

# 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

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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should be submitted within 60 days of publication in the *Federal Register* notice announcing the availability of the draft guidance.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 Dr., 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*.

Additional copies of this draft guidance document are available from the office of Communication, Training and Manufacturers Assistance (HFM - 40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by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

For questions on the content of the draft document contact Mary Buesing M.D., Office of the Center Director CBER, HFM-4, 1401 Rockville Pike, Rockville, MD 20852, or e-mail [buesing@cber.fda.gov](mailto:buesing@cber.fda.gov) or phone 301-594-5570.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
May 1998

# Table of Contents

Note: Page numbering may vary for documents distributed electronically.

I. Introduction.....	01
II. Electronic File Formats for Submissions.....	02
A. General Overview .....	02
B. Application Submission Milestones.....	03
C. Organizing The Application Files.....	04
III. Application Form Item Guidance.....	08
A. Item 1: Index.....	08
B. Item 2: Labeling .....	10
C. Item 3: Summary .....	13
D. Item 4: Chemistry Section.....	14
A. Chemistry, Manufacturing, and Controls Information.....	14
B. Samples - Lot Release Protocols.....	17
C. Methods Validation Package.....	18
E. Item 5: Nonclinical Pharmacology and Toxicology Section.....	19
F. Item 6: Human Pharmacokinetics And Bioavailability Section.....	21
G. Item 7: Clinical Microbiology.....	23
H. Item 8: Clinical Data Section.....	24
I. Item 9: Safety Update Report.....	26
J. Item 10: Statistical Section.....	28
K. Item 11: Case Report Tabulations.....	28
L. Item 12: Case Report Forms.....	28
M. Item 13: Patent Information .....	29

**Draft- Not For Implementation**

**M. Item 13: Patent Information .....29**  
**N. Item 14: Patent Certification .....30**  
**O. Item 15: Establishment Description..... 31**  
**P. Item 16: Debarment Certification.....33**  
**Q. Item 17: Field Copy Certification..... 34**  
**R. Item 18: User Fee Cover Sheet.....35**

**TABLES**

**Table 1. The *roadmap.pdf* reference table with two additions.....06**  
**Table 2. Electronic vs. Paper portions of a BLA..... 06**  
**Table 3. Summary Information for an electronic BLA..... 07**  
**Table 4. Virus Verification ..... 07**  
**Table 5. Sponsor’s Contacts..... 07**

**APPENDICES**

**APPENDIX A: File and Folder Structure..... 36**  
**APPENDIX B: Submitting Electronic Applications to CBER ..... 40**  
**APPENDIX C: CBER Contacts.. ..... 42**

## GUIDANCE FOR INDUSTRY <sup>1</sup>

# Electronic Submissions of a Biologics License Application (BLA) or Produce License Application (PLA)/Establishment License Application (ELA) to the Center for Biologics Evaluation and Research

### I. INTRODUCTION

There is increasing demand from industry for automation of the regulatory review process. This demand is being driven by a variety of factors, including: the need to expedite the availability of new drugs and biologics to the public; the need for standards/consistency in the review process; initiatives under the Prescription Drug User Fee Act (PDUFA, 1992, 1997); the Agency's Submission Management and Review Tracking (SMART) Program (1994); Reinventing Government (ReGO) Initiatives; the Paperwork Reduction Act of 1995; and the Electronic Freedom of Information Act (eFOIA, 1996).

The Food and Drug Administration's increasing paper burden (storage, routing, retrieval and filing) further necessitates a move toward electronic submissions. The Electronic Records: Electronic Signatures Regulation [21 CFR Part 11], which became effective 20 August 1997, permits the Agency to accept documents or portions of regulatory applications in electronic format—without paper. The documents which the Agency is prepared to accept have been identified by each center on an accompanying public docket 92S-0251 (<http://www.fda.gov/dockets/dockets.htm>). This guidance document is intended to provide details on the voluntary submission of electronic documents for a Biologics License Application (BLA), and a Product License Application/Establishment License Application (PLA/ELA). Throughout this guidance document both applications will be referred to as Computer-Assisted License Applications (CALA).

Over the past several years, the experience of the Center for Biologics Evaluation and Research (CBER) with electronic submissions has increased significantly. Most of these electronic submissions have employed commercial off-the-shelf (COTS) software applications, and each submission has been unique because of individual modifications ("customization") to these COTS products. Subsequently, some of these customized CALAs have created conflicts with other software on reviewers' computers. This in turn has led to delays in the review process. Archiving

---

<sup>1</sup> This guidance document represents FDA's current thinking on electronic Biologics License Applications and product/establishment License Applications. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternate approach may be used if such approach satisfies the requirements of the applicable statute, regulation, or both. Please note that the FDA's use of specific products does not constitute an endorsement of those products.

## Draft- Not For Implementation

other software on reviewers' computers. This in turn has led to delays in the review process. Archiving and retrieval dilemmas have also been confounded by a lack of standard formats, and have prevented subsequent and easy access by reviewers and FOIA staff. In addition, reviewers have not been able to apply lessons learned and experience from one submission to the next as no two have been alike. CBER has decided it will no longer accept customized submissions, software, or hardware. This document describes the electronic formats that CBER is currently able to support for review and archive. An acceptable alternative submission format is paper. FDA may refuse to file an application or supplement under 21 CFR 601.2 if either paper or electronic portions are illegible, un-interpretable or otherwise clearly inadequate. This guidance document is intended to provide a degree of uniformity to future electronically submitted applications. Adherence to the recommendations outlined in this guidance document should help to assure that subsequent electronic submissions will meet FDA acceptance criteria, be easily loaded on to the center networks, and be reviewable within specified time frames using our standard desktop tools.

Regulations in 21 CFR 601.2 provide the general requirements for submitting marketing applications to CBER. Currently, the FDA Form 356h (<http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>) outlines the components for the submission of a BLA for specified biotechnology products and is described in 21 CFR 601.2 (c). CBER will eventually be using the FDA Form 356h for all biologic products subject to licensure.

This guidance outlines the details of submitting a BLA (for specified biotech products) or PLA/ELA (for non-specified biotech products) in electronic format, and supersedes CBER's previous guidance, *Computer Assisted Product License Applications (CAPLA) Guidance Manual* (61FR11644; March 21, 1996). Consult CBER's *Guidance for Industry: Electronic Submission of Case Report Forms, Case Report Tabulations, and Clinical Data to the Center for Biologics Evaluation and Research*, May 1998, for related information.

