U.S. FOOD & DRUG ADMINISTRATION

Information to include with Cover Letter

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Learning Objectives

- To understand the purpose of a cover letter and the cover letter attachment
- To examine the FDA-issued guidance as it pertains to the cover letter and the cover letter attachment
- To evaluate pertinent information to include in the cover letter depending on the submission type
- To discuss the resources available to applicants to help create an effective cover letter for their submission's purpose

Purpose of Cover Letter

Purpose of Cover Letter

- To summarize contents of the submission
- To identify the purpose of the submission
- To highlight the key elements of the submission
- To provide required regulatory statements
- **To help the FDA route and manage the submission effectively**

Purpose of Cover Letter Attachment

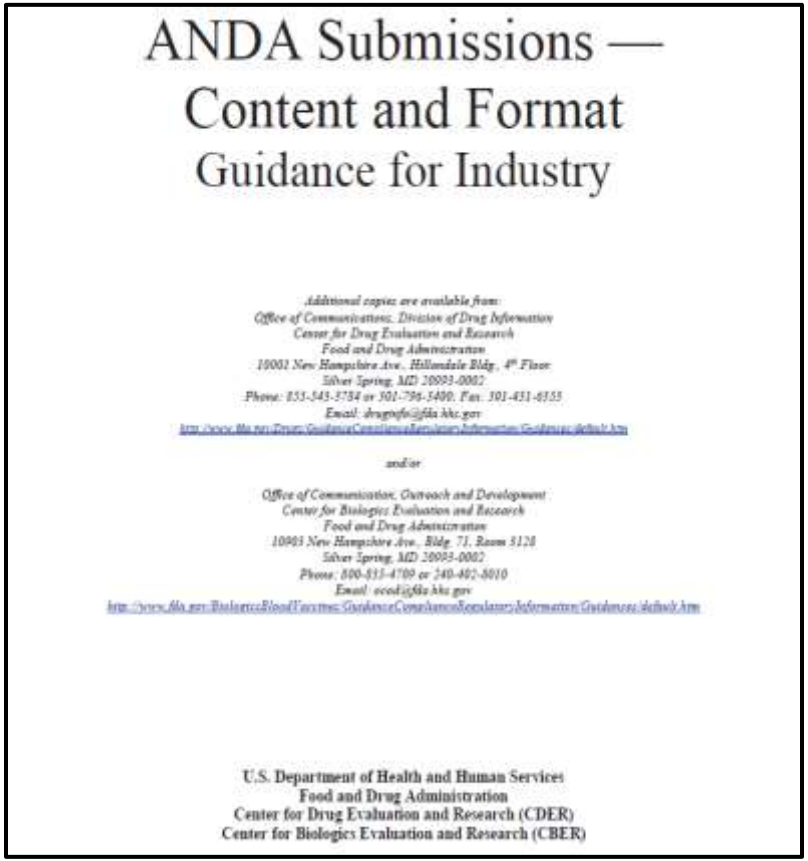
Purpose of Cover Letter Attachment

- Serves as a guide/checklist to help prepare the cover letter and submission
- Ensures that all relevant information outlined in the checklist is addressed in the corresponding cover letter
- Helps FDA in the triage/management of submissions
- Sample checklist template is provided in the guidance
- Although not a requirement, it is recommended

Guidance for Industry

Guidance for Industry

- ANDA Submissions – Content and Format
  - Current Final version: June 2019
  - Contains nonbinding recommendations
  - Applicants can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations



ANDA Submissions —
Content and Format
Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

