# Guidance for Industry

## Organization of an ANDA

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**February 1999**
**OGD # 1**
**Revision 1**

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## Organization of an ANDA

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

*(Tel) 301-827-4573*
*(Internet) http://www.fda.gov/cder/guidance/index.htm*

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## Table of Contents

# GUIDANCE FOR INDUSTRY[1]

# ORGANIZATION OF AN ANDA

## I. INTRODUCTION

This guidance describes the recommended organization of abbreviated new drug applications (ANDAs) and related submissions. This guidance summarizes suggestions for organizing an ANDA. It revises the guidance for industry on this topic issued in April 1997, which replaced the Office of Generic Drugs (OGD) Policy and Procedure Guide 30-91. During this revision, a section on the organization of an abbreviated antibiotic application was removed to make the guidance consistent with the Food and Drug Administration Modernization Act of 1997, which provides that antibiotics applications are to be treated the same as other ANDAs. Specific information on the submission of sterility assurance information also has been included.

Some ANDA submissions are difficult to review because they are complex, voluminous, or poorly organized. An application submitted in the proper format with a clear table of contents, correct folders (jackets), and correct tabulation and pagination enables the reviewer to review the submission more efficiently. For additional information, applicants are also referred to regulations at 21 CFR 314.50, 21 CFR 314.94 and 21 CFR 314.440. The suggested organization is applicable to paper and electronic submissions.

OGD strongly encourages submission of the bioequivalence, chemistry, and labeling portions of an application in electronic format to help streamline the review process. This program is currently in the ramp-up/implementation stage, with the full ANDA required in hard copy as described in this guidance. For information on how to make electronic submissions, including technical assistance, training, and free software to aid in submission preparation, applicants should access the OGD web site (http://www.fda.gov/cder/ogd/index.htm).

## II. RECOMMENDED ORGANIZATION

### A. Application Copies and General Format

Applicants should submit archival, review, and field copies of the application in English. If any part of the application is in a foreign language, an accurate and complete English translation of that part should be submitted with the application. A copy of the original reference for which an English translation is provided should also be submitted.

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[1] This guidance has been prepared by the Office of Generic Drugs (OGD), Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the organization of an abbreviated new drug application. 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 statutes, regulations, or both.

The review copy can be placed in two binders (jackets) or sets of binders (jackets) if bioavailability/bioequivalence information is needed. One binder should contain the complete chemistry, manufacturing, and controls information, and the other binder should contain the bioavailability/bioequivalence information. Both binders should contain the remaining sections of the application (e.g., table of contents, labeling) so that they can be reviewed concurrently.

Applications should be consistent with recommendations for color-coding binders (jackets), volume size and specifications, and size and quality of paper, as shown in Attachment B. Mailing instructions are also provided in that Attachment.

**B. Cover Letter**

Each submission (original, amendment, supplement, correspondence, or annual report) should be accompanied by a dated cover letter with a clear, brief introductory statement. To assist the reviewer, this cover letter should contain the following basic information about the application:

1. Purpose of the submission

2. Type of submission (ANDA, amendment, supplement, annual report, or resubmission of a previously withdrawn application)

3. Name, title, signature, and address of the applicant

4. Proprietary name (if any) and established name of the drug product

5. Number of volumes submitted

6. Commitment to resolution of any issues identified in the methods validation process after approval

7. Statement that the application or a portion of the submission is in electronic format

8. Clearly identify submissions that contain sterility assurance data

For annual reports, supplements, and amendments, either the cover letter or the narrative for the sections changed by the new submission should contain a description of the specific changes to previously submitted material. A comparison between the new and old information is often useful.

If the submission is for a specific type of supplement or amendment, the cover letter

should include a clear indication of the type of submission. Examples of supplement types include ***changes being effected*** supplements, ***expedited review requested*** supplements, and ***preapproval*** supplements. Other submissions for which a heading is helpful include bioequivalence, labeling, microbiology, or patent information. In the case of material submitted for review by the Division of Bioequivalence, the cover letter should clearly identify the type of bioequivalence submission (e.g., fasting study results, food study, multiple dose study, dissolution data, waiver request).