The FDA Form 356h is divided into nineteen items (e.g., labeling, chemistry). For an electronically submitted BLA the content of the application should follow the content described in FDA Form 356h and a copy of the completed form should be embedded in the submission as a separate portable document format (PDF) file. For an electronically submitted PLA/ELA application the electronic content should follow the content of the 356h. To address the two current license applications, FDA Form 3210 should be completed and embedded for establishment licenses and, if appropriate, the respective PLA application (e.g., FDA Form 3212 for vaccine PLAs) should be embedded in a PDF file.

## II. ELECTRONIC FILE FORMATS FOR SUBMISSIONS

### A. General Overview

CBER recommends that the electronic documents (text, tables, and images) be provided in Adobe Acrobat's Portable Document Format (PDF), and data in SAS file format. CBER has decided it will not be able to accept customized submissions, software, or hardware. This

## **Draft- Not For Implementation**

document describes those electronic formats that CBER is currently able to support for review and archive. An acceptable alternative submission format is paper.

CBER recommends that the electronic archival copy should be an identical replica of the electronic review copy. This is similar to the present receipt of paper copies which are exact reproductions of each other for all three submitted copies of license applications.

To facilitate locating information submitted between paper and electronic records, CBER encourages the applicant to use printouts of the actual PDF document when making paper filing instead of printing from the word processing software used to create the submission. This will ensure that the paper and viewed electronic documents are identical in appearance and in content. See *Guidance for Industry: Electronic Submissions of Case Report Forms (CRFs), Case Report Tabulations (CRTs) and Data to the Center for Biologics Evaluation and Research, May 1998* for specific guidance on PDF page formatting and file preparation.

Paper submitted as a part of an application should be submitted simultaneously with submitted electronic components of the application.

As outlined in the guidance (*Archiving Submissions in Electronic Format--NDAs*, (62FR49695; September 23, 1997) from the Center for Drugs Evaluation and Research (CDER) electronic review PDF submissions should be characterized by the following:

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
3. provide the ability to include a well-structured index/roadmap and the ability to easily navigate through the submission
4. offer the ability to electronically copy text and images; and
5. serve as a substitute for paper copies.

Currently, CBER is not able to accept any PDF files which would require a "plug-in," sponsor-supplied or otherwise, to Adobe Exchange/Reader in order for the file to be reviewed. CBER is also not able to accept audio or video clips as part of the PDF submission.

To produce the highest quality electronic document, 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.

### **B. Application Submission Milestones**

Timely communications with the appropriate CBER office prior to submitting an electronic application is essential for expeditious review.

## Draft- Not For Implementation

Ideally, eight to ten months before the actual submission date, sponsors should confer with CBER staff about the structure and content of any planned electronic submissions.

Four to six months before the electronic submission, sponsors should arrange to demonstrate the structure, content and navigational capability of the planned submission for CBER staff.

Thirty days before submission, sponsors should provide a mock-up version of the electronic application for testing on CBER's computer networks and a letter confirming the planned submission date.

On the day of submission, sponsors should provide all of the certifications and information requested in the *cover.pdf* file described below.

### C. Organizing the Application Files

The structure and content of electronic submissions to CBER should be based on the FDA Form 356h. The folder and file naming conventions and organization are intended to reflect the information typically contained in the FDA Form 356h (See Appendix A.)

Information submitted to CBER may be reviewed in its entirety on a computer network or in sections on individual desktop personal computers (pc). Moreover, additional electronic or paper information submitted in support of the original application should be added to the existing network and distributed to appropriate reviewers. Consequently, it is imperative that a reliable mechanism be employed for locating all of the sections of the application. The root directory of an electronic application should contain the following files to orient and direct the reviewer to the original submission and to any and all subsequent information added to the application:

1. A *roadmap.pdf* file (See Table 1 below and the folder diagram in Appendix A.)

CBER suggests that a *roadmap.pdf* file be used to establish hypertext links to the application's main table of contents (or to items in the FDA Form 356h), and to the respective folders and files of the submission. This "roadmap" or "home page" should be updated and resubmitted as additional information is added to the application. (An example of one possible roadmap format is shown in Table 1.)

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

## Draft- Not For Implementation

In addition to providing a navigable guide to the application, the *roadmap.pdf* file should include the sponsor's submission date in the DD-*MMM*-*YYYY* format (e.g., 01-Jan-1997). The contents of the original submission, and of subsequent submissions, should be briefly described in a *roadmap.pdf* table, and the location of these files and folders on the submitted CD-ROMs should be indicated in the *roadmap.pdf*. Where portions of the submission have been submitted only in paper, they should be included in the roadmap and table of contents and tagged as "paper only."

### 2. A *readme.pdf* file

This file should contain directions for installing, configuring, and navigating the submission. It should be located in the root folder for easy identification. The main table of contents of the submission should also provide a hypertext link to the *readme.pdf* file.

### 3. A *cover.pdf* file

A *cover.pdf* file hypertext linked to the main table of contents and to the *roadmap.pdf* should contain the following information for each submission: a table summarizing which portions of the submission are in paper vs. electronic format (Table 2); a table summarizing the submission size and format (Table 3); a table of virus verification information (Table 4); a table of names of sponsors points of contact for the application (Table 5); and a completed FDA Form 356h for specified biotechnology products embedded in a PDF file. This information, including the three tables, should be updated with each new addition to the application. Examples of these tables follow.

