appendix C.

J. Application Structure

An IND is a compilation of many small submissions collected over an extended period of time. Frequently, during the review of an IND submission, a reviewer will need to refer to earlier submissions. To help reviewers navigate through the entire application, you should provide with each new submission a directory that includes a list of not only the files included in the current submission but all of the previously submitted files as well (See Appendix A – example *roadmap.pdf* file).

This list should be presented in reverse chronological order, by submission, as part of a PDF file called *roadmap.pdf* (see Appendix A). This file is linked to the submission’s main table of contents, which is in turn linked to the table of contents provided in each subfolder. See section IV.E. below for additional details on the table of contents’ files.

IV. ORGANIZING THE MAIN FOLDER

You should place in the main folder all electronic documents and datasets that you intend to be part of your electronic IND. The only exception is the application directory (*roadmap.pdf* file). This document should be placed in the root directory.

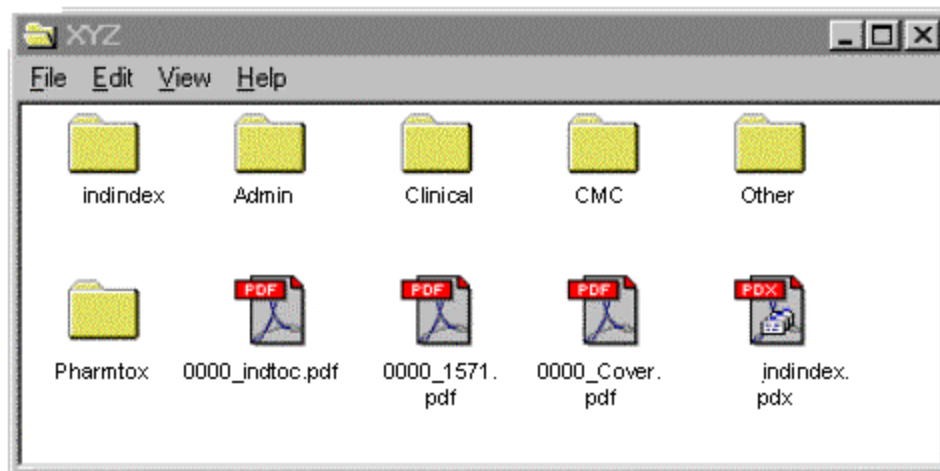


Figure 1; IND main folder

A. Naming the Main Folder

The main folder for the original submission should be named IXYZ where XYZ contains abbreviations for the sponsor name, product, and indication. For this submission, you do not know the IND number nor can you generate it before the arrival of the regulatory submission. All amendments to the application should use the same main folder name as the original submission.

B. Folders

Inside the main folder, you should provide 5 folders, Administrative (*admin*), Chemistry Manufacturing and Controls (*cmc*), Pharmacology and Toxicology (*pharmtox*), Clinical (*clinical*), and Other (*other*) to organize the documents and datasets provided in the original submission and subsequent amendments to your IND (Figure 1). See Table 1 for the types of documents that would reside in each folder. In addition, the main folder should contain an *indindex* folder (see Item F)

You should name the folders as shown in Figure 1. You should not attach an extension to the submission subfolders. Our intent is to create one set of folders per submission and upload additional supporting information into these folders. This will give our review community one central location as a repository for information germane to their review.

Place the types of documents/information listed below into the designated folders.

Table 1: Organization of Documents

Folder location	Types of document
Administration (<i>admin</i>)	Introductory statement, annual reports, change of address, change of contact, change of sponsor, letters of authorization, meeting minutes, interim reports, final reports request for closure, fast track, inactivation, reactivation, rolling BLA or NDA designation, transfer of obligations, withdrawal, meeting request, responses to a clinical hold or information request correspondence
Chemistry, Manufacturing and Controls (<i>cmc</i>)	CMC information [§312.23(a)(7)] and informational amendments related specifically to CMC [§312.31] including product characterization, device information, formulation, labeling, lot release, manufacturing information, shipment of product, source information, specifications, lot release data, stability, sterility and environmental assessment or claim for exclusion
Nonclinical Pharmacology and Toxicology (<i>pharmtox</i>)	Pharmacology and toxicology information [312.23(a)(8)] and informational amendments related specifically to pharmtox [§312.31] including pharmacology and toxicology data, preclinical information, animal models, in vitro models, pharmacokinetics, preclinical reports and protocols, toxicology