If the supplement is being submitted under a SUPAC[2] guidance document, the cover letter should include the following:

1. A brief description of the change addressed by the submission

2. An indication of which SUPAC guidance is referenced and a statement identifying the specific section of that guidance

3. A designation above the body of the cover letter (as well as on the exterior envelope) indicating that the submission is based on a SUPAC document

## C. Table of Contents

Each original application or other submission must include an index or a table of contents (21 CFR 314.50(b)). Attachment C provides an example and suggestions for assembling the contents of the application. This example should not be solely relied on for determining the contents of a submission.

If a section of the table of contents does not apply to a particular application, this should be stated in the table of contents, and a page should be inserted behind a tab for that section, stating "Not Applicable." If a new subsection within a section in the table of contents is added, it should be listed as a line item within the table of contents. Additional sections of the application should be placed at the end of the table of contents and should begin with the next number in sequence, as necessary. For example, all sterility assurance information should be placed in a new section (See Attachment C, Section XXII.)

If the archival or review copy of the application results in more than one volume, the table of contents should be duplicated and a copy placed in each volume. The same table of contents should appear in all volumes.

## D. Tabs

[2] SUPAC - Scale-up and Postapproval Changes - A series of guidances providing filing recommendations for certain changes in the manufacture of drug products

The contents of the submission should be organized by sections, and each section should be identified by a tab that corresponds to the section listed in the table of contents. The tab should show the section number and a brief descriptor of the section (e.g., Section VI - Bioavailability/Bioequivalence). Applicants can also use tabs for subsections within a section. In this event, use of a different color tab for the subsection would be helpful.

## E. Pagination

All pages of the application (except the tabs) should be numbered in sequence. The sequence should begin with page number one for the front side of the Application Form and continue to the end of the document without any breaks in numbering sequence. The section and line items in the table of contents should accurately reflect the page number of the corresponding text. Each submission (amendments, supplements) after the original application should also be numbered in the same manner. The page number should be placed on the bottom center of each sheet of paper.

Correct pagination is essential to the reviewer for locating material in an application. Consistent pagination between the text and the table of contents is especially important when an application consists of more than one volume.

If the review copy is in two sections to provide bioavailability/bioequivalence data separate from chemistry, manufacturing, and controls, it is understood that there will not be full numbering in the review copies for the separate disciplines. Review copies for each discipline will contain the common information and the data for review. The page numbers should be consistent with those sections in the archival copy.

## F. Field Copy - Additional Information

Applicants must submit a certification, as stated in 21 CFR 314.94, that a true third (field) copy of the technical sections (chemistry, manufacturing, and controls) of the application has been submitted to the appropriate FDA district office. Foreign applicants should submit the field copy to the Office of Generic Drugs. Attachment B provides the mailing address and specifications.

## GLOSSARY

**Abbreviated Application:** An application described under 21 CFR 314.94, including all amendments and supplements to the application.

**Archival Copy:** A complete copy of the abbreviated application intended to serve as the official reference source for the Agency. It is retained by the Agency and serves as the sole file copy of the approved application.

**Electronic Format:** The voluntary submission of parts of an ANDA in electronic media for use to facilitate the review process and in conjunction with the requisite hard copy of the application.

**Field Copy:** A duplicate of the archival copy to be submitted for use by FDA investigators.

**Review Copy:** A duplicate of the archival copy for use by Agency reviewers. It is destroyed after approval of the application.

## ATTACHMENT A

## COMPOSITION OF REVIEW COPIES

The following table illustrates the recommended separation of text for the red part of the review copy, containing chemistry, and for the orange part of the review copy, containing bioavailability/bioequivalence. The sections referred to are those shown on the suggested table of contents in Attachment C.