**Draft- Not For Implementation**

**Table 1: The *roadmap.pdf* reference table with two additions**

<b>BLA submission</b>	<b>Submission Date</b>	<b>Submission Content</b>	<b>CD-ROM #</b>	<b>HyperText Link to:</b>
original	DD- <b>MMM</b> - <b>YYYY</b>	FDA Form 356h content, readme.pdf, cover.pdf, imageQA.pdf, index.pdf, summary Labeling CMC PharmTox Cpbio Clinical Update Stats CRTs CRFs items13-19	0.001 0.001 0.001 0.002 0.003-0.004 0.005 0.006 0.007 0.007 0.008 0.009-0.010 0.011 0.012	original blatoc.pdf
add. Info.	DD- <b>MMM</b> - <b>YYYY</b>	new readme.pdf, new cover.pdf, Labeling CMC	1.001 1.002 1.003	updated blatoc.pdf
add. Info.	DD- <b>MMM</b> - <b>YYYY</b>	new readme.pdf, new cover.pdf CRFs	2.001 2.002	updated blatoc.pdf

**Table 2: Electronic vs. Paper portions of a BLA**

<b>Electronic vs Paper Portions of the Application</b>			
<b>Item</b>	<b>Description</b>	<b>Paper</b>	<b>Electronic</b>
1	Index	X	X
2	Labeling	X	
3	Summary	X	
4	Chemistry Section		X
5	Nonclinical Pharmacology and Toxicology	X	
6	Human Pharmacokinetics and Bioavailability section	X	

**Draft- Not For Implementation**

**Table 3 : Summary Information for an electronic BLA**

<b>Electronic Submission Summary</b>	
Media	CD-ROM
Number	5 CDs
Format	PDF Format, Adobe Exchange version 3.0
Total Submission Size	3.5 GB

**Table 4: Virus verification**

<b>Virus Verification</b>	
Software Name	
Version	
Company Name	

**Table 5 : Sponsor's contacts**

<b>Sponsor Contacts</b>				
<b>Content Section</b>	<b>Name</b>	<b>Phone</b>	<b>E-mail</b>	<b>Beeper</b>
Regulatory affairs				
Technical				
Other				

### III. APPLICATION FORM ITEM GUIDANCE

The following nineteen items are sections of page two of the FDA Form 356h.

#### A. Item 1: Index

##### 1. Regulatory Reference

This is item one on page two of FDA Form 356h.

In order to facilitate the review, a main table of contents section is critical for locating information across various media and over time as additional information is submitted. Moreover, during an interim period in which both paper and electronic applications are being received, additional record keeping obligations for CBER are compounded. The following suggestions are attempts to improve communications between CBER and industry, and to ensure that all of the application information is readily available for review.

##### 2. File and Folder Organization

All files should be placed in a main folder using the submission number (e.g., B000000.000) as the name of that folder. Amendments to the original application should be labeled B000000.001 through B000000.999. Since the BLA number is not assigned until the submission is received by CBER, it will be entered post-receipt by our Document Control Center/Information Technology (DCC/IT) staff. In the interim, use the Investigational New Drug (IND) number for the initial submission folder name.

##### 3. Document Information Fields

In the *Title* fields of the newly created PDF documents, add *roadmap*, *readme*, and *cover* to identify the respective PDF files. The submission dates (DD-MMM-YYYY) should be added to the *Title* fields.

##### 4. Table of Contents

The *roadmap.pdf* file should employ hypertext links to directly connect to the submission's main table of contents. The main table of contents should be a PDF file and should be named, *blatoc.pdf*. The *blatoc.pdf* file should provide hypertext links to all of the submitted sections of the application. Usually, these hypertext links will be from the main table of contents to the tables of contents of the major portions of the application.

## Draft- Not For Implementation

### 5. Hypertext Links and Bookmarks

These links should be created between the *roadmap.pdf* and the table of contents of each submission.

### 6. Indexing

No indexing is needed for the Index subsection.

## Draft- Not For Implementation

### B. Item 2: Labeling

#### 1. Regulatory Reference

This is item two on page two of FDA Form 356h [CFR 601.2 (c)(1)(viii)]. The content and format of the labeling text is described in 21 CFR 610.60-65, 201.57; specific information regarding blood labels may be found in 21 CFR 606.120-122. Information on licensed devices such as *in vitro* diagnostics may be found in 21 CFR 610.60, 660.28-55, and 809.10.

#### 2. File and Folder Organization

A separate folder for the labeling section of the electronic submission should be provided. It should be named *labeling*. A table of contents for all of the submitted label text and images should be provided as a single PDF file (*labeltoc.pdf*) with hypertext links to individual subfolders and subfolder tables of contents.

When multiple products are submitted under the same BLA, separate product subfolders should be created. For example, a company submitting several blood products under one BLA (e.g., plasma, platelets), may find it useful to create separate subfolders for these products.

Under each product subfolder, additional subfolders may be created for the following label types, if applicable: shipping (*ship*), template (*tmpl*), container (*cont*), blister pack (*blst*), circular or package insert (*circ*), package labels (*pack*), diluent (*dilt*), carton (*crtn*), packer (*pckr*), consistency lot (*cons*), and other (*othr*). A table of contents PDF file for each product subfolder should be produced. Appropriate and active bookmarks should be provided for each subfolder, and hypertext links to the label subfolders from the table of contents, *labeltoc.pdf*.

For multiple label types and revisions (i.e., final and drafts), each label type should be numbered with a four digit suffix to the file name. For example, two different package label files should be labeled as *pack0100.pdf* and *pack0200.pdf*. Revisions to *pack0100.pdf* and *pack0200.pdf* should be designated in chronological order as, *pack0101.pdf* and *pack0201.pdf*. A completed copy of FDA Form 2567 should be numbered, *Transmittal of Labels and Circulars*, in each of the above file types submitted under a single BLA.

#### 3. Document Information Fields

The Document Information Title field for each PDF file should contain the BLA number, a description of the label type (e.g., shipping, package, circular, etc.), the product name, and whether it is a 'final completed label' or a 'new draft label.' The label

## Draft- Not For Implementation

number should also be listed in the Title field and in the Key Words field. The date should be included in a DD-MMM-YYYY format.

### 4. Table of Contents

The Label table of contents should be a separate PDF file (*labeltoc.pdf*) within the Label folder. If any 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 the file(s) should be listed by the file/folder name.

### 5. Hypertext Linking and Bookmarks

For the table of contents, hypertext links to each item listed in the table of contents, including any product subfolders, should be provided. Active (i.e., functional) bookmarks should be provided for major sections of the table of contents.

For all subfolders with a separate table of contents file, provide hypertext links to each separate file in the subfolder. Provide active bookmarks for major sections of the table of contents.

For all documents, hypertext links should be provided to supporting references and appendices, and to table or figures that are not located on the same page. This will improve the ease of navigation through the documents and files and facilitate the overall review process.

### 6. Indexing

No indexing is necessary.

### 7. Additional Guidance

If various layouts and small fonts are used in the final printed package inserts, they may be difficult to read, print out, copy and compare. To avoid this problem, labeling text should be provided in a standard sized document (8.5 x 11 inches) with fonts sizes of 12 points or greater, in portrait orientation, and without column formatting. Because PDF documents cannot be easily edited or compared electronically, labeling text should also be provided in a word processing format as well as in PDF. The PDF file version should be supplied in a columnar or “tiled” format representative of the actual appearance of the label.

