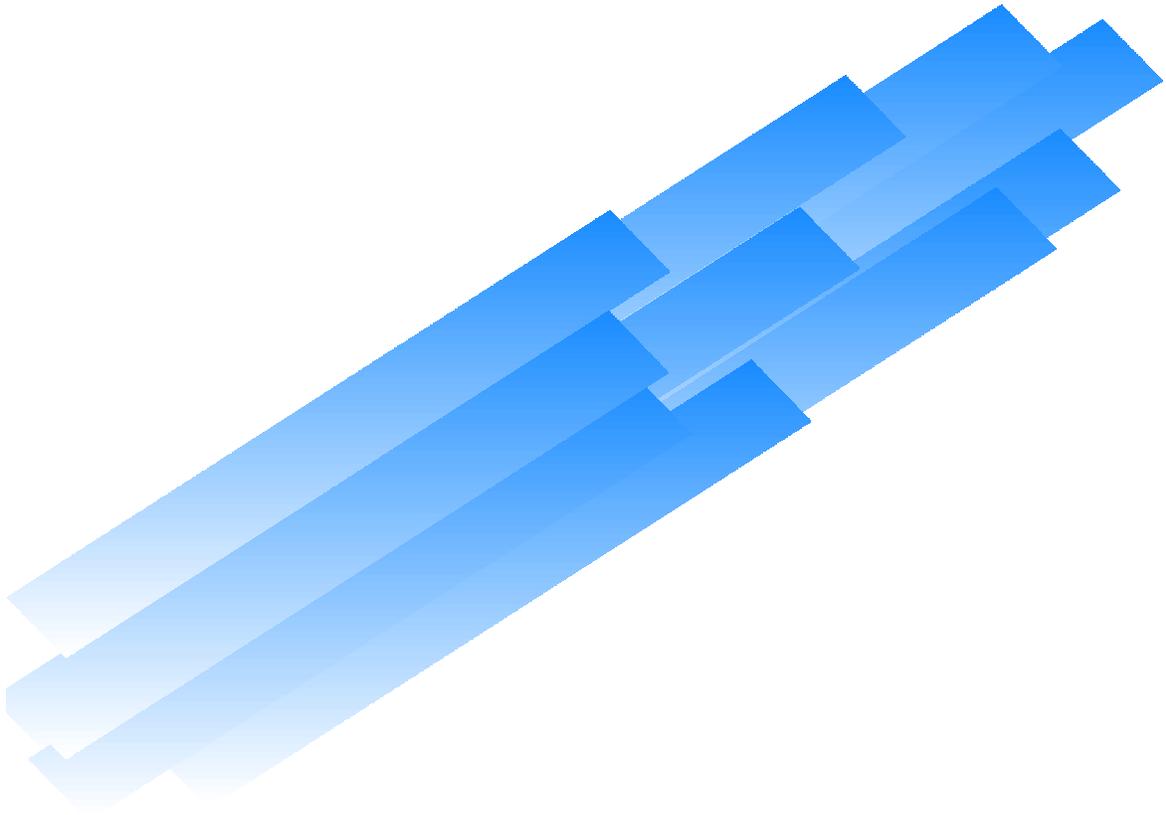


Guidance for Industry

Archiving Submissions in Electronic Format — NDAs



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
IT 1

Guidance for Industry

Archiving Submissions in Electronic Format — NDAs

Additional copies are available from:

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Submission Type: New Drug Application (NDA)

(Starred subsections have been completed.)

❖ Subsection 1.1:	Index (NDA Table of Contents)
Subsection 1.2:	Labeling-Reserved
Subsection 1.3:	Summary-Reserved
Subsection 1.4:	Chemistry Section-Reserved
Subsection 1.5:	Nonclinical Pharmacology And Toxicology Section-Reserved
Subsection 1.6:	Human Pharmacokinetics And Bioavailability Section-Reserved
Subsection 1.7:	Clinical Microbiology-Reserved
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Subsection 1.9:	Safety Update Report-Reserved
Subsection 1.10:	Statistical Section-Reserved

❖ **Subsection 1.11: Case Report Tabulations**

❖ **Subsection 1.12: Case Report Forms**

Subsection 1.13: Patent Information-Reserved

Subsection 1.14: Patent Certification-Reserved

Subsection 1.15: Establishment Description-Reserved

Subsection 1.16: Debarment Certification-Reserved

Subsection 1.17: Field Copy Certification-Reserved

Subsection 1.18: User Fee Cover Sheet-Reserved

Subsection 1.19: Other-Reserved

(Additional submission types will be announced separately.)

