

Guidance for Industry

Electronic Submissions of Case Report Forms (CRFs), Case Report Tabulations (CRTs) and Data 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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should be submitted within 60 days of publication in the *Federal Register* notice announcing the availability of the draft guidance.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Additional copies of this draft guidance document are available from the office of Communication, Training and Manufacturers Assistance (HFM - 40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by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 or phone 301-594-5570.

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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.....	03
III. ITEM GUIDANCE	07
A. Index.....	07
B. Statistical Section	09
C. Case Report Tabulations.....	13
D. Case Report Forms.....	16

APPENDICES

APPENDIX A: Formatting PDF Files and Pages.....	18
APPENDIX B: File and Folder Structure	23
APPENDIX C: File and Folder Structure for the Statistical Section.....	26
APPENDIX D: Submitting Electronic Applications to CBER	28
APPENDIX E: CBER Contacts.....	31

TABLES

Table 1: Roadmap reference table.....	05
Table 2: Electronic vs. paper portions of a BLA.....	05
Table 3: Summary Information for an electronic BLA.....	06
Table 4: Virus verification.....	06
Table 5: Sponsors points of contact.....	06

GUIDANCE FOR INDUSTRY¹

Electronic Submissions of Case Report Forms (CRFs), Case Report Tabulations (CRTs), and Data to the Center for Biologics Evaluation and Research

I. INTRODUCTION

Existing Federal regulations require industry to submit certain marketing applications using a specific form and list the information required with a submission (e.g., 21 CFR 314.50 for new drug applications (NDA) and Part 601.2 for biological product license applications (PLAs) and biologics license applications (BLAs). The Electronic Records: Electronic Signatures Regulation [21 CFR 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 the Agency is prepared to accept electronically are identified by each center on an accompanying public docket 92S-0251. The docket (<http://www.fda.gov/ohrms/dockets/dockets.htm>) 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 docket also contains reference to technical guidance on how to structure electronic submissions to meet the receiving unit's capabilities.

This draft guidance for industry on the submission of electronic CRFs, CRTs and data is one of several currently under development to provide further guidance on how the Agency is implementing 21 CFR 11. The purpose of the guidance is to provide industry with basic information on how to submit electronic CRFs and CRTs with applications such as the BLA, or PLA. The final guidance, when announced, will supersede this guidance and earlier draft guidance entitled, "Guidance for Industry: Electronic Submissions of Case Report Forms and Case Report Tabulations" (November 4, 1996), and "Guidance for Industry: Submitting Application Archival Copies in Electronic Format" (November 4, 1996).

As with other guidance documents, the Food and Drug Administration (FDA) does not intend this guidance document to be all-inclusive and cautions that not all information may be applicable to all situations. The guidance document is intended to provide information and does not set forth requirements. The methods and procedures cited in the guidance are suggestions. The FDA anticipates that sponsors and investigators may develop alternative methods and

¹ This guidance was prepared by the Quality Assurance Staff and the CALA working group at the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on submission of electronic case report forms, case report tabulations and data to CBER. It does not create or confer any rights for or on any person and does not bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirement 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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procedures and discuss them with the Agency, and the FDA may find those alternative methods and procedures acceptable. Because this is a rapidly developing field, this guidance most likely will be updated periodically.

II. ELECTRONIC FILE FORMATS FOR SUBMISSIONS

A. General Overview

The Center for Biologics Evaluation and Research (CBER) proposes that the electronic documents (text, tables, and images) be provided in Adobe Acrobat's Portable Document Format (PDF), and data in SAS Transport file format. CBER is no longer prepared to accept customized submissions, software, or hardware. This document describes those 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 specifications outlined in this guidance document should help to assure that subsequent electronic submissions will meet FDA acceptance criteria, be retrievable on our networks, and reviewable within specified time frames using standard desktop tools.

CBER recommends that the electronic archival copy 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 hard copies of license applications.

To facilitate the locating of information submitted between paper and electronic records, CBER encourages the sponsor 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 should reduce the need to validate that the paper and viewed electronic documents are identical in appearance and in content. See Appendix A for specific information 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 Center for Drug Evaluation and Research's (CDER) guidance entitled "Archiving Submissions in Electronic Format--NDAs," (62FR49695; September 9,1997) 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

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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 electronic application materials is essential for expeditious review.

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 will be based on the harmonized FDA Form 356h (available on-line at: <http://aosweb.psc.dhhs.gov/forms/fdaforms.htm>). The folder and file naming conventions and organization are intended to reflect the information typically contained in FDA Form 356h (See Appendix B).

This guidance provides an overall structure for the submission, and specifically provides

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guidance on submitting CRFs, CRTs, and data.

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 would have to be added to the existing network and distributed to appropriate reviewers. Consequently, it is imperative that a reliable mechanism be employed for locating all 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 B.)

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.

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-1998). 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 the table of contents (TOC) 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 TOC of the submission and the *roadmap.pdf* file 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 TOC and to the *roadmap.pdf* should contain

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the following information for each submission: a description of the electronic 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. Deviations from this guidance should be documented in a letter within the *cover.pdf* file. This information, including the three tables, should be updated with each new addition to the application. Examples of these tables follow.