The appropriate review division should be consulted prior to deciding on the word processor format and the frequency of supplying revisions in electronic format. Because

**Draft- Not For Implementation**

the labeling text should be used as the reference for labeling content, a letter should certify that the labeling text and the final printed package insert are identical in content, including: text, bolding, graphics and tables.

## Draft- Not For Implementation

### C. Item 3: Summary

#### 1. Regulatory Reference

This is item three on page two of FDA Form 356h [CFR 601.2].

#### 2. File and Folder Organization

In a folder named *Summary*, a separate PDF file should be provided for the summary section of the electronic submission. A table of contents with appropriate bookmarks should be included in this PDF file. This file should be named *summary.pdf*.

#### 3. Document Information Fields

The PDF file's Document Information Title field should contain the word "summary."

#### 4. Table of Contents

A separate summary table of contents file is not needed.

#### 5. Hypertext Linking and Bookmarks

Hypertext links between the *summary.pdf* file and the main table of contents (*blatoc.pdf*) should be provided.

The *summary.pdf* file should contain hypertext links to the individual summary sections (e.g., cmc, clinical data, etc.) of the submission, as appropriate.

#### 6. Indexing

No indexing is necessary.

**D. Item 4: Chemistry Section**

**Item 4A: Chemistry, Manufacturing, and Controls Information**

**1. Regulatory Reference**

This is item four on page two of FDA Form 356h [21 CFR 601.2].

**2. File and Folder Organization**

A separate folder for the CMC portion of the submission should be provided. It should be named *CMC*. A table of contents for CMC documents and images should be provided within this folder as a single PDF file.

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

**3. Document Information Fields**

For documents dealing with a biological substance, *BS* should be included in the document information Title field, the name of the active ingredient, and a brief description of the document. For documents dealing with a biological product, *BP* should be included in the document information Title field, the name of the product, and a brief description of the document. For documents dealing with an environmental assessment, *EA* should be included in the document information Title field, the name of the product, and a brief description of the document. For documents dealing with batch numbers, *BA* should be included in the document information Title field, the name of the product, and the batch number.

**4. Table of Contents**

The CMC table of contents (*cmctoc.pdf*) 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.

**5. Hypertext Linking and Bookmarks**

## Draft- Not For Implementation

All documents with a table of contents should provide bookmarks for each heading in the document's table of contents, including all tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, and tables or figures that are not located on the same page.

Providing the following hypertext links, or bookmarks in the batch records section should 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 to forced degradation data; impurity profiles to synthetic source of impurity; specifications to validation reports; packaging components to letters of authorization; names of chemical substances/degradents to their structures; and chemical names to chemical abstract registry numbers.

### 6. 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. Additional Guidance

Appropriate content folder and file names for specified products may be found in *Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1994*.

For non-specified biotech products such as autologous somatic cells see *Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information Establishment Description for Autologous Somatic Cell Therapy Products, January 1997* (62 FR 1460).

For plasma- and serum-derived products see *Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological products or Animal Plasma or Serum-Derived Products, (draft), December 1997* (63 FR 3145).

**Draft- Not For Implementation**

For recombinant and monoclonal products see *Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use*, August 1996 (61 FR 56243).

**Draft- Not For Implementation**

**Item 4B: Samples - Lot Release Protocols**

See the *Guidance for Industry: Electronic Submission of Lot Release Protocols to CBER*, May 1998.

## Draft- Not For Implementation

### Item 4C: Methods Validation Package

#### 1. Regulatory Reference

This is item four on page two of FDA Form 356h [21 601.2].

#### 2. File and Folder Organization

A separate PDF file containing descriptive information about proposed regulatory specifications should be provided for the product; methods of analysis; supporting data for accuracy, specificity, precision and robustness; and the results of analytical tests on each sample. This file should be named *methods.pdf* and placed in the *cmc* folder.

#### 3. Document Information Fields

The Document Information Title field for the *methods.pdf* file should contain the words, "methods validation." The name of the active ingredient or biologic substance under investigation should be listed in the Key Words field.

#### 4. Table of Contents

The *CMC* table of contents should contain a listing and bookmarks for the *methods.pdf* files.

#### 5. Hypertext Linking and Bookmarks

Hypertext links should be provided to supporting references and appendices, and to tables or figures that are not located on the same page. This will improve the ease of navigation through the documents and files and facilitate the overall review process.

#### 6. Indexing

No additional indexing is needed.

## E. Item 5: Nonclinical Pharmacology and Toxicology Section

### 1. Regulatory Reference

This is item five on page two of FDA Form 356h [21 CFR 601.2].

### 2. File and Folder Organization

A separate folder, named *pharmtox*, for the pharmacology/toxicology sections of the submission should be provided. A table of contents for *pharmtox* documents should be provided in this folder as a single PDF file and this file should be named *pharmttoc.pdf*.

An overall summary of the *pharmtox* section should also be provided as a separate PDF file (e.g., *pharmsum.pdf*).

Study reports should be provided as separate PDF files. The study number or study name should be included in the file name. For example, study 1234 would be named *1234.pdf*.

Published references should be provided as single PDF files. Include the reference number, preceded by *ref* for each publication file name. For example, a publication that is reference number 5 will become PDF file *ref5.pdf*. References should be listed alphabetically by first authors.

Within the *pharmtox* folder separate PDF files may need to be organized for the following submission contents, if appropriate: toxicity, pharmacology, pharmacokinetics, dosimetry (for radiolabeled studies), statements of compliance with GLP for each study, an integrated summary for all preclinical studies, and a glossary of abbreviated terms.

### 3. Document Information Fields

The integrated summary should be identified in the Document Information Title Field as *pharmtox summary*.

The word *study* should be included in the Title field, followed by the study report number and the type of study report (e.g., study 9001, mutagenicity).

The Document Information Title field for each publication or reference PDF file should be designated as *reference* and contain the reference number and a brief description or title.

## Draft- Not For Implementation

### 4. Table of Contents

The *pharmtox* table of contents should list all study reports, publications, and the summary document provided in the *pharmtox* folder. The table of contents should contain bookmarks to major headings and sections of the submission.