GUIDANCE FOR INDUSTRY¹

Archiving Submissions in Electronic Format — NDAs

I. INTRODUCTION

Traditionally, the FDA has required that regulatory submissions, such as investigational new drug (IND) applications and new drug applications (NDAs), be submitted as paper documents. Regulations in 21 CFR Part 314 provide the requirements and procedures for submitting applications to the Center for Drug Evaluation and Research (CDER) to obtain approval for the marketing of new drugs. Among other things, the regulations require the submission of three copies of an application for marketing approval: (1) a complete archival copy, (2) a review copy, and (3) a field copy (21 CFR 314.50(k)).

On March 20, 1997, the Agency published the Electronic Records; Electronic Signatures regulation [21 CFR Part 11], which provides for the voluntary submission of parts or all of an application, as defined in the relevant regulations, in electronic format without an accompanying paper copy. The regulation, effective on August 20, 1997, establishes public docket 92S-251 for the Agency to maintain a list of the specific types of records and submissions that can be accepted in electronic format. Agency unit(s) that are prepared to receive electronic submissions are to identify themselves in this docket.

The new regulation states that persons should consult with the intended Agency receiving unit for details on how to proceed with the electronic submission (e.g., method of transmission, media, file formats, and technical protocols). This guidance document is intended to reduce the need to consult CDER for details on submitting records and other documents in electronic format for the archive. Conforming to the guidance in this document will help ensure that electronic submissions can be accessed, handled, reviewed, and maintained efficiently.

This guidance document is the first in a series that will be issued on archiving electronic submissions. As a result, it is not all inclusive. CDER anticipates that, as this effort proceeds, sponsors, investigators, and CDER staff may develop alternative and more effective procedures for archiving electronic submissions. As a result, this guidance will be updated periodically.

¹ This guidance has been prepared by the Office of Information Technology in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents CDER's current thinking on the archiving of regulatory submissions in electronic format. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

II. ORGANIZATION OF THE GUIDANCE

This guidance for industry is organized in the following manner. Sections III, IV, and V of the document discuss (1) the file formats that the Center is prepared to archive and the specifications that apply to electronic submissions for archival purposes; (2) file formats and media a sponsor may supply to individual reviewers on a case-by-case basis in addition to the archival submissions; and (3) how to submit archival files to the CDER electronic document room.

Following Section V, the guidance discusses the details of submitting an NDA in electronic format. The guidance is divided into subsections, each of which addresses specific parts of the NDA. Each subsection contains guidance that applies to that specific part. Subsections have been designed independently so they can be published individually when they are completed. The Table of Contents in this document (pp. i and ii) shows how the guidance on archiving an NDA in electronic format should look once all of the subsections have been finished. CDER hopes to publish the entire guidance on NDAs as one unit when all of the subsections have been completed. The organization of this guidance sets the stage for the organization of future guidance on other submission types (e.g., INDs, supplements).

III. FILE FORMATS FOR ARCHIVING SUBMISSIONS

This section describes the file formats for electronic documents and data sets that CDER is prepared to archive. CDER may not be able to archive and review a submission that does not conform to this guidance and, therefore, may be unable to file the submission in electronic format. As with a paper submission, FDA may refuse to file an application if it is not submitted as required in 21 CFR 314.101.

Electronic archival document submissions should (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 each page as it would have been printed in a paper submission, including retaining fonts, special orientations, table formats and page numbering; (3) include a well-structured index 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. These goals can be accomplished by using Adobe Acrobat Portable Document Format (PDF). The Agency recognizes that this format has limitations with regard to data submission. In a future revision to this guidance, CDER will recommend formats for submitting data sets.