**TABLE: COMPOSITION OF REVIEW COPIES CORRESPONDS TO SUGGESTED TABLE OF CONTENTS (ATTACHMENT C)**

| SECTION | RED COPY | ORANGE COPY |
|---|---|---|
| I | X | X |
| II | X | X |
| III | X | X |
| IV | X | X |
| V | X | X |
| VI (BIO) | - | X |
| VII | X | X |
| VIII - XX (CHEM) | X | - |
| XXII (Micro) | X | - |

## ATTACHMENT B

## RECOMMENDED SPECIFICATIONS

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### 1. VOLUME SIZE AND IDENTIFICATION

A. The volumes of an application should not be more than 3 inches thick.

B. The name and address of the applicant, the name of the drug, dosage form, and strength of the drug should be displayed on the front of the binder (jacket) of each volume.

C. The volumes should not be numbered. The Agency will number the volumes.

D. All original abbreviated applications should be submitted in binders (jackets). Small amendments or supplements not contained within binders (jackets) should be bound with fasteners and without staples.

### 2. FOLDER COLOR AND ORDERING

A. The volume binders (jackets) of the application should be color coded.

| | Color | Form Number |
|---|---|---|
| Archival Copy | Blue | FDA 2626 |
| Review Copy | | |
| (l) Chemistry, Manufacturing and Controls (not containing Bio) | Red | FDA 2626a |
| (2) Bioavailability/ Bioequivalence | Orange | FDA 2626c |
| Field Copy (See Field Copy - Additional Information) | Burgundy | FDA 2626h |

B. A limited number of binders (jackets) may be obtained by calling the number below. The quantity that can be ordered at any one time is determined by the U.S. Government Printing Office (GPO). Additional information regarding binders may be obtained by accessing the FDA Internet site: http:/www.fda.gov/cder/ddms/binders.htm.

U. S. Government Printing Office
Washington, D.C. 20404-0001
(202) 512-1800
Program #B511-S

Additional binders (jackets) with the following specifications may be purchased from commercial sources:

(l) Archival Copy

- Polyvinyl .023 to .025 gauge
- Front cover (flat size): 248 x 292mm (9-3/4 x 11-l/2")
- Back cover (flat size): 248 x 305mm (9-3/4 x l2", including 13 mm (½") lip at top)
- Color: Blue
- Hidden reinforced l" hinges for front and back covers
- Rounded outside corners for front and back covers

(2) Review Copy

- Extra-heavy paper (or polyvinyl)
- Front cover (flat size): 267 x 292mm (10-1/2 x 11-1/2")
- Back cover (flat size): 267 x 305mm (10-1/2 x 12", including 13mm (½") lip at top), l/2" tab along the top edge.
- Color: Red and/or orange
- Hidden reinforced l" hinges for front and back covers
- Rounded outside corners for front and back covers

(3) Field Copy

- Extra-heavy paper (or polyvinyl)
  Specifications as noted
- Color: Burgundy

**3. PAPER SIZE AND QUALITY** (To allow photocopying)

- U. S. standard quality bond, 8-1/2" x ll" paper with three-holes punched on left-hand margin

- One-inch margins for readability after photocopying and binding

NOTE: Both sides of paper can be used if there is no bleed through to the second side.

**4. MAILING**

A. The packing carton should identify:

Drug name
Applicant's name
Applicant's address
"Archival Copy Enclosed" or "Review Copy Enclosed" (or both)

B. ANDAs should be mailed to:

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

C. Archival and review copies of abbreviated applications sent by overnight courier service or a parcel service should be sent to:

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room l50
Rockville, MD 20855

## ATTACHMENT C

## SUGGESTED TABLE OF CONTENTS

This suggested table of contents applies to an abbreviated new drug application (ANDA).

LIST PAGE

Section I. Signed Application Form (Recommended Form FDA 356h or Form FDA 3439; Original Signature) (§ 314.94(a)(1))

Section II. Basis for ANDA Submission (§ 314.94(a)(3))

Section III. Patent Certification (§ 3l4.94(a)(12)) and Exclusivity Statement (§ 3l4.94(a)(3))

Section IV. Comparison between Generic Drug and Reference Listed Drug (505(j)(2)(A))

1. Conditions of Use (§ 3l4.94(a)(4))
2. Active ingredient(s) and supporting information (§ 3l4.94(a)(5))
3. Inactive ingredients as appropriate (§ 314.94(a)(9))
4. Route of administration, dosage form, and strength (§ 3l4.94(a)(6))
5. Labeling comparison

Section V. Labeling (§ 314.94(a)(8))
Note: Four copies of draft labeling or twelve copies of final printed labeling should be submitted.