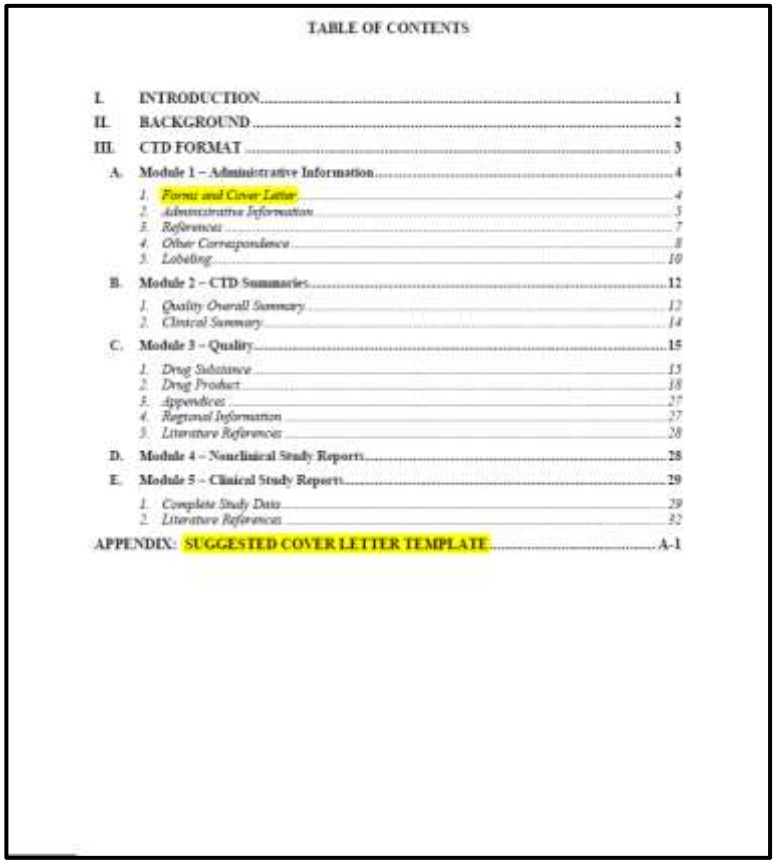
and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

Guidance for Industry

- Gives ANDA Submissions – Content and Format
- Recommendations on what generally should be included in the cover letter of submissions
- Provides a *Suggested Cover Letter Template* in the Appendix



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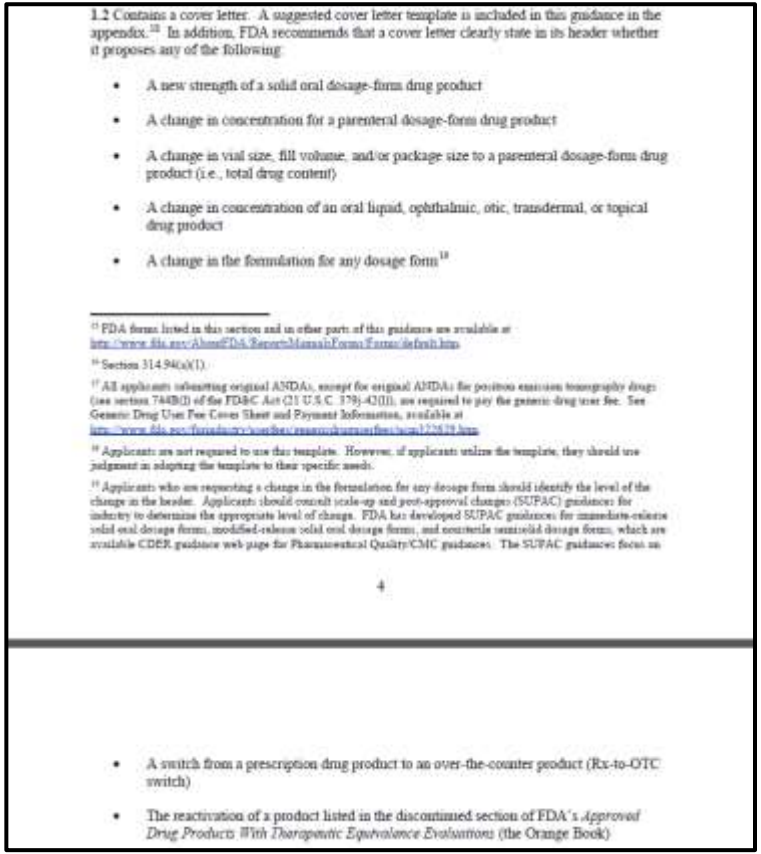
Guidance for Industry

- Cover letter is included in Module 1 of the eCTD submission
- FDA recommends that cover letter header clearly states if the applicant is proposing any major changes to the original ANDA submission (i.e., new strength, change in concentration, change in formulation, switch from RX to OTC, etc.)



1.2 Contains a cover letter. A suggested cover letter template is included in this guidance in the appendix.[18] In addition, FDA recommends that a cover letter clearly state in its header whether it proposes any of the following:

- A new strength of a solid oral dosage-form drug product
- A change in concentration for a parenteral dosage-form drug product
- A change in vial size, fill volume, and/or package size to a parenteral dosage-form drug product (i.e., total drug content)
- A change in concentration of an oral liquid, ophthalmic, otic, transdermal, or topical drug product
- A change in the formulation for any dosage form[19]

[15] FDA forms listed in this section and in other parts of this guidance are available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

[16] Section 314.94(a)(1).

