

# **Guidance for Industry**

## **Pilot Program for electronic Investigational New Drug (eIND) Applications For Biological Products**

### ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*

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

**NOTE:** Page numbering may vary for documents distributed electronically.

<b>I. INTRODUCTION.....</b>	<b>01</b>
A. Document Overview .....	01
<b>II. IMPORTANCE OF ELECTRONIC SUBMISSIONS.....</b>	<b>02</b>
A. Regulations and Guidance for Electronic Submissions .....	02
B. CBER’s Pilot eIND Program .....	03
1. Stage 1 - Pilot Program .....	04
2. Future Stages.....	04
<b>III. eIND DESIGN AND DEVELOPMENT .....</b>	<b>04</b>
A. Joint Planning .....	04
1. Three Months or More Before eIND Submission .....	05
2. Thirty Days or More Before eIND Submission .....	05
3. Day of Submission .....	05
B. Technical Overview.....	05
1. PDF File Format.....	05
2. Naming PDF Files.....	07
3. Security.....	07
4. Indexing PDF Documents .....	07
5. Hypertext Linking and Bookmarks .....	07
6. Document Information Title Fields.....	08
7. Study Reports.....	08
8. Images .....	08
<b>IV. OVERALL ORGANIZATION OF THE eIND.....</b>	<b>10</b>
A. eIND Main Folder Organization .....	10
1. Roadmap File.....	10
B. Readme File.....	13
C. Cover File .....	13
D. FDA Form1571 and/or 1572 .....	14

***Draft - Not for Implementation***

E. Table of Contents .....	14
F. Folder and File Names.....	14
G. Organizing the Subfolders .....	16
1. Item 1 - FDA Form .....	16
2. Item 2 - Table of Contents .....	16
3. Items 3 and 4 Introductory Statement and General Investigational Plan.....	16
4. Item 5 - Investigator’s Brochure .....	16
5. Item 6 - Protocols.....	17
6. Item 7 - Chemistry, Manufacturing and Control Data (CMC) .....	17
7. Item 8 - Pharmacology and Toxicology Data .....	18
8. Item 9 - Previous Human Experience .....	19
9. Item 10 - Additional Information: Administrative.....	19
10. Item 10 - Additional Information: Pre-IND Information.....	20
<b>V. SUBMITTING ELECTRONIC APPLICATIONS TO CBER.....</b>	<b>21</b>
A. Media. ....	21
B. Media Labeling .....	21
C. Packaging and Shipping.....	22

**TABLES**

<b>TABLE 1:</b> Roadmap Information .....	12
<b>TABLE 2:</b> Electronic Submission Summary .....	13
<b>TABLE 3:</b> Virus Verification Identification.....	14
<b>TABLE 4:</b> Sponsor Contacts .....	14
<b>TABLE 5:</b> Suggested Folder, File and Index names, .....	15

**FIGURES**

<b>FIGURE 1:</b> File and Folder Organization for Original Submission.....	23
<b>FIGURE 2:</b> File and folder Organization with the addition of Amendment 1 .....	24
<b>FIGURE 3:</b> File and folder Organization with the addition of Amendment 2 .....	25

**APPENDICES**

<b>APPENDIX A: ACRONYMS AND ABBREVIATIONS .....</b>	<b>A-1</b>
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**GUIDANCE FOR INDUSTRY<sup>1</sup>**

**PILOT PROGRAM FOR electronic INVESTIGATIONAL NEW DRUG (eIND)  
APPLICATIONS FOR BIOLOGICAL PRODUCTS**

**I. INTRODUCTION**

The Center for Biologics Evaluation and Research (CBER) envisions an integrated information system to support the full range of regulatory functions, from discovery through post-marketing surveillance by 2002. To achieve this vision, and in concert with the Food and Drug Administration (FDA) initiatives to move toward a paperless organization, CBER is beginning the transition to an electronic environment that facilitates the review process and fosters effective electronic interaction with industry. CBER seeks to develop in cooperation with sponsors an efficient process for electronic submissions relating to the development and marketing of biological products.

This guidance document for a pilot electronic Investigational New Drug (eIND) program includes both technical suggestions and minimal structural suggestions for the content of an eIND. It should be used by sponsors submitting an IND in which any part is in electronic format. As the first in a series of guidance documents, it is not meant to be all inclusive. CBER anticipates that as this process evolves, sponsors, investigators, and CBER staff will develop more effective procedures for electronic submissions, which will be incorporated into the process. The ultimate goal is to permit industry to submit IND documents or portions of regulatory applications in electronic format without paper.

Title 21 of the Code of Federal Regulations (CFR), Part 312, must be followed in the preparation of any Investigational New Drug (IND) or eIND application. The content of an eIND should be as similar to that of a paper IND as possible. Guidance set forth in this document does not preempt any requirement of 21 CFR Part 312, but rather provides both technical and content format suggestions for information that would be helpful to the reviewer. Sponsors seeking to submit an eIND application should be familiar with the requirements for submitting a paper-based IND application. For scientific, clinical, and regulatory requirements, please see 21CFR Part 312, and other related federal regulations, and for further guidance refer to applicable points to consider and other CBER guidance documents.

**A. Document Overview**

1. This document applies to eIND applications for products submitted to CBER under a pilot program. This program for eIND submissions is intended to serve as the basis for future inclusion of eINDs in the FDA electronic submission docket (Public Docket 92S-

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<sup>1</sup> This guidance document represents the Agency's current thinking on a pilot program for electronic Investigational New Drug (eIND) Applications For Biological Products. 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. Please note that the FDA's use of specific products does not constitute an endorsement of those products.

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051). Please note that all eINDs submitted under the first stage of the pilot program should continue to be accompanied by a paper copy for the original submission and all amendments.

2. Effective communication between sponsors and CBER is essential for a successful pilot eIND program. At least three months prior to a pilot eIND submission, sponsors should confer with CBER personnel designated to help in the preparation of an eIND (contact: Dr. Frederick Miller, 301-827-0659; e-mail: [millerf@cber.fda.gov](mailto:millerf@cber.fda.gov)).

3. Pilot eIND submissions will only be accepted with prior agreement by the appropriate CBER Division Director(s), and with the receipt of a test submission at least 30 days prior to the actual submission (see Section III.A.).

4. As a result of archival concerns for electronic formats, CBER is only prepared to receive all text and image documents for all review sections of the eIND in Adobe Portable Document Format (PDF). Statistical data should be submitted as Statistical Analysis System (SAS) transport files.

5. All PDF submissions should include a master IND folder containing a *roadmap.pdf* describing the original submission and each amendment, and be hypertext linked to the original submission and amendment table of contents (TOC). The TOC should provide for easy access to all information in the submission, including bookmarks and hypertext links for each component of the Table to the volume needed to display the correct text, graphs/images, tables, and figures relating to that component (see Section IV).

6. Two copies of all eIND information, including all amendments, should be submitted on International Standards Organization (ISO) 9660 Compact Disk-Read Only Memory (CD-ROM) disk(s). More copies may be requested as needed. When a submission is less than 10 pages, a paper only submission may be made, and an electronic version, if provided, on diskette.