Table 1: Roadmap.pdf Reference Table

BLA submission	Submission Date	Submission Content	CD-ROM #	HyperText Link to:
original	DD- MMM - YYYY	FDA Form 356h content, readme.pdf, cover.pdf, imageQA.pdf, index.pdf, Summary CRTs CRFs Statistical data	0.001 0.001 0.001 0.002-0.003 0.004 0.005 0.006	original blatoc.pdf
add. Info.	DD- MMM - YYYY	new readme.pdf, new cover.pdf, CRFs	1.001 1.002	updated blatoc.pdf

Table 2: Electronic vs. Paper Portions of a BLA

Electronic vs Paper Portions of the application			
Item	Description	Paper	Electronic
1	Index	X	
2	Labeling	X	
3	Summary	X	
4	Chemistry Section	X	
5	Nonclinical Pharmacology and Toxicology	X	
6	Human Pharmacokinetics and Bioavailability section	X	
9	Clinical	X	X
10	Statistics		X
11	Case Report Tabulations		X
12	Case Report Forms		X

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Table 3 : Summary Information for an Electronic BLA

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

Table 4: Virus Verification

Virus Verification	
Software Name	
Version	
Company Name	

Table 5 : Sponsor's Points of Contact

Sponsor Contacts				
Content Section	Name	Phone	E-mail	Beeper
Regulatory affairs				
Technical				
Other				

III. ITEM GUIDANCE

A. Index (or Overall Architecture for Electronic Submissions)

The FDA Form 356h contains nineteen items. This guidance document deals with items 1 (index), 10 (statistical data), 11 (CRTs), and 12 (CRFs). Item 1 is included in this document to provide an architectural framework for submitting electronic data, CRTs, and CRFs.

1. Regulatory Reference

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

In order to facilitate the review, a main TOC 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 the main folder using the submission number (e.g., B000000.000 for a BLA) 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, the Investigational New Drug (IND) number should be used 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. Add the submission dates (DD-MMM-YYYY) to the *Title* fields.

4. Table of Contents

The *roadmap.pdf* file should employ hypertext links to directly connect to the submission's main TOC. The main TOC 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 TOC to

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the main tables of contents of the major portions of the application.

5. Hypertext Links and Bookmarks

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

6. Indexing

No indexing is needed for the Index subsection.

B. Statistical Section

1. Regulatory Reference

This is item 10 on the harmonized FDA Form 356h [21CFR 601.2].

2. Overview

CBER prefers that the statistical data for the review of clinical safety and efficacy data be provided in SAS Transport file format. This format can be utilized by both the statistician for SAS and clinical reviewers for JMP or whatever other tools the reviewer desires to use. The data can be translated in CBER into other programs from the SAS Transport files using common translation programs such as DBMS/Copy or Stat/Transfer. SAS Transport files should be prepared by using the Xport (not Cport) procedure.

SAS Transport files should be submitted on a separate CD-ROM to facilitate migration and retrieval of federal records over time by CBER. The SAS Transport files should not be linked to the PDF submission. They should not be zipped (i.e., compressed). It is recommended that the file size be limited to less than 25MB if possible. Customarily this size can be controlled by limiting the number of variables included (usually less than 50).

The statistical data format, however, should always be discussed with the appropriate product office in CBER prior to submission as the type and amount of data vary within each product office and from study to study.

3. General Considerations for Data Sets

Each patient should be identified with a single, unique number (PID) for the entire application. This unique number needs to be provided in each data set. This is essential for joining different data sets.

For a data table, each variable should be represented as a single column heading. Each row should contain a single observation or result for an individual patient, allowing for multiple rows per patient.

The same variable names and codes should be used across studies. This is helpful when combining data sets and reduces the time for learning the data sets. For example, if glucose is checked in a number of studies, use the same name to describe this variable in all of the studies.

Duration is frequently part of the analysis. To save the reviewer time, start and stop times and dates should be provided as duration of treatment based on the start of study treatment and expressed in minutes, hours, days, whichever is appropriate. When expressed in days, the following formula should be used to calculate the study day: [(test date) - (date of first dose) + 1].

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Results are frequently analyzed based on the study, center/site, treatment assignment, sex, age, and /or race of the subjects. To save time for the reviewer, each data set should include these variables.

Quantitative variables should be numeric, and qualitative variables should be alphanumeric, or numeric and labeled.

4. File and Folder Organization

The data set files should be organized by study name and/or number and placed into their respective study subfolders. A separate subfolder should be made for each study. All study subfolders should be placed in a folder named *Stats*.

CBER recognizes that not all analyses will be produced using SAS. Some of the following comments apply primarily to SAS based analyses.

Any SAS format files (sc2) should be placed in a subfolder named *formats* and placed in the *Stats* folder.

Under the *Stats* folder a table in PDF containing descriptions of the studies should be provided. It should be called *studydef.pdf*. For example:

Study Name/Number	Description
S301	Dose - ranging study with 73 patients
S302	Pivotal study: randomized, double-blind comparing 100 mg/kg dose of treatment to placebo in 253 patients
S900	Evaluation of data from a Canadian registry

A definition file that defines the data files under each study should be provided. This should be submitted as a table containing four columns: the study name/number, no. of observations, file names in each study, and the file description. This file should be provided in PDF, named *filedef.pdf* and placed in the respective study subfolder. For example:

Study Name/Number	No. of Observations	File Name	File Description
Contrail 9701	78	AD_HX	Summary of medical history • one record per patient
Contrail 9701	110	AE	Adverse Events • multiple records per patient
Contrail 9701	88	Effic1	• Primary efficacy variable

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Similarly, a variable definition file should be provided for each study. There may be multiple variables in each study, such as: demographics, efficacy, chem-lab, blood-lab, adverse experiences, etc. This should also be provided as a table containing: the variable name, its description, type of variable (character, numeric, date, etc), SAS format (if any, for example, TX for treatment), code values (such as: 1 = mild, 2 = moderate, 3 = severe), and a column for notes (such as: 1,2,3; a,b,c). Each file should contain patient identification and treatment codes. The “notes” columns may contain some codes which can be defined at the end of the table. This file should also be provided in PDF and named *vardef.pdf* and placed in each study subfolder. An example of such a table for the dataset : AD_HX (summary of medical history) would be:

Dataset: AD_HX for study #9701

Variable	Description	Type	Format	Values/Codes	Notes
Pt_ID	Five character patient number	C			
TXGRP	Assigned treatment group	N	TX	1 = Placebo + 200 mg dose of biologic X 2 = 400 mg dose of biologic X 3 = 600 mg of biologic X	
Demographics					
DOB	Patient date of birth	D			
AGE	patient age in years	N			
HGT	patient height	N			a
RACE	Patient Race	N		1 = white, 2 = african-american, 3 = am indian, etc	
SEX	patient gender	C		M, F	

Notes:

1. “a” - height is in centimeters

Please note that SAS Proc Contents is usually not sufficient to replace the above definition files.

SAS programs/codes used to arrive at the sponsor’s final analysis for safety and efficacy should be submitted. This should be interpreted as applying to programs that produce the results, but not necessarily those that format the output. In CBER, the statisticians need to be able to reproduce a sponsor’s analysis. Toward this end, they need to appreciate how the sponsor derived their results from the data which was submitted. These programs should have sufficient comments so that a reviewer or statistician can follow the logical flow of the program. They should be provided in SAS and placed in a subfolder named *Programs* and placed in the respective study subfolder. SAS programs for integrated summaries of safety and efficacy should be placed in

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separate subfolders: *ise* for integrated summary of efficacy, and *iss* for integrated summary of safety.

Although the data sets are submitted in SAS Transport file format, the statisticians using SAS for analyses will need the SAS programs. Similarly, SAS format (sc2) files should be placed in respective study subfolders named *Formats*.

All SAS Transport file data sets for each study should be placed in a respective subfolder named *data sets* under each study subfolder.

5. Document Information fields

These are left blank for the pdf files.

6. Table of Contents

A table of contents for this section should be named *Statstoc.pdf* and placed in the *Stats* folder. The *Statstoc.pdf* should **not** be linked to the main application TOC (*blatoc.pdf*). Similarly for each study's data sets, a table of contents should be provided as a PDF file named *datatoc.pdf* and placed in the *data sets* subfolder. The *Formats* and *Programs* folders should also contain table of contents respectively named *formtoc.pdf* and *progtoc.pdf* and linked to the *Statstoc.pdf*.

7. Hypertext linking and Bookmarks

Establish hypertext links between the *statstoc.pdf* and each of the subfolders table of contents and to the *studydef.pdf* file. Subfolders TOCs should be linked to the contents of their respective file contents.

8. Indexing

No indexing is needed for the pdf files.

C. Case Report Tabulations (CRTs)

1. Regulatory References

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

2. File and Directory Organization

CRTs are provided in two formats, domain profiles and patient profiles. Consult the reviewing division to determine if both domain and patient profiles are needed, or if a single format is adequate.

a. Domain profiles

Commonly referred to as patient line listings or patient data listings, domain profiles consist of all data collected for a CRF domain (such as demographics, vital signs, labs, efficacy measures) from one study. A table should be provided for each CRF domain that displays collected variables as column headings and displays the results for each patient in rows, with multiple rows per patient, if necessary. For example, for study 2001, there should be a table that includes all of the vital sign data collected from all patients in the study. The vital sign parameters would serve as the column headings. Each row should include the results for a single patient at a single time point during the study. Include in each table the unique patient identification (PID) number and the treatment group assignment.

A single PDF file should be provided for each CRF domain, and all domain profiles for a single study should be placed in a folder identified with the study number. For example, domain profiles for *study 301* are placed in a sub-folder named *301*. Place all of these subfolders in a single folder named *domain*. There is no specific guidance for file naming conventions for the various domains.

b. Patient profiles

Patient profiles consist of one or more pages that contain all of the study data collected for an individual patient. A table should be included for each CRF domain (such as vital signs, demographics, labs, efficacy measures) including all of the data collected for the specific CRF domain for the individual patient. The table should be organized by time. For example, the patient profile for patient 2001-3-1 should have a table for each CRF domain. The table for vital signs would include all vital sign data collected at each study visit. The study visits can serve as column headings with the results for each vital sign parameter (such as systolic BP, diastolic BP, pulse) listed as rows, or vice versa. The organization of the tables should be consistent across domains and patients. Each patient in the study should have a unique PID that is included in each table. The unique patient

ID number should be a combination of the study number, study site, and patient number or a functional equivalent. Leading zeros should be avoided. For example, patient 001 in study 2001 at site 003 would have the following PID number: 2001-3-1.

Each individual patient's complete patient profile should be provided in a single PDF file. All patient profiles for a single study site should be placed in a folder identified with the site number. The term *study site* is also commonly identified as the study center or individual investigator. All site sub-folders should be identified by the study number. For example, all patient profiles for site 3 for study 301 would be placed into a folder named 3, or *site 3* which then would be placed in a sub-folder named 301. Place all patient profile sub-folders in a single folder named *profile*. There is no specific guidance for file naming conventions. The *profile* folder should be placed in a folder called *CRT*. The *CRT* TOC should be linked to the main TOC for the submission.

Alternatively, all patient profiles for an entire study could be included in one file, along with the file name and the study number.