Clinical (<i>clinical</i>)	Protocols [§312.23(a)(6)], protocol amendments [§312.30], previous human experience [§312.23(a)(9)], safety reports [§312.32] and informational amendments related specifically to clinical [§312.31] including adverse reactions, consent forms, investigator information, general investigational plan, investigator’s brochures, IRB approval, new protocols, revised protocols, site information, investigator data, CV’s, and 1572’s
Other (<i>other</i>)	Cross referenced files and other information

C. Cover Letter

You should provide a cover letter as a PDF file named XXXX_*cover.pdf* inside the main folder, where XXXX is the submission serial number. You should include in the cover letter the following:

- A description of the submission including appropriate regulatory information.
- A description of the electronic submission including the type and number of electronic media used (e.g., two CD-ROMs), and the approximate size of the submission (e.g., 1.2 gigabytes).
- 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.
- Any changes from the recommendations in this guidance document should be documented in the cover letter.
- The regulatory and information technology (IT) points of contact for the application.

D. Form FDA 1571

Inside the main folder, provide a Form FDA 1571, as a PDF file named XXXX_*1571.pdf*, where XXXX is the submission serial number. The agency is developing procedures to allow the submission of electronic signatures. Until procedures are in place, you should attach a paper Form FDA 1571 that is signed by the sponsor’s authorized representative to accompany the *1571.pdf* file.

E. IND Table of Contents

Regulations at 21 CFR 312.23(a)(2) require submission of a table of contents.

For the electronic submission, the table of contents should contain three levels of detail and the appropriate hypertext links and bookmarks (see Appendix B). The first level of detail, the main table of contents, will contain a simple listing of the items in section 12 of the Form FDA 1571. You should hypertext link and bookmark these items to the appropriate item table of contents for the IND. This single page PDF file should be named *XXXX_indtoc.pdf*, where XXXX is the submission serial number. You should place the main table of contents in the main folder.

The second level of detail is the table of contents for each folder of the IND. You should provide these tables of contents as PDF files named in the following manner, e.g., *0000_admintoc.pdf*, *0000_cmctoc.pdf*, *0000_pharmtoctoc.pdf*, *0000_clinicaltoc.pdf* and *0000_othertoc.pdf*. You should place items in the appropriate subfolder. For each table of contents, you should list all of the files pertaining to that area in the specific subfolder and provide bookmarks and hypertext links to each document or dataset listed in the table of contents. In general, these tables of contents should consist of a few pages. You should provide bookmarks to the submission's roadmap main table of contents and the item's table of contents at the highest level of the bookmark hierarchy. This will allow a reviewer to easily navigate throughout the electronic submission.

The third level of detail pertains to reports and protocols. You should fully bookmark and hyperlink the table of contents for these documents. For datasets, you should provide a data definition table as a key to the elements being used in the datasets.

F. Full Text Index for the Submission

You should provide an index of the full text and the Document Information fields of all items in the submission. The index is generated in PDF by using Acrobat Catalog. Name the index definition file *indindex.pdx*. You should place all associated index files in a folder named *indindex*. Place the *indindex.pdx* definition file and the *indindex* folder in the IND main folder. Associate the *XXXX_indtoc.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. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that word's location throughout the documents covered by the indexes loaded at the time. The *indindex* folder and file do not have numerical prefixes because they are intended to be cumulative. Index information should be updated each time an amendment is submitted to the IND.

V. ORGANIZING THE SUBMISSION

Guidance follows for providing files for each of the 5 content folders potentially included in an original submission of an IND and all of its subsequent amendments, in electronic format.

A. Administrative (*admin*)

Table 1: Organization of Documents lists the types of documents that you should provide in the *admin* folder. You should place all of these files directly into the *admin* subfolder. Do not provide any subfolders within the *admin* folder except for the full text index and publications folders.