Section VI. Bioavailability/Bioequivalence (§ 314.94(a)(7))

1. Financial certification/disclosure statement - Form 3454 or 3455
2. In vivo study protocols
3. In vivo studies
4. Request for waiver of in vivo studies
5. In vitro dissolution data
6. Formulation data (comparison of all strengths)

Section VII. Components and Composition Statements

Section VIII. Raw Materials

1. Active ingredient(s)

    a. Synthesis listing manufacturer/supplier (Type II DMF authorization letters)
    b. Certificates of analysis specifications and test results from drug substance manufacturers
    c. Testing specifications and data from drug product manufacturer(s)
    d. Spectra and chromatograms for reference standards and test samples
    e. Retesting period

2. Inactive ingredients (§ 3l4.94(a)(9))
    a. Testing specifications (including identification and characterization)
    b. Suppliers' certificates of analysis (specifications and test results)
    c. Retest schedule

Section IX. Description of Manufacturing Facility

1. Full address(es) of the facility(ies) for the manufacturing process, testing, and stability testing
2. Brief description of the facility. For sterile products, see Section XIV.
3. CGMP certification
4. Central File Number (CFNs)

Section X. Outside Firms, Including Contract Testing Laboratories

1. Full address
2. Functions
3. CGMP certification/GLP

Section XI. Manufacturing and Processing Instructions

1. Description of the manufacturing process (including microbiological verification in Section XIV, as appropriate)
2. Blank batch records for largest intended commercial production runs with equipment specified
3. Reprocessing statement

Section XII. In-Process Information

1. Copy of executed batch record with equipment specified, including packaging records, and batch reconciliation
2. In-process controls

a. Test procedures
b. Specifications and data

Section XIII. Packaging Materials Controls

1. Summary of packaging system
2. Components specification and test data (Type III DMF references)
3. Packaging configuration and sizes
4. Container/closure testing (include ingress testing in Section XXII, as appropriate)
5. Vendor qualification specifications
6. Applicants acceptance criteria
7. Retest schedule

Section XIV. Controls for the Finished Dosage Form

1. Test procedures
2. Testing specifications and data (COA)

Section XV. Analytical Methods (two additional separately bound copies if the drug substance and/or drug product are not USP articles)

1. Methods for drug substance
   a. Method validation
   b. Test specifications and data

2. Methods for drug product
   a. Method validation
   b. Test specifications and data

Section XVI. Stability of Finished Dosage Form

1. Protocol
2. Postapproval commitments
3. Expiration dating period
4. Stability data submitted
5. Stability-indicating test data of samples under various stress conditions

Section XVII. RESERVED

Section XVIII. Samples (§ 3l4.94(a)(l0)). Sample availability and identification of:

1. Drug substance
2. Finished dosage form

Section XIX. Environmental Consideration: Environmental Assessment (EA) or Claim of Categorical Exclusion (§ 3l4.94(a)(9))

Section XX. Generic Drug Enforcement Act and U.S. Agent letter of Authorization

Section XXI. Other

1. Reference to previously submitted information (§ 3l4.94(a)(11))
2. Literature publication for which English translation is submitted (§ 3l4.94(a)(11))
3. Letters of authorization (two copies)
4. Field Copy Certification

Section XXII. Sterilization Assurance Information and Data

Note: This section can be provided as a separate volume for ease of review. If the microbiology section is in a separate volume, please provide copies of the indicated information that may be in other sections of the application instead of page references.

1. General Information
    a. Copy of cover letter (or page reference)
    b. Label/package insert copy (or page reference)
    c. Summary of manufacturing process including components and composition statement (or page reference)
    d. Copies of pages from completed batch production record containing holding times, filtration integrity testing, and sterilization records (or page reference)

Follow the portions of guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* that apply to the process in the application.