3. Document Information Fields

a. Domain profiles

The document information fields for each file should include *dp* in the *Title* field, the study number, and the appropriate CRF domain name. For example, the domain profiles for vital signs in study 2001 would have the following in the *Title* field: *dp*, study 2001, vital signs.

b. Patient profile

The document information fields for each file should contain *pp* in the *Title* field, as well as the study number, site number, and the unique PID number used in the submission. The unique PID number should be composed of elements of the study number, investigator's number, and patient number, or a functional equivalent. Leading zeros should not be included. For example, the patient profile for patient 001 in study 2001 at site 003 would have the following in the *Title* field: *pp*, study 2001, site 3, PID 2001-3-1 .

The patient profile for patient 12345 in study 2001 at site 1234 would have the following in the *Title* field: *pp*, study 2001, site 1234, PID 2001-1234-12345.

If the profiles for one study are included as a single file, *pp* and the study number should be included in the *Title* field. For example the patient profiles for study 2001 would have the following in the *Title* field: *pp*, study 2001.

4. Table of Contents

a. Domain profiles

A TOC for all domain profiles should be provided in the form of a PDF file. In the domain profiles TOC, all CRF domains should be listed by study. Hypertext links between the CRF domain listing in the domain profiles TOC and the corresponding CRF domain profiles files should be provided. The domain profiles TOC should have the file name *dptoc.pdf* and be placed in the *domain* folder. The domains folder should be placed in a folder called *CRT*. The *CRT* TOC should be linked to the main TOC for the submission.

b. Patient profiles

A TOC of all patient profiles should be provided in the form of a PDF file. The patient profiles TOC should list unique PID numbers by study. Hypertext links between the patient listings in the patient profiles TOC and the corresponding patient profile PDF files should be provided, named *pptoc.pdf*, and placed in the *profile* folder.

If the profiles for a study are included in a single file, the patient profiles TOC should list all of the studies and provide a hypertext link between the study listing in the TOC and the corresponding study patient profile PDF file.

The patient profile TOC should be linked to the application TOC for the submission.

5. Hypertext Linking and Bookmarks

If the patient profiles for a study are included in a single file, the file should provide a bookmark to each individual patient's profile.

6. Indexing

a. Domain profiles

An index of the document information *Title* field of all domain profiles, accessible using the search tools available in Acrobat Exchange, should be provided. The index definition file should be named *domain.pdx* and placed in the *domain* folder.

b. Patient profiles

An index of the document information *Title* field of all patient profiles, accessible using the search tools available in Acrobat Exchange, should be provided. The index definition file should be named *profile.pdx* placed in the *profile* folder.

D. Case Report Forms (CRFs)

1. Regulatory references

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

For guidance information related to remote data entry (RDE)—including electronic signatures, audit trails, and date/time stamps—see, “Guidance for Industry: Computerized Systems Used in Clinical Trials,” (62FR33094; June 18, 1997), available at the following FDA Web site: <http://www.fda.gov/cder/guidance/guidance.htm#Compliance>. This reference is helpful for situations in which no electronic or paper CRF is available; that is, data is directly entered into a database for the study. Please confer with the appropriate product office on how to deal with these situations.

2. Organizing the files

Each individual patient's complete CRF should be provided in a single PDF file, and all CRFs for a single study site should be placed in a folder identified with the site number. Alternatively, if each patient's CRF is brief, then all CRFs for a single site or study may be placed in a single PDF file as long as the file size is less than 50MB. The term *study site* is sometimes identified as the study center or individual investigator. All study site sub-folders should be placed in a single folder identified by the study numbers. For example, all CRFs for site 3 for study 301 would be placed into a sub-folder named 3, which then would be placed in a folder named 301. All sub-folders should be placed in a single overall study folder named *CRF*. There is no specific guidance for naming individual PDF files.

If a paper CRF was used in the clinical trial, the electronically submitted CRF should be an exact image (scanned at 300-600 dpi) or series of images of the paper CRF that contains all original entries with all modifications, addenda, corrections, comments, annotations, and any extemporaneous additions.

3. Document Information Fields

The document information fields for each file should include, in the *Title* field, *crf* as well as the study number, study site number, and the unique PID number used in the submission. The unique PID number should be composed of elements of the study number, site number and patient number or a functional equivalent. Do not include leading zeros in any of the numbers. For example, the CRF for patient 001 in study 2001 at site 003 will have the following in the *Title* field: *crf, study 2001, site 3, PID 2001-3-1*.

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The CRF for patient 12345 in study 2001 at site 1234 should have the following in the *Title* field: *crf*, study 2001, site 1234, PID 2001-1234-12345

4. Table of Contents

A TOC of all CRFs should be provided in the form of a PDF file. In the CRF TOC, list the unique patient ID numbers by study, site, investigator, and arm, if possible. Hypertext links between the patient listings in the CRF TOC and the corresponding patient CRF files should be provided. The CRF TOC file should be named *crftoc.pdf* and placed in the *CRF* folder. The CRF TOC should be linked to the main application TOC.

5. Hypertext Linking and Bookmarks

Each patient's CRF file should provide a bookmark link to each study visit with each CRF domain (such as demographics, vital signs, labs, etc.). Bookmarks will improve the ease of navigation of the CRF, which may be especially important for CRFs from pivotal trials. As an alternative, a TOC could be provided as page one of each patient's CRF, listing the page location of all CRF domains collected at each study visit.

6. Indexing

An index of the document information Title field of all CRFs should be provided that is accessible using the search tools available in Acrobat Exchange. The index definition file should be named *crf.pdx* and placed in the *CRF* folder.