1. Letter of Authorization

When referencing information submitted to the agency by another sponsor, you must provide a written statement that authorizes the reference and that is signed by the person who submitted the information [21 CFR 312.23(b)]. You should provide this letter of authorization as an individual PDF file and place it in the *admin* folder.

2. Responses to Center Correspondence

You should include the actual comments, questions, and requests for additional information communicated in our letter sent to you, as well as your response to these items. You should bookmark each item to facilitate information access. You should make additional supporting information accessible through a hypertext link contained within your response.

3. Annual Report

Except for the investigator's brochure (21 CFR 312.33(d)), you should provide the required information for an annual report as a single PDF file. You will find the items required for the annual report listed in 21 CFR 312.33. As part of the annual report file, you should provide a table of contents listing each item detailed in 21 CFR 312.33. You should bookmark and hyperlink each item in the table of contents to its referenced information in the document. Information on providing the investigator's brochure is provided below.

4. Other Documents

You should provide other documents in this subfolder including those described in Table 1: Organization of Documents as individual PDF files.

5. Publications

You should provide each publication as a separate PDF file. You should place all publications that are cited in files contained in the *admin* folder, in alphabetical order, into a single folder named *pubs*. You should establish a hypertext link between the citation and the publication in the *pubs* folder. Place the *pubs* folder in the *admin* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. You should include the first author's last name, the year of the publication and the title of the article in the citation.

6. Full Text Index

You should provide an index of the full text and the Document Information fields of all documents in this folder. You should name the index definition file *admin.pdx*. You should place all associated index files in the *admin* index folder. You should place *admin.pdx* definition file and the *admin* index folder in the *admin* folder. You should associate the *XXXX_admintoc.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. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that word's location throughout the documents covered by the indexes loaded at the time. Index files and folders do not have numerical prefixes because they are intended to be cumulative. They should be updated each time an amendment is submitted to the IND.

B. Chemistry, Manufacturing and Control (CMC)

Table 1: Organization of Documents lists the types of documents that you should provide in the *cmc* folder. You should place all files directly into the *cmc* folder. You should not provide any subfolders within the *cmc* folder except for the full text index and the publications folder.

1. Documents and Datasets

See the "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 Application (NDA)]," November 1999, Revised, for guidance on the format of specific documents and datasets files for CMC submissions.

For documents not described in the marketing applications, you should provide documents as individual PDF files and place them in the *cmc* folder.

2. Publications

You should provide each publication as a separate PDF file. You should place all publications that are cited in files contained in the *cmc* folder, in alphabetical order, into a single folder named *pubs*. Establish a hyperlink between the citation and the publication in the *pubs* folder. You should place the *pubs* folder 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.

3. Full Text Index

You should provide an index of the full text and the Document Information fields of all documents in this folder. You should name the index definition file *cmc.pdx*. You should place all associated index files in the *cmc* index folder. Place the *cmc.pdx* definition file and the *cmc* index folder in the *cmc* folder. You should associate the *XXXX_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. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that word's location throughout the documents covered by the indexes loaded at the time. Index files and folders do not have numerical prefixes because they are intended to be cumulative. They should be updated each time an amendment is submitted to the IND.

C. Nonclinical Pharmacology and Toxicology (Pharmtox)

Table 1: Organization of Documents lists the types of documents that you should provide in the *pharmtox* folder. You should place all files directly into the *pharmtox* folder. You should not provide any subfolders within the *pharmtox* folder except for the full text index and the publications folder.

1. Documents and Datasets

See the "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 Application (NDA)]," November 1999, Revised, for guidance on the format of specific documents and datasets files for *pharmtox* submissions.

For documents not described in the marketing applications, you should provide documents as individual PDF files and place them in the *pharmtox* folder.

2. Publications

You should provide each publication as a separate PDF file. You should place all publications that are cited in files contained in the *pharmtox* folder, in alphabetical order, into a single folder named *pubs*. Establish a hyperlink between the citation and the publication in the *pubs* folder. You should place the *pubs* folder in the *pharmtox* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. You should include the first author's last name, the year of the publication and the title of the article in the citation.