7. CBER has established a Desktop Standardization Project (DSP) to ensure that each CBER reviewer has standard computer hardware and software on their desktop.

8. Sponsors should submit at the same time the eIND application or components and their respective paper copy directly to CBER's Document Control Center (DCC) (see Section V). In the interest of accountability, sponsors should not submit copies of any pilot eIND text or images to individual reviewers.

## **II. IMPORTANCE OF ELECTRONIC SUBMISSIONS**

### **A. Regulations and Guidance for Electronic Submissions**

The FDA has gained increased experience with computer-assisted licensing applications, and has concluded that reliance on customized formats is cumbersome for the Agency and for sponsors. As a result, the FDA is working to standardize electronic submission of applications. It is the FDA's goal to establish a process for submitting electronic applications

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that creates minimal additional work for sponsors and reviewers, provides maximal flexibility for sponsors and reviewers, establishes consistency in information transfer requirements across the Agency, and expedites the review process. The FDA is proposing to move from paper regulatory submissions to electronic regulatory submissions in incremental and evolutionary stages. This section discusses electronic submissions generally and CBER's pilot eIND submission project specifically.

The FDA is implementing important regulatory changes, harmonizing Center policies whenever possible, and participating in a range of initiatives to enhance the development of electronic submissions. In the Federal Register of March 20, 1997, the FDA published new regulations, 21 CFR Part 11, *Electronic Signatures, Electronic Records*, which provides for the voluntary submission of parts or all of an application, as defined in the relevant regulations, in electronic format without an accompanying paper copy or requesting a specific waiver (62 FR 13429). This rule applies to any paper records required by statute or Agency regulations. In addition, it provides for the Agency to establish a docket (Public docket 92S-051) on electronic submissions (62 FR 13467) in which the Agency will notify the public when it is ready to accept specific types of electronic submissions. The docket describes those submissions that may be made in electronic form in whole or in part and identifies the corresponding Agency units ready to receive these submissions.

The new regulation states that persons should consult with the intended Agency receiving unit for details on how to proceed with the electronic submission (e.g., method of transmission, media, file formats, and technical protocols). This guidance is intended to reduce the need to consult CBER for details on submitting records and other documents in electronic format for the electronic submission. Following the guidance provided will help ensure that electronic submissions can be accessed, handled, reviewed, and maintained efficiently. This pilot program for eIND submissions is intended to serve as the basis for future inclusion of eINDs in the FDA electronic submissions docket.

Other electronic initiatives with which this document has been harmonized include: *Guidance for Industry: Electronic Submissions of a Biologics License Application (BLA) or Product License Application (PLA)/Establishment License Application (ELA) to the Center for Biologics Evaluation and Research (CBER)* (draft); *Guidance for Industry: Electronic Submissions of Case Report Forms (CFRs), Case Report Tabulations (CRTs) and Data to the Center for Biologics Evaluation and Research (CBER)* (final); *Guidance for Industry: Instructions for Submitting Electronic Lot Release Protocols to the Center for Biologics Evaluation and Research (CBER)* (draft), and the Center for Drug Evaluation and Research (CDER)'s *Guidance for Industry: Providing Regulatory Submissions in Electronic Format -- New Drug Applications (NDAs)* (draft). All of these documents have been or will soon be published in the Federal Register.

### B. CBER's Pilot eIND Program

A key goal of this program is efficient information transfer between sponsors and the FDA. The pilot eIND guidance project also addresses both near- and long-term goals for structured content of the eIND. Near-term goals, Stage 1, are detailed in this guidance document.

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Because the later stages will be dependent on the pilot eIND experience and available technologies, we offer only a general framework for future eIND development.

1. **Stage 1 - Pilot Program:** “Electronic Paper” which includes the embedding of FDA Form 1571 or 1572, [for forms contact: <http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>], with the requested information in the eIND (Section IV). Suggestions for some content structure following FDA Form 1571, Section 12, Contents of Application, items 1-10, and their corresponding CFRs have been provided. In this stage CBER will accept selected *pilot* eIND submissions in order to gain experience in the handling of eIND applications. Pilot eIND submissions shall be accepted only with prior agreement by CBER and receipt of a test submission at least 30 days prior to the actual submission.

a. **Pilot Evaluation:** Members of the eIND Working Group who prepared this guidance document will discuss ‘lessons learned’ as each eIND is reviewed, updating periodically the pilot eIND guidance where appropriate. It is anticipated that Stage 1 will involve the review of four to six eINDs received over a 12 month time period.

b. **Industry Input:** The Agency actively requests input from industry and sponsors in developing the formats, structures and processes necessary for efficient eIND submissions and reviews and expects that their experience and suggestions will be invaluable in this cooperative developmental process.

2. **Future Stages:** It is suggested that in addition to the “electronic paper” IND, selected data items and text from the IND be incorporated in an IND document database through a staged process which would be expanded and modified based upon experience gained from the receipt of eINDs in this pilot program. The ability to search and retrieve on such designated data items could be helpful to the review process.

### **III. PILOT eIND DESIGN AND DEVELOPMENT**

This section discusses the interaction between sponsors and the FDA and suggests the use of acceptable technologies and tools. It clarifies technical requirements for the electronic submission of IND applications as described in the current regulations (21 CFR Part 312). This guidance is not meant to be all inclusive, however, it has, where possible, been harmonized with the current practice of other FDA centers and offices.

#### **A. Joint Planning**

Developing useful pilot eIND submissions requires effective communication between sponsors and appropriate CBER staff. These interactions should begin early in the planning process. FDA participants in the planning process will include appropriate scientific reviewers, Consumer Safety Officers (CSO), and information systems personnel. Sponsor participants may include regulatory affairs staff, sponsor-investigators, and technical staff, including specialists in electronic submissions and third party system developers.

CBER suggests the time-frames shown below. CBER understands that these suggested time-frames may require the sponsor to give more advance notice than sponsors can provide in some circumstances, and therefore candidates for the pilot eIND program should be carefully selected.

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1. **Three (3) Months or More Before eIND Submission:** Contact CBER (Dr. Frederick Miller: 301-827-0659; e-mail: [millerf@cber.fda.gov](mailto:millerf@cber.fda.gov)) for initial information regarding a potential submission of an eIND. Appropriate CBER and sponsor representatives will then confer on network system, other hardware and software requirements, and eIND document structure and content. Acceptance of pilot eIND submissions requires prior agreement by the Director(s) of the appropriate CBER Division(s) that will review the electronic submission for that product.

2. **Thirty (30) Days or More Before Submission:** Sponsors should provide a demonstration or prototype of the pilot eIND for evaluation in order for CBER to:

- a. Identify and resolve any technical problems that could hinder the review.
- b. Gain experience with the prototype to assure that the pilot eIND may be efficiently reviewed at the time of submission.
- c. Confirm that the electronic submission is fully functional in the CBER environment.

3. **Day of Submission:** Sponsor provides the eIND, paper IND, and certifications (see Section V).