[17] All applicants submitting original ANDAs, except for original ANDAs for positron emission tomography drugs (see section 744B(l) of the FD&C Act (21 U.S.C. 379j-42(l)), are required to pay the generic drug user fee. See Generic Drug User Fee Cover Sheet and Payment Information, available at http://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm125270.htm.

[18] Applicants are not required to use this template. However, if applicants utilize the template, they should use judgment in adapting the template to their specific needs.

[19] Applicants who are requesting a change in the formulation for any dosage form should identify the level of the change in the header. Applicants should consult scale-up and post-approval changes (SUPAC) guidances for industry to determine the appropriate level of change. FDA has developed SUPAC guidances for immediate-release solid oral dosage forms, modified-release solid oral dosage forms, and semisolid dosage forms, which are available CDER guidance web page for Pharmaceutical Quality/CMC guidances. The SUPAC guidances focus on

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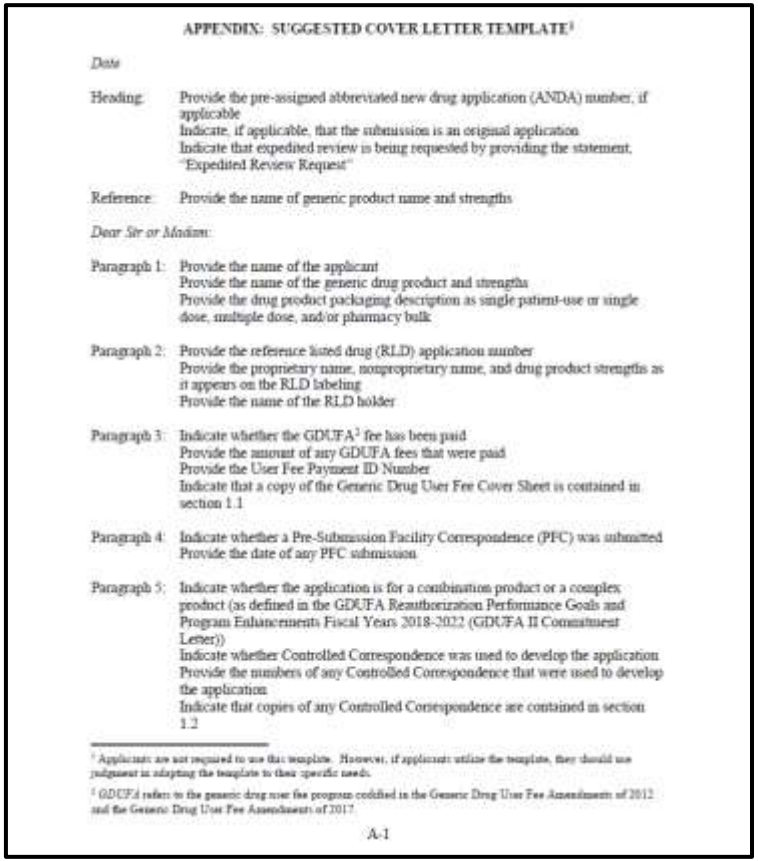
- A switch from a prescription drug product to an over-the-counter product (Rx-to-OTC switch)
- The reactivation of a product listed in the discontinued section of FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book)

Guidance for Industry

- Applicants are encouraged to use the template
- Not all paragraphs are recommended to be included for all submissions
- Applicants should adapt the cover letter to meet the specific needs and submission type



APPENDIX: SUGGESTED COVER LETTER TEMPLATE[1]

Date

Heading: Provide the pre-assigned abbreviated new drug application (ANDA) number, if applicable
Indicate, if applicable, that the submission is an original application
Indicate that expedited review is being requested by providing the statement, "Expedited Review Request"

Reference: Provide the name of generic product name and strengths

Dear Sir or Madam:

Paragraph 1: Provide the name of the applicant
Provide the name of the generic drug product and strengths
Provide the drug product packaging description as single patient-use or single dose, multiple dose, and/or pharmacy bulk

Paragraph 2: Provide the reference listed drug (RLD) application number
Provide the proprietary name, nonproprietary name, and drug product strengths as it appears on the RLD labeling
Provide the name of the RLD holder

Paragraph 3: Indicate whether the GDUFA[2] fee has been paid
Provide the amount of any GDUFA fees that were paid
Provide the User Fee Payment ID Number
Indicate that a copy of the Generic Drug User Fee Cover Sheet is contained in section 1.1

Paragraph 4: Indicate whether a Pre-Submission Facility Correspondence (PFC) was submitted
Provide the date of any PFC submission

Paragraph 5: Indicate whether the application is for a combination product or a complex product (as defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter))
Indicate whether Controlled Correspondence was used to develop the application
Provide the numbers of any Controlled Correspondence that were used to develop the application
Indicate that copies of any Controlled Correspondence are contained in section 1.2

[1] Applicants are not required to use this template. However, if applicants utilize the template, they should use judgment in adapting the template to their specific needs.