APPENDIX A

FORMATTING PDF

FILES AND PAGES

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1. Fonts

a. Font styles and point size

For electronic documents to be viewed consistently on different platforms, the text of electronic documents should be produced using fonts available on a reviewer's computer. If a font is not available to a reviewer, it is replaced automatically by another font; this could affect the document's appearance and structure. To ensure that the correct fonts are always available, they should be embedded in the PDF files. To limit the storage space used by embedded fonts, use as few fonts as possible (preferably five or fewer fonts in each PDF file). 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.

Font sizes should be restricted to 10-12 points for text and 8-12 points for tables.

b. Font Color

The font color should be dark since printouts will normally be produced in grayscale. Font colors can be viewed on the screen, but color characters that are printed in grayscale tend to look either black, faded or unclear. Test the color reproduction by printing sample pages from the application prior to submission to CBER.

c. Page Format and Orientation

Page margins should not be less than one half-inch (0.5") on all sides of the electronic protocol document. The paper size should be 8.5 x 11 inches.

To make it easier to read PDF files, the pages should be properly and consistently oriented. If a postscript file contains pages in both orientations, on-screen viewing and printing may be effected once the pages are converted to PDF files. To avoid this problem, make separate PDF files for those pages in landscape and portrait, and then use the "insert pages" under the Document command in Adobe Exchange to compile the PDF document. Alternatively, one may convert all pages into one orientation prior to converting it into PDF.

2. Naming PDF Files

At this time, limitations in CBER prevent the use of long file names. For this reason, files of no more than 8 characters with PDF as the extension (e.g., *report12.pdf*) should be used. Do not use punctuation (/ \ : * ? < > \ ! ~), spaces or other non-alphanumeric symbols in the filename. For uniformity, some submission types will need specific naming conventions for

certain files. Specific subsections should be reviewed for more information on naming conventions.

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

Some subsections use indexes that are functionally accessible using the search tools available in Acrobat Exchange to find specific documents and/or search for text within documents. These indexes should not be confused with a TOC and are included in subsections to make it easier to review the submission. 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. Each subsection should be reviewed for more complete information.

5. Hypertext Linking and Bookmarks

Hypertext links and bookmarks are tools used to improve navigation through PDF documents. Hypertext links should be designated by a visible colored box or underline where appropriate. The preferred color is blue to avoid the potential problem of red-green color blindness.

During the review process, a reviewer may occasionally download their specific subsections (e.g., clinical data section, nonclinical pharmacology, etc.) from the CBER network. Downloading a particular section often resulted in the loss of hypertext links unless the entire submission is downloaded. Therefore, in creating the hypertext links for electronic submission, CBER prefers that a sponsor use links relative to the location of the file containing the links rather than absolute links that include specific drive letters and root directories.

CBER would also like to access information off the CD-ROM (see Table 1) for situations in which the network is inaccessible. Please do not attempt to provide links across CD-ROMs, that is, external to the documents. We do not want to recreate the entire electronic application on the PC in this situation. We simply want to locate the information and then put in the specific CD-ROM.

Individual files, and particularly files containing a TOC, should have a readily identifiable "Home" button available for quickly returning to the submission's main TOC or "roadmap" file (see Appendix B). Using hypertext links and bookmarks to move through the layers of the submission's electronic structure can quickly become disorienting. A hypertext linked

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“Home” button provides a quick return to the beginning of the application.

6. Document Information Fields

The document information fields in PDF files are used to search through the submission documents. The document name, date, submission number, and other information are important in searching and indexing the contents of an application. The individual subsections should be reviewed for specific recommendations on adding information to the document information fields.

7. Images

For purposes of this document, the term “image” includes: photographs (e.g., Western Blots, SDS-PAGE, and ELISA); plotter output graphics (e.g., HPLC); and plant and manufacturing flow and floor diagrams.

a. Preparation of Images

Resolution of captured images should be sufficient to support protocol review on both a computer monitor and paper. Preferably images should be grayscale (as opposed to textual documents in PDF). Color images may be submitted providing color quality is not degraded appreciably or altered in the process. Note that converting some color postscript files into PDF files may cause colors to become muted or transformed; clarity may be compromised.

Where practical, images should be sized to fit on a 8.5 x 11 inch 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 greatly enhance the details to be viewed, although it may significantly increase file size.

CBER is not accepting compressed images until agreed upon standards for compression and data integrity validation can be established.

During the transition from paper to complete electronic submissions, the applicant should certify that the electronic versions of submitted images are equivalent to paper images.

b. Case Report Forms (CRF)

When possible, CRFs should be scanned within the 300-600 dpi range.

c. Gels and Karyotypes (photographs)

Gels should be scanned directly rather than from photographs.

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A scanner's ability to resolve an image, and the quality of the original image, can affect the clarity of the captured image. The recommended minimum capture resolution for photographs is 600 dots per inch (dpi) or minimum 8-bit grayscale depth. A captured image should be saved as a picture file, (i.e., Tagged Image File Format (TIFF), Macintosh Vector File (PICT), Windows Bitmap File (BMP), etc.) and not be compressed or subjected to non-uniform scaling (i.e., sizing). The image can then be converted into a PDF document.

Scanned images of data (e.g., western blots, SDS-PAGE) should note the resolution at which the image was captured in a caption.

A quality assurance checklist file (*imageQA.pdf*) for scanned images should note the following useful information for scanned images: brightness and contrast settings; text resolution; picture resolution; and picture color depth or grayscale.

d. Plotter Output Graphics

The recommended minimum capture resolution for scanned plotter output graphics is 300 dpi.