### B. Technical Overview

#### 1. PDF File Format

As a result of archival concerns for electronic formats, CBER is only prepared to accept all documents (text, tables, schematics and images) for all review sections of the eIND in Adobe's Portable Document Format (PDF). PDF has been accepted as a standard for providing documents in electronic format by the International Conference on Harmonization (ICH). Manufacturers are free to produce protocols in the word processing program they currently have available to them. Once an electronic protocol has been produced using a word processing program, the protocol should be converted to a PDF format before submission. The PDF format can be created by using applications like Adobe's Acrobat Distiller (preferred over PDF Writer) and read by applications like Adobe's Acrobat Reader and Acrobat Exchange. Currently, CBER cannot accept any PDF files which would require a plug-in to Adobe Exchange/Reader in order for the file to be reviewed, nor can it accept audio or video clips as part of the PDF submission.

To facilitate consistency between the paper and electronic submissions, an electronic source document should be used to produce PDF documents whenever one is available. Scanned images of paper source documents should be used only if an electronic form is unavailable.

To facilitate information location between the paper and electronic submitted documents, CBER encourages the sponsor to use printouts of the actual PDF document when making paper filing rather than printing from the word processing software used to create the submission. The print driver used for conversion to the PDF file should support sufficient resolution for graphic images, both on the reviewers' screen and on the printed page.

CBER and CDER consensus for PDF formats is that electronic submissions should have

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the following characteristics (as per CDER's recently published "Guidance for Industry: Archiving Submissions in Electronic Format - NDAs" (62FR49695; Sept. 9, 1997), (<http://www.fda.gov/cder/guidance/index.htm>): (1) display a clear, legible, easily viewed replica of the information that was originally on paper; (2) provide the ability to print an exact replica of the information that was originally on paper, including retention of fonts, special orientations, table formats and page numbering, (i.e. print final document from electronic document); (3) include a well-structured index/roadmap and the ability to easily navigate through the submission; and (4) offer the ability to electronically copy text and images.

The following general recommendations will help applicants create electronic submissions using PDF that CBER and CDER can handle efficiently (see Drug Information Association: Information Technology Initiative in Drug Registration Submissions-Jan 12-14, 1998 [<http://www.fda.gov/cder/handbook/index.htm>]).

### a. Submission Media

The preferred submission media is CD-ROM ISO 9660.

### b. Fonts:

To ensure that protocols may be viewed consistently on different platforms, the text should be produced using fonts available on CBER's computers. If a font is not available to a reviewer, it is replaced automatically by another font, and this could affect the document's appearance and structure. For this reason, the fonts used should be embedded in the PDF files. To limit the storage space used by embedded fonts, always select fonts carefully and use as few fonts as possible (preferably five or fewer fonts in each PDF file). Only True Type or Adobe Type 1 fonts should be used, and the use of highly customized fonts is discouraged. If only a small percentage of the characters of a particular font are used in the document, only those actually used should be embedded. Also consider the following points:

- i. Font size should be restricted to 10 - 12 points for text and 8 - 12 points for tables.
- ii Font colors should be selected carefully for optimal display on the screen and printing, (e.g., red, blue and green). There is a tendency for font colors to look either black, faded or unclear when printed in grayscale.

### c. Page Size and Formats

- i. Page margins should not be less than one half inch (0.5") on all sides of the electronic document with the preferred paper size 8 ½" x 11". This will help avoid errors if pages are printed and avoid obscuring information if the page is subsequently bound.
- ii. Use of Headers and Footers: Headers and footers are not normally visible when viewing a document on screen with a word processing program, but are seen on the printed version and the PDF document. The use of headers and footers is acceptable.

## *Draft - Not for Implementation*

iii. Page Orientation: Portrait pages should not be displayed as landscape, or viseversa, in the final PDF document.

### 2. Naming PDF Files

To avoid problems associated with the use of long file names by the sponsor, (e.g., using a Novell server), use files names of no longer than 8 characters with PDF as the extension (e.g., *report12.pdf*). Do not use punctuation (/ \ : \* ? < > ! ~), underscores, spaces, or other non-alphanumeric symbols in the filename. Naming conventions are suggested to increase uniformity among submissions and facilitate the review process (see Table 5).

### 3. Security

Security settings or password protection for PDF files should not be used. Printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields should be allowed. The integrity of the submitted files will be secure since they will be archived to CD-ROM, and a network, read-only copy will be provided to the reviewer.

### 4. Indexing PDF Documents

Indexes, which should not be confounded with a table of contents, should be included to facilitate the review by assisting the reviewer in finding specific word text and documents. When a document or group of documents are indexed, all words and numbers in the file and all information stored in the Document Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat Exchange. Electronic documents should be indexed by folder. Portions of a document that are imaged are not indexed. Even if the file only contains images, however, the Document Information fields of the file should be indexed. Adobe Acrobat Catalog is one example of a tool that can be used to index PDF documents. Indexes should not require extensions or additions to off-the-shelf Acrobat programs.

Associate an item's table of contents file with the corresponding index file so that whenever the table of contents file is opened, the associated index is automatically added to the available index list.

Name the index definition file by the file name. For example, if the toxicity studies include studies 6001, 6002, and 6003 as separate PDF files, then, if indexed by file, they should be correspondingly named: 6001.pdx, 6002.pdx, and 6003.pdx.

### 5. Hypertext Linking and Bookmarks

Hypertext links and bookmarks are tools used to improve navigation through PDF documents. Providing a hypertext link to supporting references and appendices, and to tables or figures that are not located on the same page will improve the reviewer's ease of navigation and review. The preferred color for hypertext links is blue; this avoids the potential problem of red-green color blindness.

The initial view of the electronic protocol should be set to 'Bookmarks and Page'. If there are no bookmarks, the initial view should be set as Page only, and the magnification and page layout to default.

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During the review process, the reviewer may wish to copy specific subsections (e.g., clinical, chemistry, manufacturing and controls (CMC), pharmacology and toxicology (pharmtox), etc.) from a network location to their workstation. Downloading a particular section often results in the loss of hypertext links unless the entire submission is downloaded. Therefore, in creating the hypertext links, CBER prefers that a sponsor use relative rather than absolute hypertext links in constructing the electronic submission, i.e. relative to the location of the file containing the links. Specific drive letters and root directories should not be included.

To enhance flexibility in the review process, CBER would like to have the option of accessing information directly from the CD-ROM (see Table 1). To enhance the review of a particular eIND section (CMC, Clinical protocols, etc.), such sections should not be divided between CD-ROMs.

Individual files, and particularly files containing a table of contents, should have a readily identifiable "Home" button available to allow for a rapid return to the submission's main table of contents or roadmap file.

### 6. Document Information *Title* Fields

The document information fields are used to search for individual documents and to provide the name of the document when found. The document information *Title* field should include the sponsor's serial number. For example, for the original submission enter S0000 in the title field, for the first amendment enter the sponsor's serial number S0001 in the title field, for the second amendment enter the sponsor's serial number S0002, etc.

The document information *Title* field for each publication file should include the word *reference* followed by the reference number and a brief description or title.

Appendix A provides additional *Title* field information for each item on Form FDA 1571.

### 7. Study Reports

The study reports should include the summary data tables, individual animal data listings, and all other appendices. Provide bookmarks and hypertext links for the complete sections in each study report.

### 8. Images

For purposes of this document the term 'image' includes photographs e.g., Western Blots, plotter output graphics, High Performance Liquid Chromatographs (HPLC) or like data images, and plant or manufacturing flow and floor diagrams.