### 5. Hypertext Linking and Bookmarks

All documents with a table of contents should provide bookmarks for each item in the document's table of contents, including tables, figures, and appendices. Hypertext links should be provided between the documents listed in the table of contents and the corresponding PDF files.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables or figure that are not located on the same page.

The summary document, *pharmsum.pdf*, should provide a hypertext link between each reference to a data summary table or figure supporting a conclusion and the corresponding data table or figure (whether located in a study report or elsewhere).

### 6. Indexing

An index of the full text, and the Document Information Title fields of all documents should be provided. The index file should be named *pharmtox.pdx* and placed in the *pharmtox* folder.

To facilitate searching the *pharmtox* folder and files, use Adobe Exchange to associate the *pharmtox.pdx* file with the table of contents (*pharmtoc.pdf*) file. This will automatically open the *pharmtox* index and make it available for searching whenever the *pharmtoc.pdf* file is opened.

## Draft- Not For Implementation

### F. Item 6: Human Pharmacokinetics and Bioavailability Section

#### 1. Regulatory Reference

This is item six on page two of FDA Form 356h [21 CFR 601.2].

#### 2. File and Folder Organization

A separate folder should be provided for the Pharm/Bio portion of the submission and be named *cpbio*. A table of contents for pharmacokinetics and bioavailability documents should be provided in this folder as a single PDF file and named *cpbiotoc.pdf*. A summary of the pharmacokinetics and bioavailability section should also be provided as a separate PDF file (*cpbiosum.pdf*). The *cpbio* folder should contain the following subfolders:

A *PkPd* folder for information related to pharmacokinetics, pharmacodynamics, bioavailability, and any subpopulation studies. Each study should be submitted as a separate PDF file. Animal studies may be placed in one PDF file as they often constitute one or two paragraphs per study. If biological interactions with other compounds, or *in vitro* information is appropriate, include it in this folder.

A comparability folder (*compare*) should contain studies related to comparisons of different formulations of the biologic in determining safety and efficacy.

An assay folder (*assay*) should contain assay descriptions and their validation reports.

Publications should be included in a folder (*pubs*) to support the clinical pharmacology and bioavailability data of the BLA or PLA.

#### 3. Document Information Fields

The Document Information Title field for each PDF file should contain a brief description of the document, (e.g., *assay*, *pub*) and the name of the active ingredient or biological substance.

For the section summary, *summary* should be included in the Document Information Title Field. Study Reports should include the word *study* in the Title Field followed by the study report number and the type of study report (e.g., study 9001, *PkPd*). For publications, the word *pub* should be included in the Title Field followed by the publication number and a brief description or title.

#### 4. Table of Contents

Hypertext links should be provided from the table of contents (*cpbtoc.pdf*) to the corresponding table of contents for each subfolder of the PharmBio submission as appropriate.

#### 5. Hypertext Linking and Bookmarks

All documents with a table of contents should provide bookmarks for each item in the document's table of contents, including tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, publications, appendices, tables or figure that are not located on the same page.

The summary document should provide a hypertext link between each publication to a data summary table or figure supporting a conclusion and the corresponding data table or figure (whether located in a study report or elsewhere).

#### 6. 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 Adobe Exchange. The index definition should be named *cpbio.pdx* and placed in the *cpbio* folder.

To facilitate searching the *cpbio* folders and files, Adobe Exchange should be used to associate the *clphbio.pdx* file with the *cpbiotoc.pdf* file. This should automatically open the *cpbio* index and make it available for searching whenever the *cpbiotoc.pdf* file is opened.

**Draft- Not For Implementation**

**G. Item 7: Clinical Microbiology**

If relevant to the CALA, this information is usually supplied as a part of the CMC submission and not as a distinct line item.

## H. Item 8: Clinical Data Section

### 1. Regulatory Reference

This is item eight on page two of FDA Form 356h [21 CFR 601.2]. Additional information on the content of this section can be found in the ICH E3, "Structure and Content of Clinical Study Reports" (61FR37320; July 17, 1996, available on-line at: <http://www.ifpma.org/ich5e.html>).

### 2. File and Folder Organization

A separate *clinical* folder for the clinical data section should be provided. A table of contents for each study protocol should be provided within this folder as a single PDF file with hypertext links to the individual study files. This file should be named, *clintoc.pdf*.

Within the clinical data folder, individual clinical studies should be provided as separate PDF folders. A single PDF file should be provided for each document. An integrated summary of safety (ISS) and an integrated summary of efficacy (ISE) should also be provided as separate PDF files. (Note that all case report tabulations (CRT) and case report forms (CRF) should be placed under items 11 and 12 of FDA Form 356h, respectively.)

### 3. Document Information Fields

The Document Information Title field for each PDF file should include a brief description of the document. Specifically, all study reports should include the word *study*, and study number as a description (e.g., *study 9001*). Publications should include the reference number. The integrated summaries of safety and efficacy should contain the respective descriptions, *ISS* and *ISE*.

### 4. Table of Contents

The clinical data table of contents should be a separate PDF file within the *clinical* folder. The table of contents should list all study by indication, formulation, population (e.g., adult, pediatric), and type of trial (e.g., controlled, open label), as appropriate. All other documents in the clinical section should be listed. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided.

### 5. Hypertext Linking and Bookmarks

## Draft- Not For Implementation

All documents with a table of contents should provide bookmarks for each item in the document's table of contents, including tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables or figure that are not located on the same page.

The summary document should provide a hypertext link between each reference to a data summary table or figure supporting a conclusion and the corresponding data table or figure (whether located in a study report or elsewhere).

For study reports, a bookmark to the appropriate case report tabulations that are found in the domain and profile folder should be provided. This bookmark may consist of a single link that would take the reviewer to the place in the domain or profile table of contents where the study's case report tabulations are listed, or to the single file that contains the appropriate domain or patient profiles. A similar bookmark should be provided to the appropriate case report forms.

### 6. 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 Adobe Exchange. The index file should be named *clinical.pdx* and be placed in the *clinical* folder.

To facilitate searching the *clinical* folders and files, Adobe Exchange should be used to associate the *clinical.pdx* file with the *clintoc.pdf* file. This will automatically open the *clinical* index and make it available for searching whenever the *clintoc.pdf* file is opened.

## I. Item 9: Safety Update Report

### 1. Regulatory Reference

This is item nine on page two of FDA Form 356h [21 CFR 601.2].