This type of graph is typically plotted on lined graph paper by the plotter output printer. This full-page image can be captured by using a scanner, or a digital camera. Handwritten notes on the plotter graph output should be done in black ink. Black ink is preferred for its clarity.

e. HPLC or Similar Images

For most fonts, the minimum acceptable resolution for alphanumeric characters for on screen viewing is about 8-pt., but most HPLC graphs have a font size of 6-pt. If possible, the font size should be increased to a minimum of 8-pt to improve subsequent screen clarity.

If an 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.

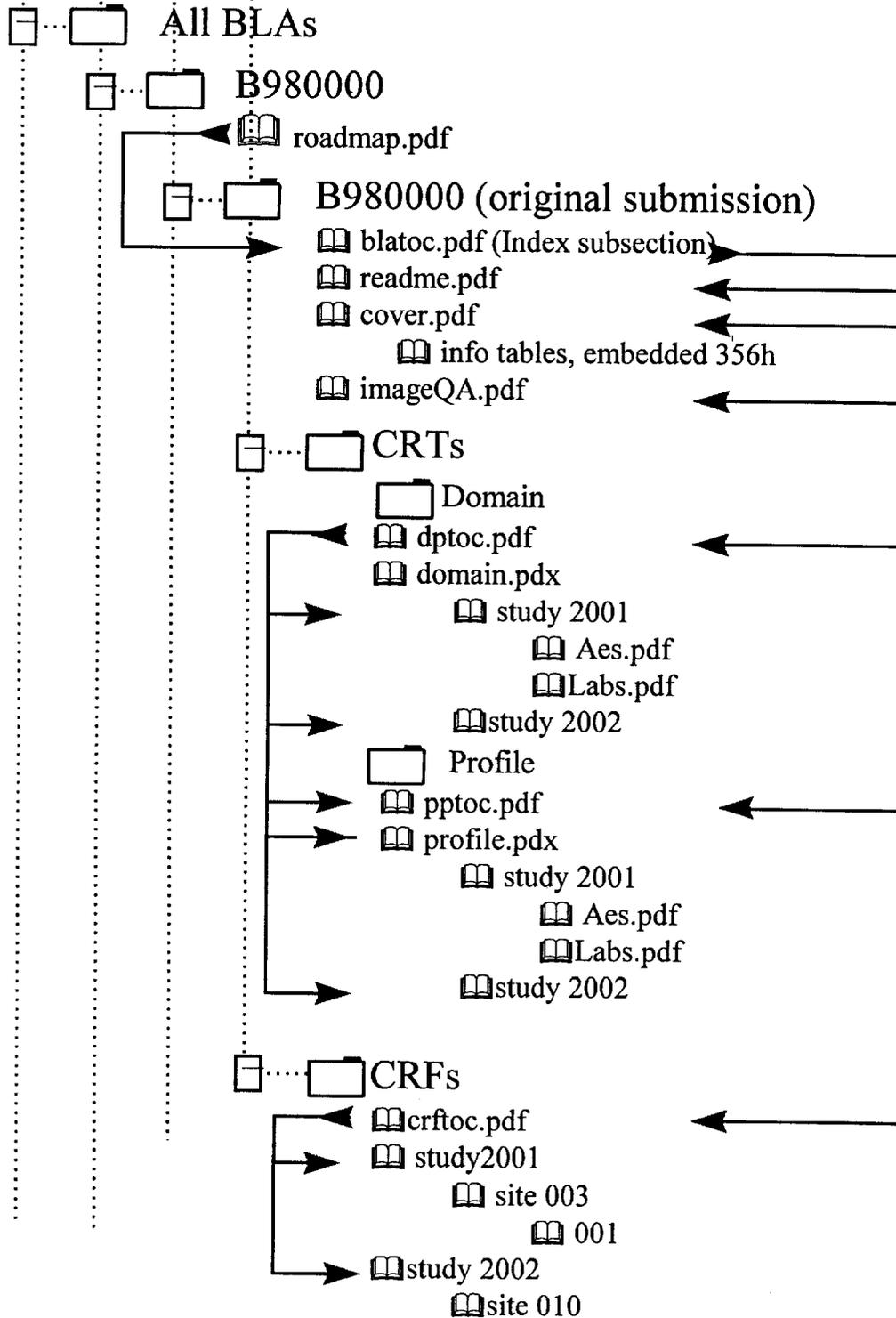
f. Manufacturing Facilities Floor and Flow Diagrams

These diagrams are often used to illustrate the facility layout in a given geographical area as well as to illustrate the actual flow of a manufacturing process(es). Ideally, these diagrams would be best provided in color at 600 dpi, or 24-bit RGB depth. Utilizing different colors to contrast the different production processes would be helpful.