#### a. Preparation of Images:

Resolution of captured images should be sufficient to support document review on both the computer monitor and paper. Images should be sized to fit on a single page; limiting one image per page will decrease the access time to a page. Whenever possible, a digital captured image, as opposed to a scanned image, will enhance the details to be viewed, although it may significantly increase file size. CBER and

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CDER will not accept compressed images until standards have been established for compression and validating data integrity. When embedding an image file in the Adobe Distiller, one should *deselect* any compression features under 'Job Options' located in the menu selection: 'Distiller'.

Dot matrix and impact printers are not recommended for creating images for scanning or digital capture. However, laser printers can create clear, dark, and sharp images of all data including graphs and computed results.

### b. Gels and Karyotypes (photographs)

A scanner's ability to resolve an image and the quality of the original image can affect the clarity of the image captured. The recommended minimum capture resolution for photographs is 600 dots per inch (dpi) and a minimum 8-bit grayscale depth.

A captured image should be saved as a picture file, i.e. Tagged Image File Format (TIFF), a Macintosh Vector File (PICT), a Windows Bitmap File (BMP), etc., and not compressed. This allows for easier conversion of the image into a PDF document.

### c. Plotter Output Graphics: The recommended minimum capture resolution for scanned plotter output graphics is 300 dpi.

In scanning images, the scanner software allows one to capture images by various methods which effect the resolution, the quality and the file size of an image. As the resolution increases, the quality of the image improves and the file size increases. For example, if all other parameters are equal, a change of 300 dpi to 600 dpi resolution in a text or graphics file will introduce a 4-fold increase in the file size (i.e. if the original file size is 2MB, it will increase to 8MB). Usually 300 dpi is acceptable, however one may need to capture the output at 600 dpi for acceptable monitor clarity and quality.

This type of graph is typically plotted on graph paper by the plotter output printer. Since graph paper has grid-lines, this full page image can only be captured by using a scanner, alternatively one may use a digital camera to capture the printed image. Since most graphs of this type also contain handwriting, care should be taken when writing, otherwise this information could lose clarity when scanned. For this purpose black ink is preferred for its clarity.

### d. HPLC or Similar Images

For most fonts, the minimum acceptable resolution for alphanumeric characters for on screen viewing is about 8 point, but most HPLC type graphs have a font size of about 6 points. If possible, please increase the font size to a minimum of 8 point as screen clarity would be improved.

If a HPLC file is printed to a laser printer, the printed document can be scanned in at a recommended minimum of 300 dpi. Increasing the document's magnification before printing may be preferable if each image is not a full page view.

### e. Manufacturing Facilities Diagrams

## *Draft - Not for Implementation*

These diagrams are often used to illustrate the manufacturing layout in a given geographical area as well as to illustrate the actual flow of a manufacturing process. Ideally, these would be best provided in color at 600 dpi, or 24-bit red, green, blue (RGB) depth. Utilizing different colors to contrast the different production processes is helpful. The preferred page size of 8.5" x 11" may not be applicable in the production of manufacturing facilities diagrams.

### **IV. OVERALL ORGANIZATION OF THE eIND**

eINDs submitted to CBER may be reviewed in their entirety on a computer network or in sections on individual desktop personal computers. Because additional electronic or paper information in support of an original IND will need to be added to the existing network, it is important that a reliable mechanism be employed for locating all of the sections of an eIND. The following is a suggested organization of an eIND.

#### A. eIND Main Folder Organization

All files should be placed in an IND folder using the submission number as the name of the folder, and preceded by the letter "I" for IND. For example, the folder for IND xxxx would be called Ixxxx. Because the IND number is not assigned until the submission is received, it will be entered post receipt by the DCC/IT staff. Sponsors should use their own reference or serial number to identify the original submission (Amendment 000) and each subsequent submission (Amendment 001, 002, etc.).

The following illustrates the functionality requested by CBER review staff. CBER realizes that one example cannot represent all situations, and alternative approaches may be useful.

The IND folder contains:

##### 1. A *roadmap.pdf* file

A reliable *roadmap.pdf* file (Table 1) is needed which describes each amendment. Each amendment row entry is chronologically entered and hypertext linked to the specific Amendment's Table of Contents (TOC). For each new amendment the following information should be provided:

- Sponsor's serial number
- Sponsor's submission date
- Description of the amendment
- CD-ROM serial number and number of CD-ROMs
- Indication if amendment is *paper only*
- Specific table of contents' file name (*indtoc.pdf*)

Subsequent amendments to the eIND should incorporate amendment changes in a corresponding **new** or **updated** *roadmap.pdf* file which would replace the previous *roadmap.pdf* file. This would serve to re-establish the hypertext links to both the old sections of the eIND and the new amendment(s), and is intended to discourage the

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resubmission of the entire eIND each time there is amendment. The original links in the original 'roadmap' would be the same in this new or updated 'roadmap', but new links for the new documents in the amendment would be added (see Figures 1, 2, and 3).

The original *roadmap.pdf* files may be easily updated by Adobe's Exchange (3.0 or higher) by using the 'Replace file' command under the 'Document' menu option. This will automatically replace the old links to previously submitted sections of the IND, leaving only the task of creating the new links corresponding to the newly submitted amendment.

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**Table 1: Roadmap Information**

<b>eIND Main Table of Contents Information Where Each line is Hypertext Linked to the Appropriate Section's Table of Contents</b>					
<b>Sponsor's Serial Number*</b>	<b>Sponsor's Submission Date</b>	<b>Description of Submission</b>	<b>CD Serial Number**</b>	<b>Paper Only</b>	<b>File or Folder Name***</b>
Original Submission 000	25 Oct 1997	Clinical Protocol-Phase 1, Pre-Clinical information CMC information, CVs	CD 000.001 CD 000.002 CD 000.003		...S0000/ <i>indTOC.pdf</i>
001	12 Nov 1997	Administrative response to request for information	CD 001.001		.../S0001/ <i>indTOC.pdf</i>
002	15 Jan 1998	Revised clinical protocol	CD 002.001		.../S0002/ <i>indTOC.pdf</i>
003	28 Jan 1998	Consent form IRB approval	CD 003.001		.../S0003/ <i>indTOC.pdf</i>
004	22 Feb 1998	Revised product information, Lot release & lot release specs	CD 004.001 CD 004.002		.../S0004/ <i>indTOC.pdf</i>
005	02 Apr 1998	Adverse event report		✓	S0005
006	10 Jun 1998	Adverse event follow-up written report		✓	S0006
007	15 Aug 1998	Preclinical information Pharmacokinetics	CD 007.001 CD 007.002		.../S0007/ <i>indTOC.pdf</i>
008	01 Oct 1998	Clinical protocol-Phase 2	CD 008.001		.../S0008/ <i>indTOC.pdf</i>

\* The Sponsor's Serial Number will not necessarily be the same as the Amendment number assigned by the FDA. The S number assigned by the sponsor under the File or Folder name (column 6) should be the Sponsor's Serial Number (column 1).

\*\* The CD-ROM serial number (column 4) is the sponsor's serial number followed by a period, and then the number of CDs submitted, numbered consecutively (e.g., 004.001, 004.002 for submission serial number 004 where there were two (2) CDs submitted).