[2] *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

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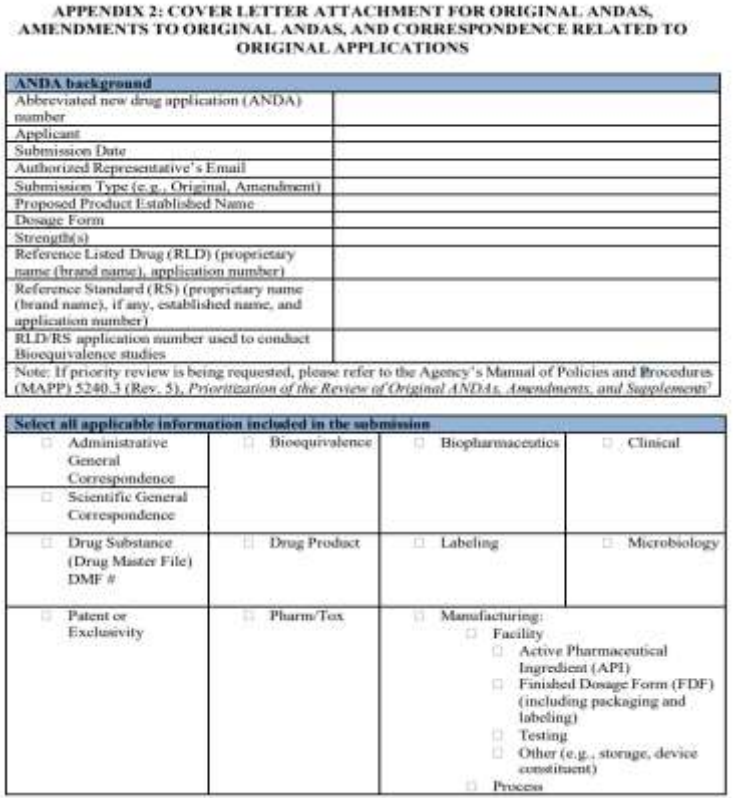
Guidance for Industry

- Cover Letter Attachments for Controlled Correspondences and ANDA Submissions
  - Current *Draft* Version: December 2021
  - Cover letter attachment templates provided for controlled correspondences, originals, amendments, and supplements
  - Modify the cover letter attachment to meet the specific needs and submission type
  - Does not replace the cover letter and is intended as an add on to the cover letter instead



APPENDIX 2: COVER LETTER ATTACHMENT FOR ORIGINAL ANDAS, AMENDMENTS TO ORIGINAL ANDAS, AND CORRESPONDENCE RELATED TO ORIGINAL APPLICATIONS