3. Full Text Index

You should provide an index of the full text and the Document Information fields of all documents in this folder. You should name the index definition file *pharmtox.pdx*. You should place all associated index files in the *pharmtox* index folder. Place the *pharmtox.pdx* definition file and the *pharmtox* index folder in the *pharmtox* folder. You should associate the *XXXX_pharmtoc.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. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that words location throughout the documents covered by the indexes loaded at the time. Index files and folders do not have numerical prefixes because they are intended to be cumulative. They should be updated each time an amendment is submitted to the IND.

D. Clinical

Table 1: Organization of Documents lists the types of documents that you should provide in the *clinical* folder. You should place all files directly into the *clinical* folder. You should not provide any subfolders within the *clinical* folder except for the full text index, publications, protocol and adverse events folders.

1. Protocol and Protocol Revisions (amendments)

You should provide each protocol in a separate PDF file in a subfolder labeled Protocols. To help us easily identify the file, use the protocol number as part of the filename. Each protocol should have a table of contents. You should hypertext link and bookmark the table of contents. For protocol revisions or amendments, you should use the same protocol number that identifies the original protocol. You should submit to the file a complete copy of any revised protocol. This will facilitate the use of the “text compare” function in Adobe Acrobat by our clinical reviewers.

You should create a PDF file named *protocolctoc.pdf* (i.e., protocol cumulative table of contents) within the Protocols subfolder. The *protocolctoc.pdf* is a cumulative list of the protocols and revisions with the date of submission presented as a PDF file. The cumulative list should be in inverse chronological order with the most recent protocol submission at the top of the list. Because this file is cumulative, it does not have a numerical prefix. The *protocolctoc.pdf* should not affect the submission content in any fashion. You should hypertext link the protocols and revisions listed in this file to the documents they reference. You should update this file with the submission of any protocol or protocol revision. The document should function in a manner similar to the *roadmap.pdf* file (see Appendix A and Appendix B, Figure VI-4)

2. Adverse Events

You should provide each adverse event report as a separate PDF file in a subfolder labeled “Adverse Events”. To aid Center staff in identifying each PDF file, please use a combination of the protocol number, patient number and event date in each file name (e.g., RIT-02-004_010-023_07132001). Within the Adverse Events subfolder you should provide a PDF file named *adverse_eventsctoc.pdf* (i.e., adverse events cumulative table of contents). The *adverse_eventsctoc.pdf* is a cumulative list of all adverse events that occurred during the clinical investigation. The cumulative list should be in inverse chronological order with the most recent submission at the top of the list. Because this file is cumulative, it does not have a numerical prefix. The *adverse_eventsctoc.pdf* should not affect the submission content in any fashion. You should hypertext link the adverse event reports listed in this file to the documents they reference. You should update this file with the submission of any adverse event report. The document should function in a manner similar to the *roadmap.pdf* file (see Appendix A and Appendix, B Figure VI-5).

3. Investigator’s Brochure

You should provide the investigator’s brochure as a single PDF file. You should include a table of contents in the investigator’s brochure. You should name the file *XXXX_investbrochuretoc.pdf*. You should bookmark and hypertext link the table of contents for this file.

4. General Investigational Plan

You should provide the general investigational plan as a single PDF file. You should include a table of contents in the general investigational plan. You should name the file *XXXX_geninvestplantoc.pdf*. You should bookmark and hypertext link the table of contents for this file.

5. Clinical Trials Data Bank

We have established a clinical trials data bank to collect information on your clinical trials protocols. Please list your protocols for serious and life-threatening conditions (Food and Drug Administration Modernization Act of 1997 (FDAMA) section 113). When finalized, you should list your protocols in accordance with our “Draft Guidance for Industry – Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Implementation Plan,” June 2001.

6. Investigator Information

You should provide the investigator information as a single PDF file. If more than one investigator is included in the file, you should provide a bookmark to each investigator.