The following recommendations will help create electronic submissions using PDF that CDER can handle efficiently.

- Fonts

Select fonts carefully. Ideally, all fonts used in a PDF document should be available on a reviewer's computer. If a font is not available to a reviewer, it is replaced automatically by another font, and this could affect the document's appearance and structure. 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). Only True Type or Adobe Type 1 fonts should be used, and the use of highly customized fonts is discouraged. If only a small percentage of the characters of a particular font are used in the document, only those actually used should be embedded.

Font sizes should be restricted to 10 points or greater for text and 8 points or greater for tables.

- Page Orientation

To make it easier to read PDF files, the pages should be properly oriented. For example, page orientation becomes a problem when pages originally oriented in landscape mode are presented in portrait mode. To ensure correct page presentation for the reviewer, set the page orientation of these pages to landscape prior to saving the PDF document in final form.

- Original Documents — Paper Versus Electronic

To produce the highest quality electronic document, use an electronic source document to produce PDF documents whenever one is available. Scanned images of paper source documents should be used only if an electronic form is unavailable.

- Creating PDF Documents From Electronic Documents

Choose the methods for creating electronic documents carefully. For example, the use of Acrobat Distiller is preferable to Acrobat PDF Writer because of the ability to obtain a more precise replication of the printed page. The PDF document will be the same as the paper document if the same PostScript file is used to print and distill the document.

- Creating PDF Documents From Paper Documents

Documents that are available only in paper should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed. Because of size constraints, the use of gray scale or color is discouraged. If black and white photos are required, consider 8-bit gray scale images. If color photos are required, consider 24-bit RGB images.

- Hypertext Linking and Bookmarks

Hypertext links and bookmarks are techniques used to improve navigation through PDF documents. See specific subsections for specifications on bookmarks and hypertext.

- Document Information Fields

The document information fields are used to search for individual documents and to provide the name of the document when found. See specific subsections for directions on filling in the document information fields.

- Open Dialog Box

The open dialog box sets the document view when the file is opened. The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, set the initial view as *Page* only. Set the *Magnification* and *Page Layout* to default.

- Naming PDF Files

At this time, limitations in CDER prevent the use of long file names. For this reason, use files names of no more than 8 characters with PDF as the extension (e.g., report12.pdf). Do not use punctuation, underscores, or spaces. For uniformity, some submission types will need specific naming conventions for certain files. See specific subsections for more information on naming conventions.

- Security

Do not select any security settings or password protection for PDF files. Allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. The integrity of the files will be secure since they will be archived directly to tape, and a read-only copy will be provided to the reviewer.

- Indexing PDF Documents

Some subsections use indexes that are functionally accessible using the search tools available in Acrobat Exchange to help find specific documents and/or search for text within documents. These indexes should not be confused with a table of contents 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.

All indexes should be placed in a subdirectory called *indexes* in the main directory. See specific subsections for directions on the use of indexing.

IV. OTHER FILE FORMATS

Submitting parts or all of an application in electronic format as described above replaces the need for paper submissions to the archive. CDER will provide a copy of the electronic archive submission to reviewers to serve as the review copy. Because the Agency is in a transition with regard to the archiving of electronic submissions, for a limited time period, sponsors also may supply an individual reviewer with portions of the submission in paper or in another electronic format to be used with a specific review tool (e.g., database, spreadsheet, data analysis and/or word processor program). Such additional files or records would not be considered part of the archival submission. The decision to provide a specific reviewing division with files or records in a customized format should be made on a case-by-case basis after consulting with that reviewing division. The media to be used for these files should be chosen based on the type of media that can be handled by the specific review division. Possibilities include 3.5 inch floppy disks, CD ROM, and other removable media. These electronic files should be sent directly to the review division document room.