\*\*\* The file or folder name is the name of the directory or folder, or sub-directory or file to which one hypertext links from the roadmap.pdf

All eIND submissions in the pilot program should be submitted as both electronic and paper and it is encouraged that these are submitted simultaneously. We understand that under exceptional circumstances such as when a submission is equal to or less than 10 pages, portions of the eIND may be submitted as paper only as noted in the example in Table 1 above for amendments 005 and 006. An electronic version of a submission may be submitted on a diskette rather than on a CD-ROM with very small submissions (equal to or less than 10 pages).

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### **B. Readme File**

The *readme.pdf* file provides directions for installing, configuring, and navigating the submission. It should be located in the main IND folder or root directory. Each *Table of Contents* should also provide a hypertext link to the *readme.pdf* file.

### **C. Cover File**

The *cover.pdf* file provides summary information about the electronic submission. This cover letter should also be included with any a paper portion of the submission. The cover letter should include:

- Appropriate regulatory information as described in 21 CFR Part 312.
- A description of the submission.
- A description of which portions of the submission are presented only in paper, and which portions only in electronic format with accompanying paper for this pilot program.
- A description of the electronic submission including the contents of the media, their number and format, a description of the file types, and the total size of the submission (e.g., megabytes, gigabytes), (see Table 2).
- Verification that the submission is virus free with a description of the software used to check the files for viruses (see Table 3). The sponsor should state which files were scanned since some programs, by default, only scan (\*.exe) files.
- Any changes from recommendations in this guidance should be documented in the cover letter.
- Sponsor contacts for this submission (see Table 4).

**Table 2: Electronic Submission Summary**

<b>Electronic Submission Summary</b>	
Media	CD-ROM
Number	5 CDs
Format	PDF Format, Adobe Exchange version 3.0
Total Submission Size	3.42 GB

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**Table 3: Virus Verification Identification**

<b>Virus Verification</b>	
Software Name	McAfee Virus Scan 95
Version	3.01
Company Name	McAfee

**Table 4: Sponsor Contacts**

<b>Sponsor Contacts</b>			
<b>Content Section</b>	<b>Name</b>	<b>Phone</b>	<b>Pager</b>
Regulatory Affairs			
Technical			

D. FDA Forms 1571 or 1572 should be submitted as files *1571.pdf* and *1572.pdf* respectively.

E. Table of Contents

1. The Table of Contents (TOC) for each amendment is accessed from the roadmap. It contains appropriate bookmarks and hypertext links to the various files and folders contained in a given submission. This enables the reviewer to navigate more easily throughout the submission.

F. Folder and File Names

A suggested organization of files and folders is presented in Appendix A.

1. The folder and file names presented here are consistent with the outline provided in the FDA Form 1571 (Section 12), [21 CFR 312.23 (a) (1-10)] for the IND submission content (see Table 5).

2. An example of files and folders for the original submission and associated amendments is provided in Figures 1,2, and 3.

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**Table 5: Suggested Folder, File and Index Names**

<b>1571 Page 2 Item No</b>	<b>Contents of Application Description with Corresponding CFR Reference</b>	<b>Folder Name</b>	<b>File Name</b>	<b>Index Name</b>
---	Readme (textual information about the submission)	<i>na</i>	<i>readme.pdf</i>	<i>na</i>
---	Cover File (cover letter)	<i>na</i>	<i>cover.pdf</i>	<i>na</i>
1	FDA Form 1571/1572 [21 CFR 312.23(a)(1)]	<i>na</i>	<i>1571.pdf</i>	<i>na</i>
2	Table of Contents [21 CFR 312.23(a)(2)]	<i>na</i>	<i>indTOC.pdf</i>	<i>na</i>
¾	Introductory Statement & General Plan [21 CFR 312.23(a)(3)]	<i>na</i>	<i>intro.pdf</i>	<i>na</i>
5	Investigator's Brochure [21 CFR 312.23(a)(5)]	<i>na</i>	<i>ib.pdf</i>	<i>na</i>
6	Protocols <ul style="list-style-type: none"> <li>• Form FDA 1572</li> <li>• Study</li> <li>• Investigator data</li> <li>• Facilities data</li> </ul> Institutional Review Board (IRB) data [21 CFR 312.23(a)(6)]	<i>protocol</i>	<i>proTOC.pdf</i> <i>1572.pdf</i> <i>studyxxx.pdf</i> <i>invest.pdf</i> <i>facility.pdf</i> <i>irb.pdf</i>	<i>na</i>
7	Chemistry, Manufacturing & Control Data (CMC) including Environmental Assessment or Claim for Exclusion [21 CFR 312.23(a)(7)]	<i>cmc</i>	<i>cmcTOC.pdf</i>	<i>cmc.pdx</i>
8	Pharmacology and Toxicology <ul style="list-style-type: none"> <li>• Summary</li> <li>• Study Reports</li> <li>• Publications</li> </ul> [21 CFR 312.23(a)(8)]	<i>pharmtox</i>	<i>pharmTOC.pdf</i> <i>pharmsum.pdf</i> <i>studyxxx.pdf</i> <i>refno.pdf</i>	<i>pharmtox.pdx</i>
9	Previous Human Experience [21 CFR 312.23(a)(9)]	<i>prevhum</i>	<i>prevTOC.pdf</i>	<i>prevhum.pdx</i>
10	Additional Information [21 CFR 312.23(a)(10)] <ul style="list-style-type: none"> <li>• Administrative Information</li> <li>• PreIND information</li> </ul>	<i>adminfo</i> <i>preind</i>	<i>addTOC.pdf</i> <i>preTOC.pdf</i>	<i>na</i> <i>preind.pdx</i>

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### G. Organizing the subfolders of an eIND Submission

This suggested organization follows items listed on FDA Form 1571, page 2. Please note that all information is not required for each item.

**Hypertext Linking:** For all documents with a table of contents, bookmarks should be provided for each item in the document's table of contents including all tables, figures and appendices. Throughout the body of the document, providing a hypertext link to supporting references and appendices, and to tables or figures that are not located on the same page will improve the reviewer's ease of navigation and review.

**Document Information Fields:** Document Information *Title* field should include a brief description of the document and document name.

#### **1. Item 1-FDA Form**

*File and Folder Organizations:* Provide the completed form FDA 1571 in a PDF file. Name the file *1571.pdf*.

#### **2. Item 2-Table of Contents**

*File and Folder Organization:* The Table of Contents should be provided as a single PDF file. The table of contents for the initial IND should be named */S0000/indTOC.pdf* with additional submissions numbered in sequential order, followed by its corresponding table of contents, e.g., */S0001/indTOC.pdf*, */S0002/indTOC.pdf*.

*Table of Contents:* The table of contents should be provided in the form of a PDF file and list all items of the IND as listed on page 2 of Form FDA 1571. If an item is included as paper, the volumes and page numbers should be listed for that item. If the item is included in the electronic submission, the location of files should be listed by the folder name. For example, protocols are in the protocol folder. In the same way that page numbers provide a user with a road map to a document, a hypertext link should be provided from this table of contents to the corresponding table of contents for each item.