### 2. File and Folder Organization

A safety update folder (*update*) for all submitted safety update reports should be provided. A table of contents PDF file should be included in this folder (*updattoc.pdf*). Individual safety update reports should be submitted as PDF files and should be numbered chronologically (e.g., *upd000.pdf*, *upd001.pdf*). Safety update reports should contain new information affecting statements of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

All of the case report forms (CRFs) for each patient who died or who failed to complete a study due to an adverse event—as per item 12—should be included in the safety update files.

### 3. Document Information Fields

The Document Information Title and Key Words fields for each PDF file should contain the words, *safety update report*.

### 4. Table of Contents

The Safety Update Reports table of contents should be a separate PDF file within the Safety Update folder. Hypertext links between the documents listed in the table of contents and the corresponding PDF file should be provided.

### 5. Hypertext Linking and Bookmarks

All documents with a table of contents should provide bookmarks for each item in the document's table of contents, including tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables or figures that are not located on the same page.

## 6. 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 Adobe Exchange. The index definition file should be named *update.pdx* and placed in the *update* folder.

To facilitate searching the *update* folders and files, Adobe Exchange should be used to associate the *update.pdx* file with the *updattoc.pdf* file. This will automatically open the *clinical* index and make it available for searching whenever the *updattoc.pdf* file is opened.

**Draft- Not For Implementation**

**J. Item 10: Statistical Section**

**K. Item 11: Case Report Tabulations**

**L. Item 12: Case Report Forms**

For details on submitting these three items refer to the *Guidance for Industry: Electronic Submission of Case Report Forms, Case Report Tabulations, and Clinical Data to CBER*, May 1998.

**M. Item 13: Patent Information**

**1. Regulatory Reference**

This is item thirteen on page two of FDA Form 356h [21 U.S.C. 355 (b) (2) or (j) (2) (A)].

**2. File and Directory Organization**

The patent information should be embedded in a PDF file and labeled *patinfo.pdf*.

**3. Document Information Fields**

The Document Information Title field for the *patinfo.pdf* file should contain the words, "patent information."

**4. Table of Contents**

Not applicable.

**5. Hypertext Linking and Bookmarks**

Not applicable.

**6. Indexing**

Not applicable.

## **Draft- Not For Implementation**

### **N. Item 14: Patent Certification**

#### **1. Regulatory Reference**

This is item fourteen on page two of FDA Form 356h [21 U.S.C. 355 (b) (2) or (j) (2) (A)].

#### **2. File and Directory Organization**

The Patent Certification should be embedded in a PDF file and labeled *patcert.pdf*.

#### **3. Document Information Fields**

The Document Information Title field for the patent.pdf file should contain the words, "patent certification."

#### **4. Table of Contents**

Not applicable.

#### **5. Hypertext Linking and Bookmarks**

Not applicable.

#### **6. Indexing**

Not applicable.

## Draft- Not For Implementation

### O. Item 15 : Establishment Description

#### 1. Regulatory Reference

This is item fifteen on page two of FDA Form 356h [21 CFR 601.2]. For specified biotech products, Item 15 does not apply.

#### 2. File and Directory Organization

A separate folder named *estab* for the Establishment Description section of the submission should be provided. A table of contents for establishment documents and images should be provided within this folder as a single PDF file. This file should be named, *estabtoc.pdf*.

Within the folder, separate PDF files should be created for the following submission contents: water systems (*water.pdf*); heat, ventilation and air-conditioning (HVAC) systems (*HVAC.pdf*); contamination and cross contamination (*contamin.pdf*); formulation and filling (*formfill.pdf*); and computer systems (*computer.pdf*). Floor and flow diagrams should—when practical—be provided as single-page images embedded in PDF files.

Additional information, as outlined in FDA Form 3210, “*Application for Establishment License for Manufacture of Biological Products*” may be needed for some submissions and appropriate files should be organized for such information. The completed FDA Form 3210 may be embedded in a PDF file (*3210.pdf*). Contact the Division of Establishment Licensing about how and when to submit this form.

#### 3. Document Information Fields

The Document Information Title field for each PDF file should contain a brief description of the document, (e.g., HVAC, formulation, etc.) and the name of the active ingredient, and biological substance or product.

#### 4. Table of Contents

The establishment table of contents may include files for the following information: Water systems, HVAC, contamination and cross contamination, and computer systems. Please refer to the appropriate establishment guidance (below) for more details on appropriate content.

#### 5. Hypertext Linking and Bookmarks

## Draft- Not For Implementation

All documents with a table of contents should provide bookmarks for each item in the document's table of contents, including tables, figures, and appendices.

To facilitate review, hypertext links should be provided throughout the body of the document to supporting annotations, related sections, references, appendices, tables or figure that are not located on the same page.

### 6. 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 Adobe Exchange. The index definition file should be named *estab.pdx* and placed in the *estab* folder.

To facilitate searching the *estab* folders and files, Adobe Exchange should be used to associate the *estab.pdx* file with the *estabtoc.pdf* file. This will automatically open the *clinical* index and make it available for searching whenever the *estabtoc.pdf* file is opened.

### 7. Additional Guidance

For more detailed descriptions of appropriate Establishment content see *Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products or Animal Plasma or Serum-Derived Products (draft), December 1997*, and *Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls information and Establishment Description for Autologous Somatic Cell Therapy Products, January, 1997*.

**P. Item 16: Debarment Certification**

**1. Regulatory Reference**

This is item sixteen on page two of FDA Form 356h [21 U.S.C. 335a(k)(1)].

**2. File and Directory Organization**

A Debarment Certification should be in the form of a PDF file, and contain a debarment statement in accordance with 21 U.S.C. 335 a(k)(1). The file should be labeled *debar.pdf*.

**3. Document Information Fields**

The Document Information Title field for the *debar.pdf* file should contain the words, "debarment certification."

**4. Table of Contents**

Not applicable.

**5. Hypertext Linking and Bookmarks**

Not applicable.

**6. Indexing**

Not applicable.

**Draft- Not For Implementation**

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

**1. Regulatory Reference**

This is item seventeen on page two of FDA Form 356h [21 U.S.C. 335 a(k)(1)].

This section of the FDA Form 356h is not relevant to BLAs or PLA/ELAs.

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

**1. Regulatory Reference**

This is item eighteen on page two of FDA Form 356h.