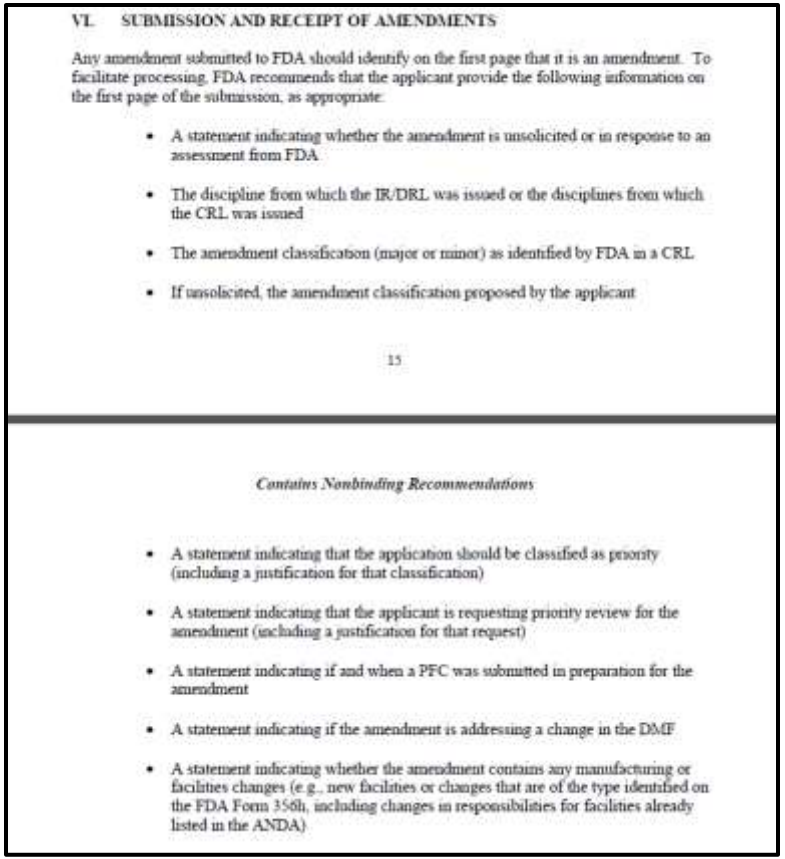
ANDA background	
Abbreviated new drug application (ANDA) number	
Applicant	
Submission Date	
Authorized Representative's Email	
Submission Type (e.g., Original, Amendment)	
Proposed Product Established Name	
Dosage Form	
Strength(s)	
Reference Listed Drug (RLD) (proprietary name (brand name), application number)	
Reference Standard (RS) (proprietary name (brand name), if any, established name, and application number)	
RLD/RS application number used to conduct Bioequivalence studies	

Note: If priority review is being requested, please refer to the Agency's Manual of Policies and Procedures (MAPP) 5240.3 (Rev. 5), *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*

Select all applicable information included in the submission			
☐ Administrative General Correspondence ☐ Scientific General Correspondence	☐ Bioequivalence	☐ Biopharmaceutics	☐ Clinical
☐ Drug Substance (Drug Master File) DMF #	☐ Drug Product	☐ Labeling	☐ Microbiology
☐ Patent or Exclusivity	☐ Pharm/Tox	☐ Manufacturing: ☐ Facility ☐ Active Pharmaceutical Ingredient (API) ☐ Finished Dosage Form (FDF) (including packaging and labeling) ☐ Testing ☐ Other (e.g., storage, device constituent) ☐ Process	

Guidance for Industry

- ANDA Submissions – Amendments to Abbreviated New Drug Applications under GDUFA
  - Current Final version: July 2018
  - Recommendations of what to include in cover letter for amendments to an ANDA
  - Again, applicants should tailor the cover letter to meet the specific needs and amendment type



VI. SUBMISSION AND RECEIPT OF AMENDMENTS

Any amendment submitted to FDA should identify on the first page that it is an amendment. To facilitate processing, FDA recommends that the applicant provide the following information on the first page of the submission, as appropriate:

- A statement indicating whether the amendment is unsolicited or in response to an assessment from FDA
- The discipline from which the IR/DRL was issued or the disciplines from which the CRL was issued
- The amendment classification (major or minor) as identified by FDA in a CRL
- If unsolicited, the amendment classification proposed by the applicant

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Contains Nonbinding Recommendations

- A statement indicating that the application should be classified as priority (including a justification for that classification)
- A statement indicating that the applicant is requesting priority review for the amendment (including a justification for that request)
- A statement indicating if and when a PFC was submitted in preparation for the amendment
- A statement indicating if the amendment is addressing a change in the DMF
- A statement indicating whether the amendment contains any manufacturing or facilities changes (e.g., new facilities or changes that are of the type identified on the FDA Form 356h, including changes in responsibilities for facilities already listed in the ANDA)

Guidance for Industry

- Information to include in the cover letter can also be found:
  - in specific guidances for submission types or
  - in a specific MAPP (Manual of Policies and Procedures)

- FDA has a quick access page to guidances and sections of the FDA MAPP
  - GDUFA Guidances and MAPPS

Cover Letter Components

Cover Letter Components

- Generally recommended for **ALL** submissions
  - On Company letterhead
  - Submission Type
  - Submission Date
  - Heading and Reference
    - ANDA number, name of generic product and strengths, sequence number

Cover Letter Components

- Generally recommended for **ALL** submissions
  - Statement of how documents were submitted and file structure
  - Name, signature, and contact information of person submitting information
  - A regulatory and technical point of contact for the submission, including email address
  - Reference, if any, to relevant FDA action letters, emails, or correspondences