#### **3. Items 3 and 4 Introductory Statement and General Investigational Plan**

*File and Folder Organization:* The introductory statement and general investigational plan should be provided as a single PDF file, and the file be named *intro.pdf*.

#### **4. Item 5-Investigator's Brochure**

*File and Folder Organization:* The Investigators brochure should be provided as a single PDF file, and the file be named *IB.pdf*.

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### **5. Item 6-Protocols**

*File and Folder Organization:* Each protocol should be provided as a single PDF file. A single PDF file should be provided for the investigator and IRB data. The files should be placed in a folder named *protocol*.

*Table of Contents:* A table of contents should be provided for all files in this section in the form of a PDF file. In the Protocol table of contents, all documents included in the section should be listed. Hypertext links should be provided between the documents listed in the table of contents and the corresponding PDF file. The table of contents should be named *proTOC.pdf* and be placed in the *protocol* folder.

*Indexing:* An index of the full text and the Document Information Title field of all documents in this item should be provided. The index file should be named *protocol.pdx*, be placed in the *protocol* folder and associated it with the *proTOC.pdf* file. This association will automatically open the *protocol* index and make it available for searching whenever the *proTOC.pdf* file is opened.

### **6. Item 7-Chemistry, Manufacturing and Control Data (CMC)**

*File and Folder Organization:* A separate folder should be provided for the CMC portion of the submission and be named *CMC*. A table of contents for CMC documents and images should be provided within this folder as a single PDF file. This file should be named *cmcTOC.pdf*.

Within the CMC folder, separate sub-folders may need to be organized for the following submission contents: biological substance (*substan*); biological product (*product*); investigational product/formulation (*invest*); environmental assessment (*environ*); and others as appropriate.

*The Document Information Fields:* The Document Information Title field for each PDF file should contain the name “cmc” and a brief descriptor of the document, (e.g., BP for biological product, EA for environmental assessment). The name of the active ingredient or product under investigation should be listed in the Key Words field.

*Table of Contents:* The CMC table of contents should be a separate PDF file (*cmcTOC.pdf*) within the CMC folder and should list all of the documents in this section. The contents of this file will vary according to the type of product (specified, non-specified, and blood/plasma products) being submitted to CBER. The sponsor is referred to the appropriate guidance document (see below) for information on requested content.

Providing the following hypertext links, possibly in a summary document or table, can also improve the efficiency of the review: Batch numbers to stability data, biological product batch numbers to formulation composition, clinical protocol numbers to the appropriate batch numbers, formulation composition to biological substance batch numbers, stability studies to descriptions of container/closure systems, impurity profiles

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to forced degradation data, impurity profile to synthetic source of impurity, specifications to validation reports, packaging components to letters of authorization, name of chemical substances/degradents to their structures, and chemical names to chemical abstract registry numbers.

***Indexing:*** An index of the full text and the Document Information Title field of all documents in this item should be provided that is accessible using the search tools available in Acrobat Exchange. Name the index file *cmc.pdx*. Place the *cmc.pdx* file and the index fields in the *cmc* folder.

To facilitate searching the *cmc* folders and files, use Adobe Exchange to associate the *cmc.pdx* file with the *cmcTOC.pdf* file. This association will automatically open the *cmc* index and make it available for searching whenever the *cmcTOC.pdf* file is opened.

### **7. Item 8- Pharmacology and Toxicology Data**

***File and Folder Organization:*** All documents for this section should be placed in a single folder named *pharmtox*. There are three types of documents included in this section.

#### ***a. Summary***

The entire summary of the nonclinical pharmacology and toxicology section should be provided in a single PDF file. Name this file *pharmsum.pdf*.

#### ***b. Study reports***

Each study report, including all appendices, should be included as a single PDF file. The study number should be included in the name of the file. For example study 1234 can be named *1234.pdf*.

#### ***c. Publications***

Each publication should be provided in a single PDF file. The reference number should be included, preceded by *ref* for each publication. For example a publication that is reference number 12 would be *ref12.pdf*. If there is more than one reference number used, then add letters for subsequent references. For example, if publication is reference 12 and there is already a *ref12.pdf* then name the file *ref12a.pdf*.

#### ***Document Information Fields:***

##### ***a. Summary***

The document information fields for the summary file should have *pharmtox summary* in the *Title* field.

##### ***b. Study reports***

The document information field for each study report should include in the *Title* field *Study*, followed by the study report number and the type of study. Other helpful information that can be included in the title field is the species, treatment duration, dosing schedule used in the study and route of administration. For example, information for the report for study 2001, a 12 month toxicity study in dogs in which the drug was administered orally on a daily basis is as follows: study 2001, toxicity study, dog, 12 month, daily dosing, oral route

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### ***c. Publications***

The document information field for each publication file should include the Title field *reference* followed by the reference number and brief description or title.

***Table of Contents:*** A table of contents should be provided for all files in this section in the form of a PDF file. In the Pharmtox table of contents, all study reports (including study report numbers), publications and the summary document should be provided in the pharmtox section. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided. The table of contents should be named *pharmTOC.pdf* and placed in the pharmtox folder.

***Indexing:*** An index of the full text and the document information Title field of all documents in this section should be provided that is accessible using the search tools available in Acrobat Exchange. The index definition file should be named *pharmtox.pdx*. Place the pharmtox.pdx file and the index files in the *pharmtox* folder.

### **8. Item 9-Previous Human Experience**

***File and Folder Organization:*** Each document should be provided for this item as a single PDF file. All files should be placed in a single folder named *Clinical*.

***Table of Contents:*** A table of contents for all files in this section should be provided in the form of a PDF file. In the Clinical table of contents, all of the document provided in the previous human experience section should be listed. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided. The table of contents should be named *prevTOC.pdf* and place in the *prevhum* folder.

***Indexing:*** An index of the full text and the document information Title field of all documents in this section should be provided that is accessible using the search tools available in Acrobat Exchange. The index definition file should be named *prevhum.pdx*. Place the *prevhum.pdx* file and the index files in the *prevhum* folder.

### **9. Item 10-Additional Information: Administrative**

***File and Folder Organization:*** Each document should be placed in a single PDF file and be placed in a single folder named *adminfo*.

***Table of Contents:*** A table of contents for all files in this section should be provided in the form of a PDF file. In the Additional information table of contents, all of the documents provided in the Additional information section should be listed. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided. The table of contents should be named *addTOC.pdf* and be placed in the *adminfo* folder.

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### **10. Item 10-Additional Information: Pre-IND Information**

**File and Folder Organization:** Each document for this item should be provided as a single PDF file and placed in a single folder named *preind*.

***Table of Contents:*** A table of contents for all files in this section should be provided in the form of a PDF file. All of the documents provided in the preind information section should be listed. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided. The table of contents should be named *preTOC.pdf* and placed in the *preind* folder.

***Indexing:*** An index of the full text and the document information Title fields of all documents in this section should be provided that is accessible using the search tools available in Acrobat Exchange. The index definition file should be named *preind.pdx*. Place the *preind.pdx* file and the index files in the *preind* folder.