**2. File and Directory Organization**

If appropriate, a copy of the User Fee Cover Sheet (FDA Form 3397) should be embedded in a PDF file and labeled *userfee.pdf*.

**3. Document Information Fields**

The Document Information Title field for the *userfee.pdf* file should contain the words, "user fee."

**4. Table of Contents**

Not applicable.

**5. Hypertext Linking and Bookmarks**

Not applicable.

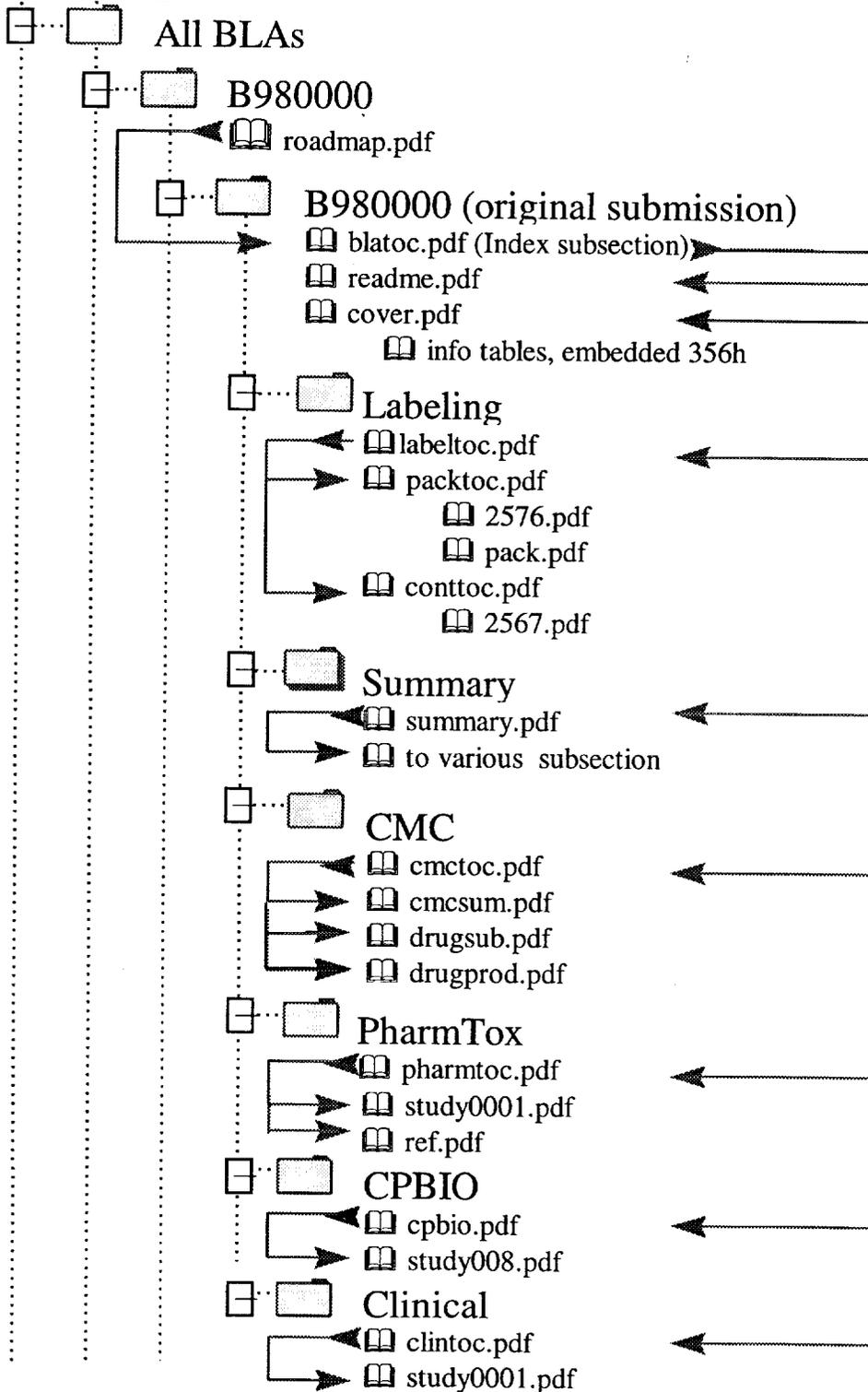
**6. Indexing**

Not applicable.