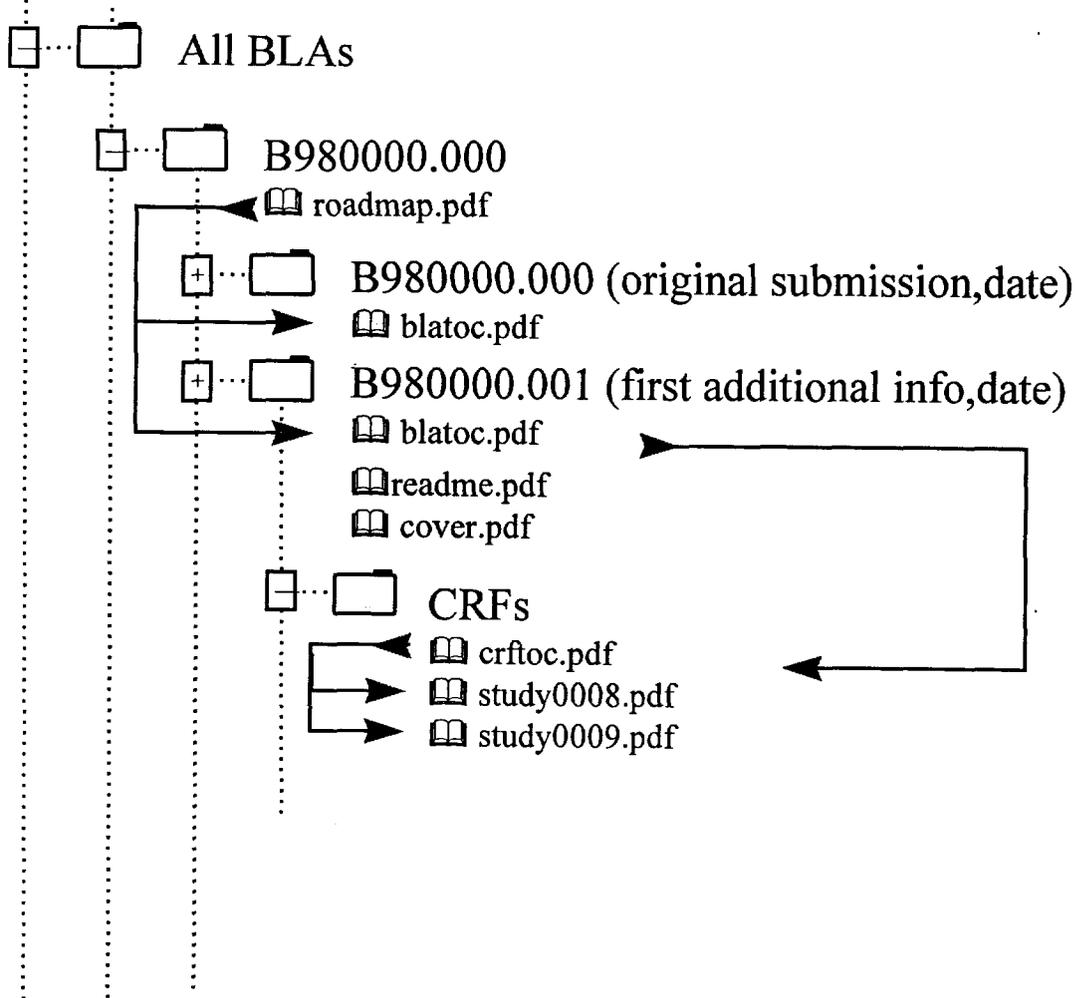
APPENDIX B

FILE AND FOLDER STRUCTURE

eBLA File and Folder Structure- Original submission: B980000



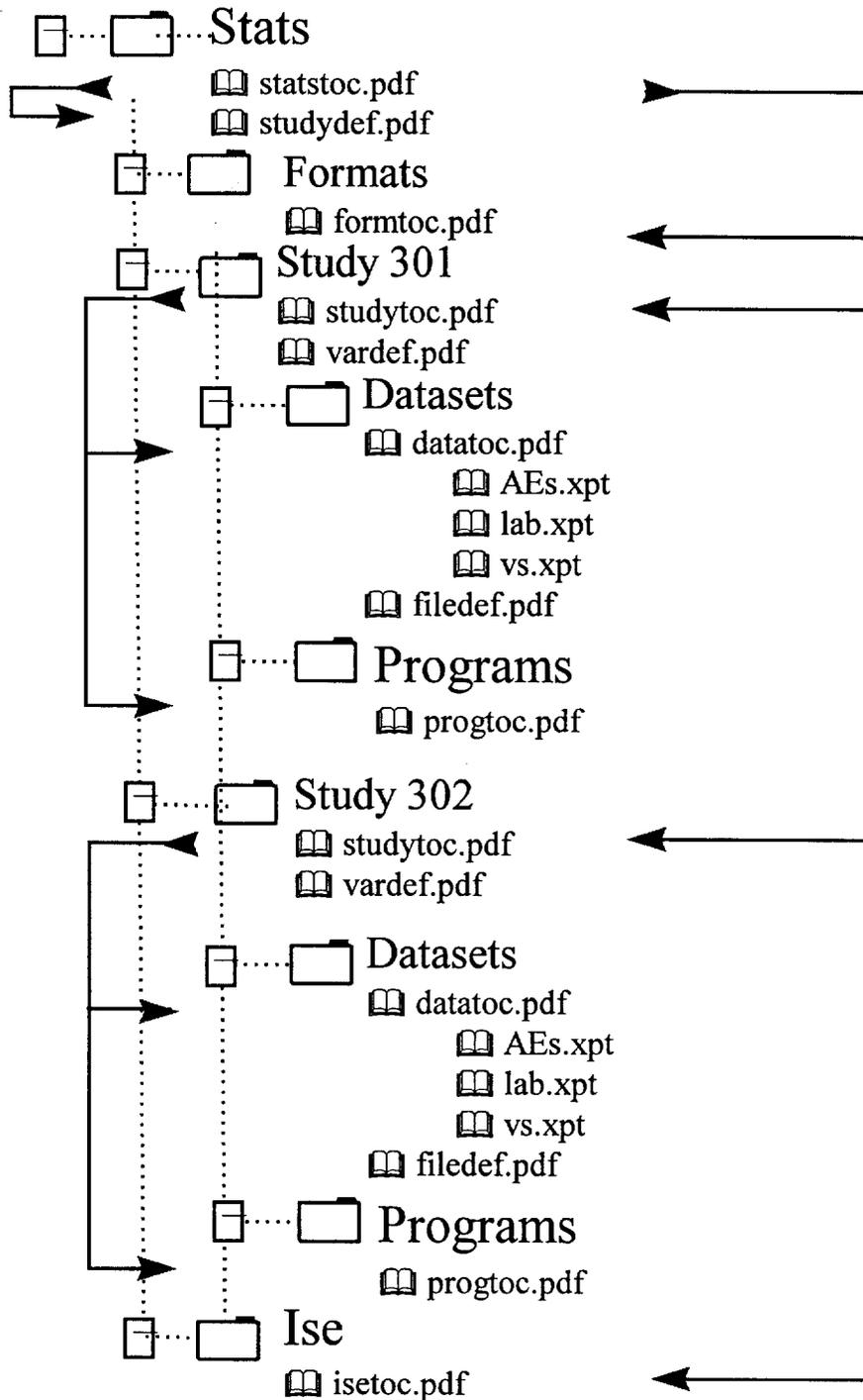
eBLA File and Folder Structure - first addition of information: B980000.001