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**V. SUBMITTING ELECTRONIC APPLICATIONS TO CBER**

**A. Media**

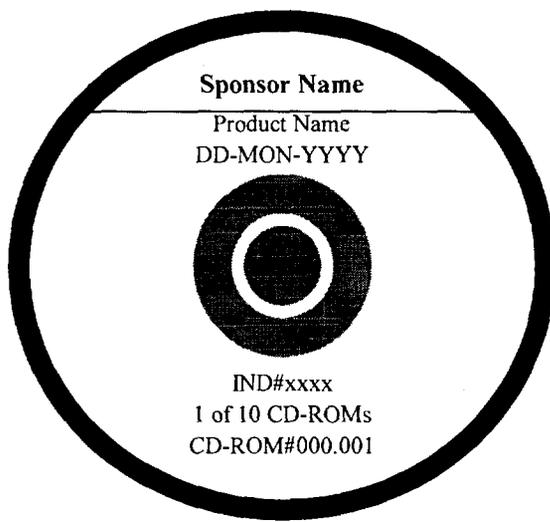
CBER requests that two copies of a eIND be submitted on CD-ROM disks in ISO 9660 format. One of these CDs will be retained by the Document Control Center (DCC) as an archival or back-up copy. More copies may be requested as needed.

**B. Media Label**

Physical labels should be attached to 3.5" Disks, CD-ROMs and CD jewel cases to provide visible identification. Each label should provide information sufficient to identify the item independent of any additional documentation. Number the CD-ROMs from 0.001 through 0.XXX for the original submission; for the first submission of additional information, number the CD-ROMs 1.001 through 1.XXX. The CD-ROMs for the second submission of additional information will be numbered as 2.001 through 2.XXX. The following information should also be included on the label:

1. Sponsor or manufacturing name and license number, if available
2. Regulatory ID number
3. Application type
4. Document date in the format of DD-MMM-YYYY (e.g. 01-Jan-1998)
5. Media series as 1 of 10 for a submission set of ten CD-ROMs, or 1 of 3 diskettes for a submission set of three diskettes.
6. Serial number plus number of CD-ROMs, (e.g., 000.001 is serial number 000, CD-ROM number 1; 000.002 is serial number 000, CD-ROM number 2), per each copy

Sample Label of a CD-ROM for an Original eIND Submission



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### C. Packaging and Shipping

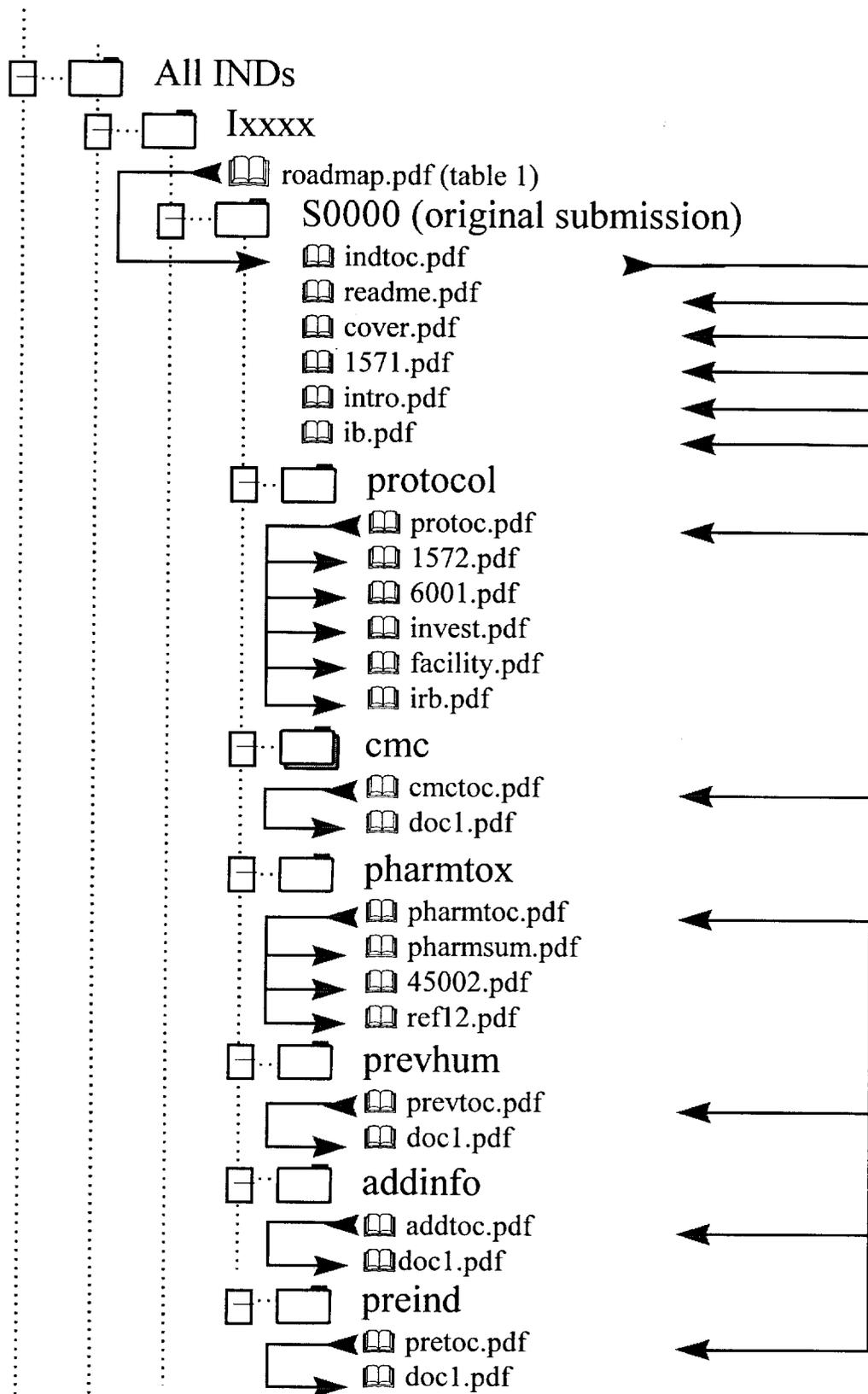
Shipping differs for media and paper documents. CDs should be packaged carefully to ensure that they arrive in a usable condition. Particularly vulnerable are diskettes and jewel cases shipped in envelopes without bubble type protective material or stiff backing. The use of a “jiffy”-type bag by itself to ship media does not provide adequate protection for shipping electronic media.