7. Previous Human Experience

You should provide previous human experience in a separate PDF file that is reserved for summary information. You should include a table of contents in the previous human experience file. You should name the file *XXXX_prevhumexptoc.pdf*. You should bookmark and hypertext link the table of contents for this file. If you are providing study reports, you should provide them as described in the appropriate marketing guidance document.

8. Other Files

See the “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 Application (NDA)],” November 1999, Revised, for guidance on the format of specific documents and datasets files for clinical submissions.

For documents not described in the marketing applications, provide documents as individual PDF files and place them in the *clinical* folder.

9. Publications

You should provide each publication as a separate PDF file. You should place all publications that are cited in files contained in the *clinical* folder, in alphabetical order, into a single folder named *pubs*. You should establish a hypertext link between the citation and the publication in the *pubs* folder. You should place the *pubs* folder in the *clinical* folder. You should include the citation for the publication in the Title portion of the Document Information field for each publication file. You should

include in the citation the first author's last name, the year of the publication, and the title of the article.

10. Full Text Index

You should provide an index of the full text and the Document Information fields of all documents in this section. You should name the index definition file *clinical.pdx*. You should place all associated index files in the *clinical* folder. Place the *clinical.pdx* definition file and the *clinical* index folder in the *clinical* folder. You should associate the *XXXX_clinicaltoc.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. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that word's location throughout the documents covered by the indexes loaded at the time. Index files and folders do not have numerical prefixes because they are intended to be cumulative. They should be updated each time an amendment is submitted to the IND.

E. Other

Table 1: Organization of Documents lists the types of documents that you should provide in the subfolder. You should place all files directly into the *other* folder. You should not provide any subfolders within the *other* folder except for the full text index.

1. Documents

You should provide an individual PDF file for each document.

2. Full Text Index

You should provide an index of the full text and the Document Information fields of all documents in the other section. You should name the index definition file *otherindex.pdx*. You should place all associated index files in a folder named *otherindex*. Place the *otherindex.pdx* definition file and the *otherindex* folder in the main *other* folder. You should associate the *XXXX_othertoc.pdf* file with this index so that whenever the other table of contents is opened, the associated index is automatically added to the available index list. This will facilitate the use of the search function in Adobe Acrobat. The function enables a reviewer to enter a specific word and search the document for that word's location throughout the documents covered by the indexes loaded at the time. Index files and folders do not have numerical prefixes because they are intended to be cumulative. They should be updated each time an amendment is submitted to the IND.

VI. APPENDICES

Appendix A: Roadmap file

You should use the *roadmap.pdf* file to establish a hypertext link to the submission's table of contents. You should locate the *roadmap.pdf* file in the root directory of the submission. You should update and resubmit the file when you submit amendments to the application. An example of the *roadmap.pdf* file format is shown in Figure VI-1.

Figure VI-1: Example of a roadmap file

Electronic Roadmap				
IND Submission	Submission Date	Submission Content	CD-ROM	Hypertext link Destination
IND 12345.0003	04-Jul-2001	Cover letter	3.01	amendtoc.pdf
		1571	3.01	
		Protocol 12-345	3.01	
		Investigator Information	3.01	
IND 12345.0002	19-Jun-2001	Cover letter	2.01	amendtoc.pdf
		1571	2.01	
		Lot Release	2.01	
IND 12345.0001	10-Feb-2001	Cover letter	1.01	amendtoc.pdf
		1571	1.01	
		Revised Protocol	1.01	
Sponsor Name	15-Jan-2001	Cover letter	0.01	Indtoc.pdf
		1571	0.01	
		Table of Contents	0.01	
		Introductory Statement	0.01	
		General	0.01	
		Investigational Plan		
		Investigator Brochure	0.01	
		Protocols	0.01	
		CMC	0.01	
		Pharmacology and Toxiology	0.01	
		Previous Human Experience	0.01	
		Additional Information	0.01	

The *roadmap.pdf* 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. You should replace the *roadmap.pdf* file with each new submission of regulatory information.