APPENDIX C

**FILE AND FOLDER
STRUCTURE FOR
THE STATISTICAL
SECTION**

File and Folder structure for the Statistical Section



APPENDIX D

SUBMITTING

ELECTRONIC

APPLICATIONS

TO CBER

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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 currently not 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 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:

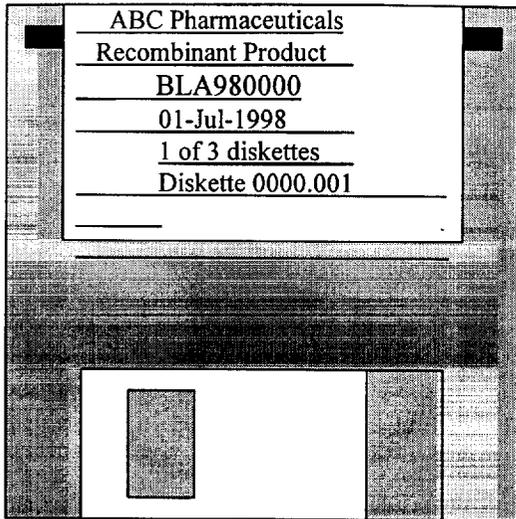
- a) Sponsor or manufacturing name and license number, if available
- b) Regulatory ID number if available
- c) Application type
- d) Document date in format of DD-MMM-YYYY (e.g. 01-Jan-1998)
- e) Media series as 1 of 10 for a submission set of ten CD-ROMs, or 1 of 3 diskettes for a submission set of three diskettes
- f) CD-ROM number in 0000.000 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 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.

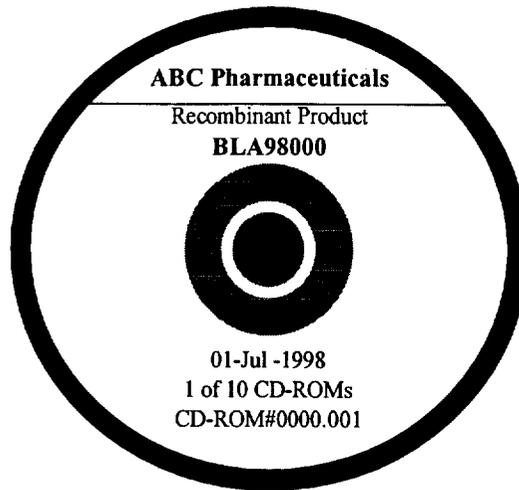
Applications should be submitted directly to CBER's DCC as follows:

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

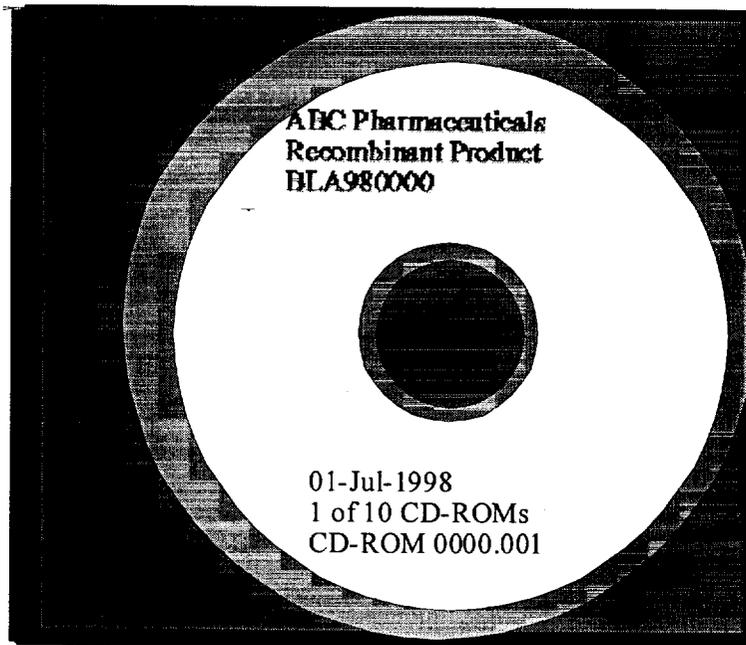
Sample Label of a 3.5" diskette



Sample Label of a CD-ROM



Sample of a CD-ROM jewel case label:



APPENDIX D

CBER CONTACTS

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Office of the Center Director

Mary A. Buesing M.D.
FDA/CBER
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-5570
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: 31-827-3528

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

Office of the Center Director

Peter A. Lachenbruch, Ph.D. (Statistics)
WOC1, HFM-215
FDA/CBER
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-6055
Fax: 301-827-3529

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: 301-827-1368
Fax: 301-827-3053

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