V. SUBMITTING ARCHIVAL FILES

A. Organizing the Files

All files should be placed in a main directory using the submission number as the name of the directory. For example I025987 and N025598 are used for IND and NDA numbers, respectively. The main directory should include the following:

1. A PDF file of the cover letter named *cover.pdf*, which should include:
 - Appropriate regulatory information.
 - A description of the submission.
 - A description of which portions of the submission are presented only in paper, only in electronic format, or in both paper and electronic format.
 - A description of the electronic submission including the contents of the media, their number and format, a description of the file types, and the total size of the submission (e.g., megabytes, gigabytes).
 - Verification that the submission is virus free with a description of the software used to check the files for viruses.

- A description of any deviation from the specifications in this guidance document.
2. An overall table of contents for the submission.
 3. A directory named *indexes* containing the individual subsection indexes, if appropriate. These indexes are created by a tool, such as Adobe Acrobat Catalog, and are not to be confused with the table of contents for each subsection.
 4. A separate directory for each subsection. For example, for an NDA submission, there would be a directory for case report forms (CRFs) and for case report tabulations (CRTs). All of the PDF documents for the subsection should be placed in the appropriate subdirectory. See specific subsections for information on subdirectory names and further structuring information.

B. Sending the Archival Submission to the Center

1. Media

One copy of the submission should be provided to the CDER Central Document Room (CDR) along with any paper portions of the submission. The CDR is prepared to accept electronic submissions provided on the media listed below. To optimize processing efficiency, the CDR recommends choosing media with a capacity most appropriate to the size of the submission. Whenever possible, sponsors should choose media capable of holding the submission on the fewest number of units.

<u>Size of Submission</u>	<u>Recommended Media</u>	<u>Recommended Maximum Units</u>
● Less than 10MB	3.5 inch DOS Formatted Floppy Disks	1 - 10 Floppy Disks
● Less than 3.25GB	ISO 9660	1 - 5 CDS
● Greater than 3.25GB	Digital Equipment Corp. DLT 20/40 and 10/20 GB format (exabyte 8mm format) using OPENVMS with VMS backup or NT server 4.0 with NT backup or backup exec.	1 or More Tapes

All media should arrive adequately secured in a standard binder. Label the media with the following information:

- IND or NDA number preceded by an I or N, respectively.
- Proprietary and Generic Name.
- Company name.
- Submission serial number, if applicable.
- Submission date: in the format of DD-MMM-YYYY (for example, 01-Jan-1997).
- Disk/CD-ROM/tape number (the number should include the total number submitted such as Disk # of #)

A paper copy of the cover letter described above and the appropriate regulatory forms should be included with each submission.

2. Processing

The CDR personnel will copy the PDF files to tape to create a permanent archival copy of the submission and to a server to create a read-only review copy.

C. Technical Support

Questions regarding the preparation of all submissions in electronic format should be directed to the Electronic Submissions Coordinator, Office of Information Technology, email ESUB@CDER.fda.gov.

SUBMISSION TYPE: NEW DRUG APPLICATION (NDA)

❖ **Subsection 1.1: Index (NDA Table of Contents)**

This is one of a series of subsections being developed to facilitate the electronic submission of an NDA to CDER. Subsections are published independently as they are completed, but are intended for use with the other subsections in the series.

1. Regulatory reference

Section 314.50(b) states that the archival copy of an NDA, whether in paper or electronic format, is required to contain a comprehensive index to the summary, technical sections and supporting information contained in the submission. This index is commonly referred to as the *NDA Table of Contents*.

2. Organization of files

The comprehensive index should be provided as a single PDF file named *ndatoc.pdf*.

3. Document information fields

No information is necessary.

4. Table of contents

The NDA table of contents should be provided in the form of a PDF file and list all sections of the NDA. If a section is included as paper, the volumes and page numbers should be listed for that section. If the section is included in the electronic submission, the location of files should be listed by directory. For example, case report forms (CRFs) are in the CRF directory. In the same way that page numbers provide a user with a roadmap to a document, a hypertext link should be provided from the NDA table of contents to the corresponding table of contents for each subsection.

5. Hypertext linking

No linking in addition to that described above is needed.

6. Indexing

No indexing is needed.

SUBMISSION TYPE: NEW DRUG APPLICATION (NDA)

❖ Subsection 1.11: Case Report Tabulations (CRTs)

This is one of a series of subsections being developed to facilitate the electronic submission of an NDA to CDER. Subsections are published independently as they are completed, but are intended for use with the other subsections in the series.