In addition to providing a navigable guide to the application (i.e., a correspondence history), the *roadmap.pdf* file should include the sponsor’s submission date in the DD-MM-YYYY format (e.g., 15-01-2000). You should describe briefly the contents of the original submission and of subsequent amendments in a *roadmap.pdf* table. You should indicate in the *roadmap.pdf* file the location of these files and folders on the submitted CD-ROMs (Compact Disk – Read Only Memory).

Appendix B: IND Table of Contents

The IND table of contents should facilitate access to the submission text and data. Examples of the first, second, and third levels for the IND table of contents are shown in Figures VI- 2 through 7. These examples portray the intent of the IND’s multiple TOC’s. Protocol is highlighted as a specific example. These files will facilitate a reviewer’s ability to navigate throughout an electronic dossier. Bookmarks should mirror the contents of each table of contents. At the top of the bookmark hierarchy, three bookmarks (Roadmap, Main TOC, Section/Item TOC) should always reside.

Figure VI-2: IND Main Table of Contents for Original Submission 12345. This is the first level TOC.

Main IND Table of Contents		
Section	Description	Electronic folder/filename
-	Coverletter	0000_coverletter.pdf
1	Form FDA 1571	0000_1571.pdf
2	Table of Contents	0000_indtoc.pdf
3	Introductory Statement	0000_intro.pdf
4	General Investigational Plan	Clinical\0000_clintoc.pdf
5	Investigator Brochure	Clinical\0000_clintoc.pdf
6	Protocols	Clinical\0000_clintoc.pdf
7	Chemistry, Manufacturing and Controls	Cmc\0000_cmctoc.pdf
8	Pharmacology and Toxicology Data	Pharmtox\0000_pharmtoxtoc.pdf
9	Previous Human Experience	Clinical\0000_clintoc.pdf
10	Additional Information/Pre-IND Information	Admin\0000_admintoc.pdf
11	Other	Other

Figure VI-3: Section Based Table of Contents. This is the second level TOC.

Clinical Table of Contents – Items contained within the Clinical Folder		
Item	Description	Folder/File
1	General Investigational Plan	Clinical\0000_geninvestplantoc.pdf
2	Investigator Brochure	Clinical\0000_investbrochuretoc.pdf
3	Protocol – XOXOXO	Clinical\protocols\protocolctoc.pdf
4	Sample Informed Consent	Clinical\0000_consent.pdf
5	Previous Human Experience	Clinical\0000_prevhumexptoc.pdf
6	Adverse Events	Clinical\adverse events\adverse_eventsctoc.pdf

Pharmtox Table of Contents – Items contained within the Pharmtox Folder		
Item	Description	Folder/File
1	Pharmacology and Toxicology Summary	Pharmtox\0000_summarytoc.pdf
2	Immunopathology Report: Cross-Reactivity of XXX with Normal Human Tissue	Pharmtox\0000_Immunopath568toc.pdf
3	Immunopathology Report: Cross-Reactivity of XXX with Limited Normal Tissue from Rhesus and Cynomolgus Monkeys	Pharmtox\0000_Immunopath767toc.pdf
4	An MTD/Dose Range Finding Intravenous Toxicity Study in Male CD-1 Mice	Pharmtox\0000_Toxicitytoc.pdf
5	A Single-Intravenous Dose Pharmacokinetic Study in Cynomolgus Monkeys	Pharmtox\0000_SingleDoseetoc.pdf

Figure VI-4: Protocol Cumulative Table of Contents

Submission Date	Protocol Title	Hyperlink Destination
15-Jan-2001	The Real Deal	0005_Pnca101.01.pdf
25-Dec-2000	Pure Profit	0003_Shazam100.pdf
30-May-2000	Home Cooking	0002_Tcencore50.01.pdf
22-Nov-1999	The Real Deal	0000_Pnca101.pdf
22-Nov-1999	Home Cooking	0000_TCencore50.pdf

Figure VI-5: Adverse Event Cumulative Table of Contents

Submission Date	Adverse Event	Hyperlink Destination
13-Jul-2001	Thrombocytopenia	0015_RIT-02-004_01023_07132001.pdf
04-Jul-2001	Leukocytopenia	0012_RIT-02-004_711_07042001.pdf
01-Apr-2000	Alopecia	0007_SUC-01-001_061968_04012000.pdf

Figure VI-6: Part of a Protocol Table of Contents – Pure Profit. This is the third level TOC.