#### 1. Delivery Address

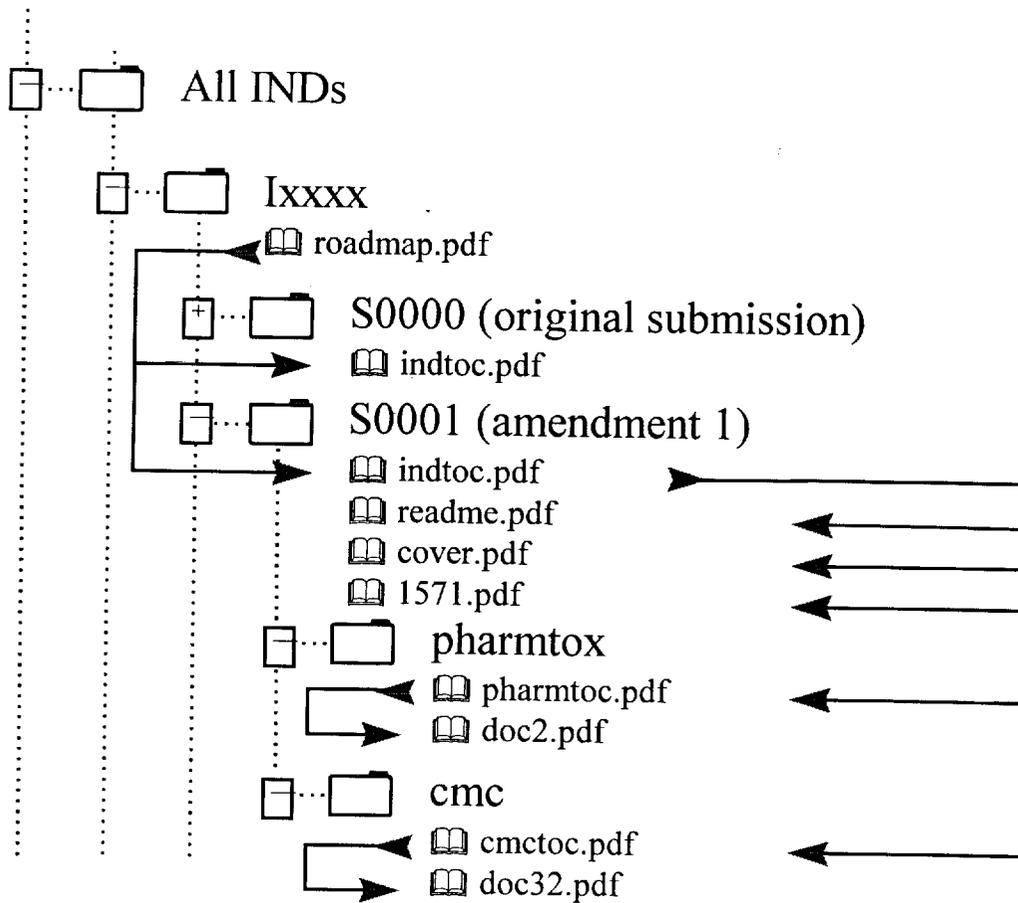
Center for Biologics Evaluation and Research  
Document Control Center, HFM-99  
Attn: (Insert “Responsible Application Division“)  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

FIGURES

Figure 1: File and Folder Organization for Original Submission

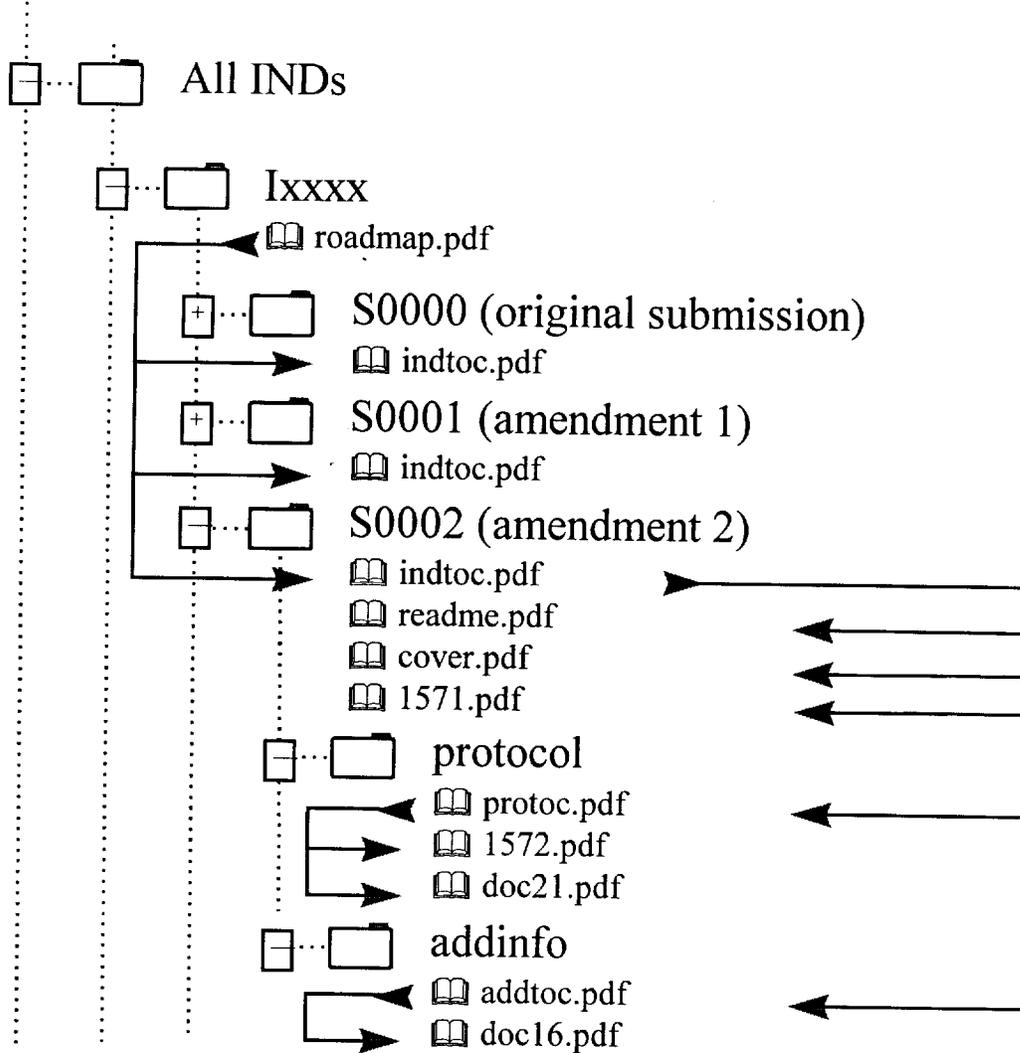


**Figure 2: File and Folder Organization with the addition of Amendment 1**



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**Figure 3: File and Folder Organization with the addition of Amendment 2**



## **Appendix A: Acronyms and Abbreviations**

BLA	Biologics License Application
BMP	Windows Bitmap File
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CD-ROM	Compact Disk - Read Only Memory
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing Controls
CRF	Case Report Forms
CRT	Case Report Tabulations
CSO	Consumer Safety Officer
DCC	Document Control Center
DPI	Dots Per Inch
DSP	Desktop Standardization Project
eIND	Electronic Investigational New Drug
ELA	Establishment License Application
FDA	Food and Drug Administration
FR	Federal Register
GB	Gigabyte
HPLC	High Performance Liquid Chromatograph
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug

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ISO	International Standards Organization
MB	Megabyte
NDA	New Drug Application
PDF	Portable Document Format
PDX	Portable Document Index
PDUFA	Prescription Drug User Fee Act
PICT	Macintosh Vector File
PLA	Product License Application
RGB	Red, Blue, Green,
REF	Reference
SAS	Statistical Analysis System
TIFF	Tagged Image File Format
TOC	Table of Contents
WWW	World Wide Web