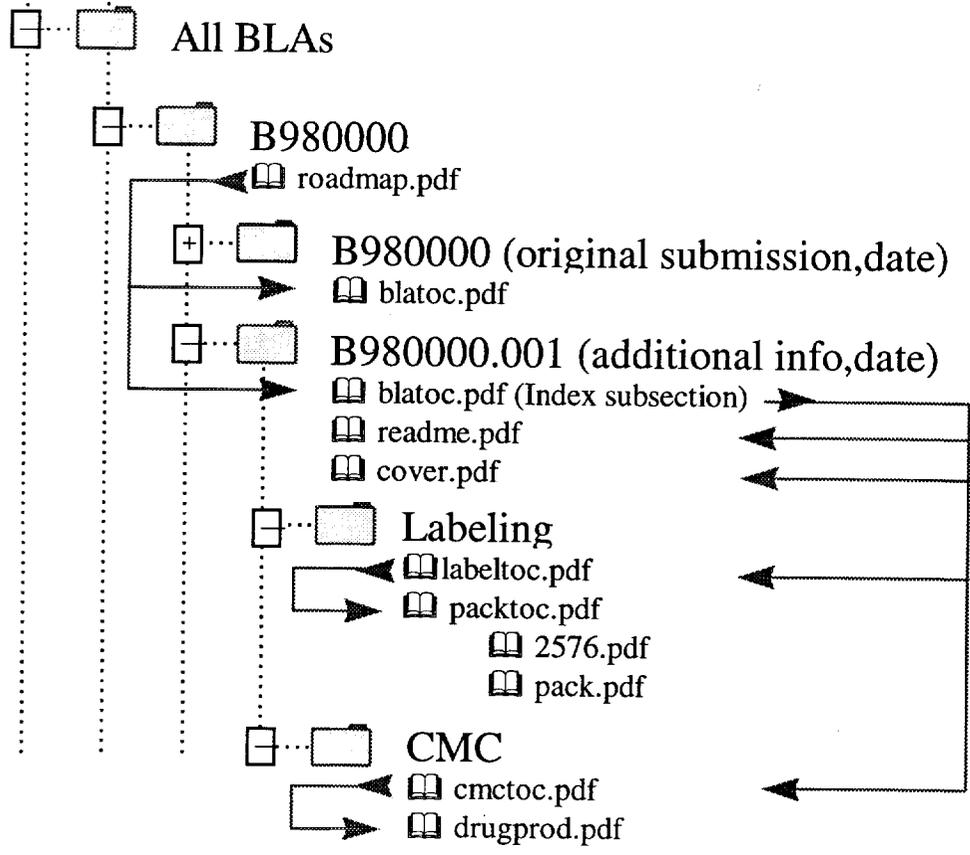
# **Appendix A**

## **File and Folder Structure**

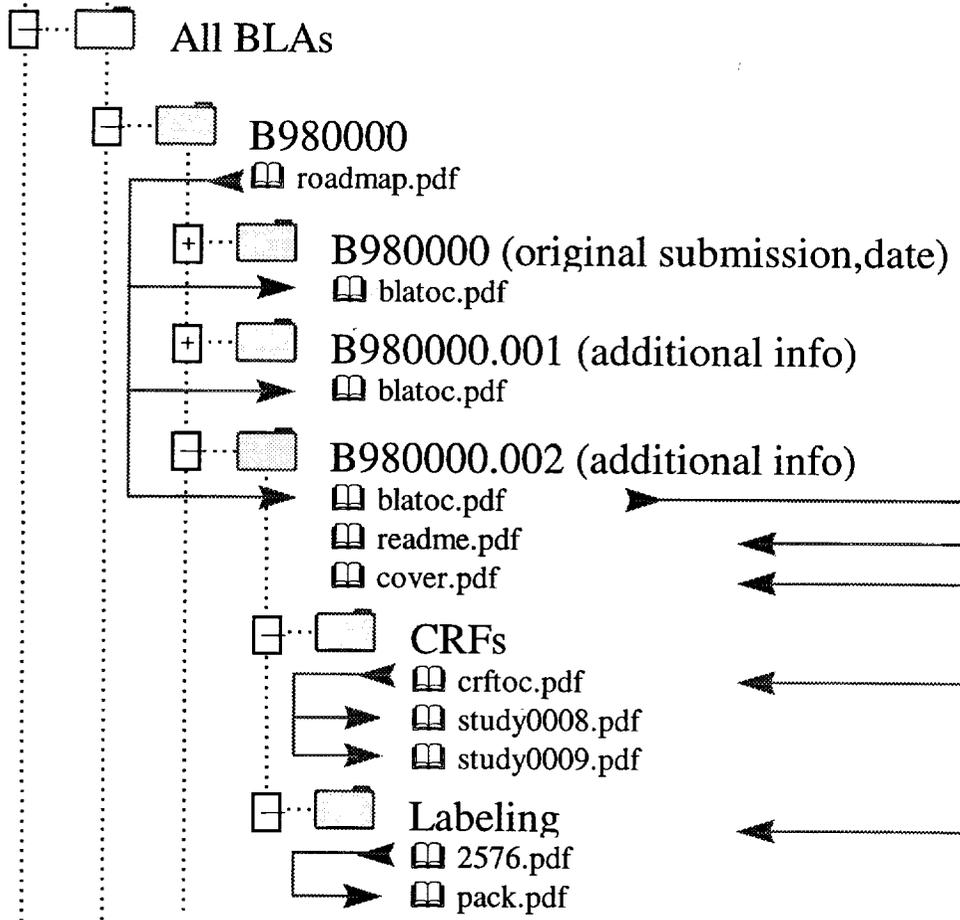
# eBLA File and Folder Structure- Original submission: B980000



# eBLA File and Folder Structure - first addition to B980000.001



## eBLA File and Folder Structure - second addition to B980000.002



## **Appendix B**

# **Submitting Electronic Applications to CBER**

## Draft- Not For Implementation

CBER requests that two copies of an application be submitted on CD-ROM disks in ISO 9660 format. For submissions of small size (e.g., data sets, labels), 3.5" diskettes may be used. Tape is not currently accepted by CBER. More copies may be requested as needed.

Physical labels should be attached to 3.5" Diskettes, 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. The CD-ROMs should be numbered from 0.001 through 0.XXX for the original submission, and 1.001 through 1.XXX for the first submission of additional information. The following information should also be included on the label:

- a) Sponsor or manufacturing name and license number, if available.
- b) Regulatory ID number if available.
- c) Application type.
- d) Document date in format of DD-MMM-YYYY (e.g. 01-Jan-1998).
- e) 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.
- f) CD-ROM number in B000000.000 format.

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 CD jewel cases shipped in envelopes without bubble type protective material or stiff backing. The use of "jiffy"-type bag by itself to ship media does not provide adequate protection for shipping electronic media.

Applications should be submitted directly to CBER's DCC as follows:

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

# **Appendix C**

## **CBER Contacts**

**Draft- Not For Implementation**

**Office of the Center Director**

Mary A. Buesing M.D.  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-5405  
Fax: 301-827-2920

**Office of Therapeutics Research and Review**

Office of Therapeutics Research and Review HMF-588  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-5101  
Fax: 301-827-5397

**Office of Vaccines Research and Review**

Jeffrey Smith/David Dickerson  
Office of Vaccines Research and Review HFM-475  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-3070  
Fax: 301-827-3532

**Office of Compliance and Biologics Quality**

Robert Sausville (Establishment)  
HFM-206  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-3031  
Fax: 301-827-3528

Patricia Holobaugh (Compliance/BIMO)  
HFM-650  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-6221  
Fax: 301-594-1944

**Draft- Not For Implementation**

**Office of the Center Director**

Peter A. Lachenbruch, Ph.D. (Statistics)  
HFM-215  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-6055  
Fax: 301-827-3529

**Office of Office of Information Technology Management, Division of Information  
Technology Management**

Robin Jones/Joseph Montgomery  
Office of Management HFM-185  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-0995  
Fax: 301-827-1170

**Document Control Center**

Jules Meisler  
Document Control Center HFM-99  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-594-2059  
Fax: 301-594-0149

**Office of Blood Research and Review**

Susan Yu  
OBRR, HFM-370  
FDA/CBER  
1401 Rockville Pike  
Rockville, MD 20852-1448  
Phone: 301-827-3524  
Fax: 301-827-2857