TABLE OF CONTENTS

SYNOPSIS	ii
LIST OF ABBREVIATIONS	vii
1.0 OVERVIEW	1
2.0 BACKGROUND	2
2.1 Overview	2
2.2 Toxicology	3
2.3 Pharmacokinetics	4
2.4 Human Clinical Trials	5
2.5 Rationale for Study Design	6
3.0 OBJECTIVES	7
4.0 INCLUSION AND EXCLUSION CRITERIA	8
4.1 Inclusion Criteria	8
4.2 Exclusion Criteria	9
5.0 INVESTIGATIONAL PLAN	10
5.1 Study Design	10
5.2 Dose-Limiting Toxicity and Maximum Tolerated Dose	11
5.3 Sample Size	12
5.4 Treatment	12
5.4.1 Clinical Trial Material	12
5.4.2 Drug Administration	17
5.4.3 Dosage Modification	17
5.4.4 Criteria for Continuation of Treatment Beyond Cycle 1	18
5.4.5 Retreatment Eligibility Criteria	19
5.4.6 Concomitant Therapy	20
5.5 Outcome Measures	21

Figure VI-7: Part of a CMC Table of Contents. This is the third level TOC.

TABLE OF CONTENTS		
LIST OF ABBREVIATIONS		vii
1.0	CHEMISTRY	1
1.1	Development of the Expression Construct	1
1.1.1	Construction of Genes Encoding the Light and Heavy Chain Variable Regions	1
1.1.2	Construction of the Light and Heavy Chain Plasmids, p1933 and p1937	1
1.1.3	Construction of the Expression Plasmid, p1937	2
1.1.4	Cloning and Expression of Soluble	10
1.1.4.1	Expression Plasmid for Soluble	10
1.1.4.2	Cloning of the cDNA Encoding and Development of Expression Plasmid	10
1.1.4.3	Development of Cell Line for Production of	10
1.1.4.4	Production and Purification of	11
1.2	Development of the Production Cell Line for	15
1.2.1	History of Cell Line	15
1.2.2	Development of the Producing Cell Line	15
1.2.3	Preparation and Characterization of the Clone Master Cell Bank and Working Cell Bank	15
1.2.4	Preparation and Storage of MCB	15
1.2.5	Preparation and Storage of MWCB	16
1.2.6	Characterization of MCB and MWCB	16
1.2.6.1	Growth and ING-1 Productivity of MCB and MWCB	17
1.2.6.2	Sterility Testing	19
1.2.6.3	Mycoplasma Testing	19
1.2.6.4	Isoenzyme Analysis	19
1.2.6.5	Karyotyping	20
1.2.6.6	Hamster Antibody Production (HAP) Assay	21
1.2.6.7	In Vitro Assay for the Presence of Viral Contaminants	21
1.2.6.8	Detection of Inapparent Viruses by In Vitro Inoculation	22
1.2.6.9	Detection of Viral Particles by Thin Section Electron Microscopy	22
1.2.6.10	Assay for Murine Xenotropic Viruses by Extended S+ L- Focus Assay	23
1.2.6.11	Assay for Bovine Adventitious Agents	23
1.2.6.12	Reverse Transcriptase Testing	24
1.2.6.13	Summary of Characterization of MCB and MWCB	25

Appendix C: CBER Electronic Submission Coordinators

Office of the Director	Mr. Michael B. Fauntleroy Director, Electronic Submissions	(301) 827-5132
Office of Therapeutic Research and Review, Division of Application Review and Policy	Dr. Bradley Glasscock, Pharm.D Ms. Lori Tull	(301) 827-5101
Office of Vaccines Research and Review, Division of Vaccines and Related Product Applications	Dr. Rakesh Pandey, Ph.D. Ms. Gale Heavner, R.N. Dr. Joseph Temenak, Ph.D.	(301) 827-3070
Office of Blood Research and Review, Division of Blood Applications	Ms. Daria Reed	(301) 827-3524