1. Regulatory references

Under 21 CFR 314.50(f)(1), the NDA is required to contain tabulations of the data from each adequate and well-controlled study under 314.126 (phase 2 and phase 3 studies as described in 312.21 (b) and (c) of the chapter), tabulations of the data from the earliest clinical pharmacology studies (phase 1 studies as described in 312.21(a) of the chapter), and tabulations of the safety data from other clinical studies. The tabulations are required to include the data on each patient from each study, except that the applicant may delete those tabulations the Agency agrees in advance are not pertinent to a review of the drug's safety or effectiveness.

2. File organization

CRTs are provided in two forms, domain profiles and patient profiles (described below). Consult the reviewing division to determine if both domain and patient profiles are needed, or if a single form 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 would 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 would include the results for a single patient at a single time point during the study. Include in each table the unique patient ID 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 directory identified with the study number. For

example, domain profiles for study 301 are placed into a subdirectory named *301*. Place all of these directories in a single directory named *domains*. There is no specific guidance for file naming.

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 demographics, vital signs, 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 patient ID 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 ID 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 directory identified with the site number. The term *study site* is also commonly identified as the study center or individual investigator. All site directories in a single directory should be identified by the study number. For example, all patient profiles for site 3 for study 301 would be placed into a directory named *3* which then would be placed in a directory named *301*. Place all patient profile directories in a single directory named *profile*. There is no specific guidance for file name.

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 patient ID number used in the submission. The unique patient ID 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 table of contents for all domain profiles should be provided in the form of a PDF file. In the domain profiles table of contents, all CRF domains should be listed by study. Hypertext links between the CRF domain listing in the domain profiles table of contents and the corresponding CRF domain profiles PDF files should be provided. The domain profiles table of contents should have the file name *dptoc.pdf* and be placed in the *domain* directory.

The domain profiles table of contents should be linked to the NDA table of contents for the submission.

b. Patient profiles

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

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

The patient profile table of contents should be linked to the NDA table of contents for the submission.

5. Hypertext linking

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 *domains.pdx* and placed in the subdirectory *indexes* in the main directory.

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*. and placed in the subdirectory *indexes* in the main directory.

SUBMISSION TYPE: NEW DRUG APPLICATION (NDA)

❖ Subsection 1.12: Case Report Forms (CRFs)

This is one of a series of subsections being developed to facilitate the electronic submission of an NDA to CDER. Subsections are published independently as they are completed, but are intended for use with the other subsections in the series.

1. Regulatory references

Under current regulations [21 CFR 314.50(f)(2)], an NDA “must contain copies of individual CRFs for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not....” The CRFs contain information on those patients receiving the drug and those receiving a placebo. The requirement for CRFs may be waived by FDA for specific studies if the CRFs are unnecessary for a proper review of the study. The regulation states further that the applicant “must submit to FDA additional case report forms and tabulations...as requested by the director of the FDA division responsible for reviewing the application”[21 CFR 314.50(f)(3)].

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

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 directory identified with the site number. The term *study site* is sometimes identified as the study center or individual investigator. All study site directories should be placed in a single directory identified by the study number. For example, all CRFs for site 3 for study 301 would be placed into a subdirectory named 3, which then would be placed in a directory named 301. Place all CRF directories in a single overall study directory named *CRF*. There is no specific guidance for naming individual PDF files.

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 patient ID number used in the submission. The unique patient ID 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*.

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

4. Table of contents

A table of contents of all CRFs should be provided in the form of a PDF file. In the CRF table of contents, list the unique patient ID numbers by study. Hypertext links between the patient listings in the CRF table of contents and the corresponding patient CRF PDF files should be provided. The CRF table of contents file should be named *crftoc.pdf* and placed in the CRF directory.

The CRF table of contents should be linked to the NDA table of contents.

5. Hypertext linking

Each patient's CRF file should provide a bookmark link to each study visit and/or 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 table of contents 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 subdirectory indexes in the main directory.