Cover Letter Components

- Generally recommended for **ALL** submissions
  - Regulatory description of the submission, including appropriate regulatory information, and any desired hyperlinks to submitted information
  - MMA/verification statement
  - Technical description of the submission, including the approximate size of the submission (e.g., 2 gigabytes)
  - Statement that the submission is virus free, with a description of the software (name, version, and company) that was used to check the files for viruses

Cover Letter Components

- Generally recommended for submissions based on submission type
  - Consult applicable guidances for recommended information specific to submission type
  - Reference the aspect of CFR that is the basis of the submission (i.e., §314.65 if you are withdrawing an unapproved ANDA)

Cover Letter Components

Heading and Reference examples

April 29, 2021

Office of Generic Drugs (HFD-600),
Center for Drug Evaluation and Research,
Food and Drug Administration,
10903 New Hampshire Avenue,
Silver Spring, MD 20993

ANDA #999999
RESUBMISSION MAJOR
COMPLETE RESPONSE
AMENDMENT
FACILITY INSPECTION /LABELING
Sequence # 0031

Curallprofen Capsules, 5 mg and 10 mg (ANDA #999999) – Resubmission Major Complete Response Amendment Facility Inspection/Labeling

April 29, 2021

Office of Generic Drugs
Generic Drugs (HFD-600), CDER
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

INFORMATION REQUEST
QUALITY

Reference: **ORIGINAL ABBREVIATED NEW DRUG APPLICATION**
ANDA # 999999
eCTD Sequence # 0006
Curallprofen Capsules, 5 mg and 10 mg

Frequently Observed Errors

Frequently Observed Errors

- Missing MMA/Verification Statement [21 CFR 314.96(d)(1)]

- Missing Priority Requests on **every** resubmission after action letter after priority was granted

- Unsolicited Information
  - Information not requested by the FDA (gratuitous) but necessary for application assessment
  - Labeling updates included in submission but not requested as a part of an action letter

Frequently Observed Errors

- New or revised patent certification, litigation, or carve out updates are not noted

- Significant changes are noted on latter pages of a long cover letter
  - i.e., identifying a new strength amendment on page 10 of cover letter

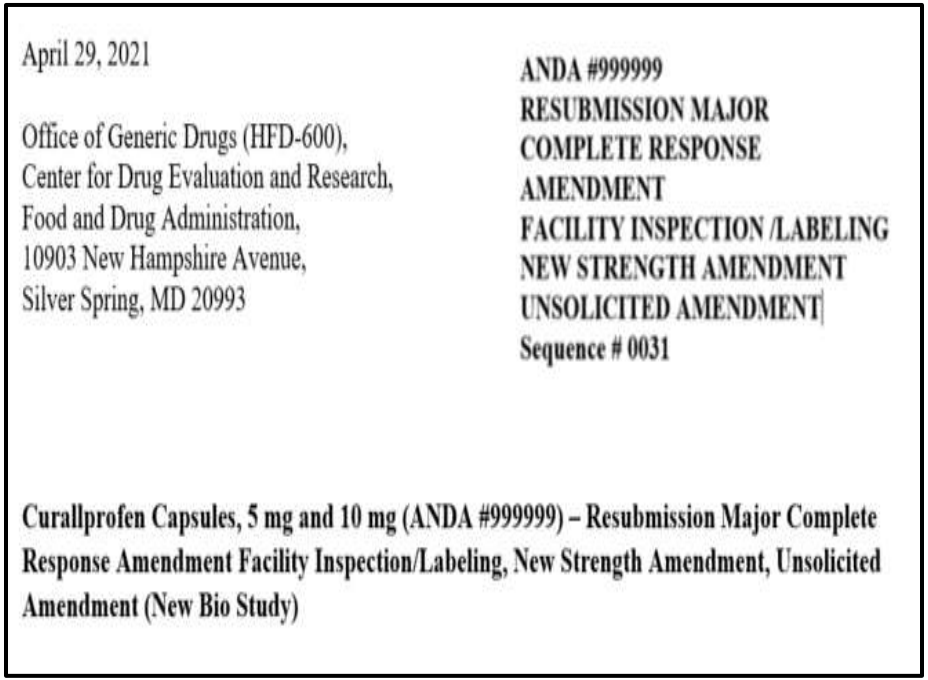
Frequently Observed Errors

- Major Amendment Information not noted
  - New batch/studies in response to deficiencies
  - Changes in manufacturing sites
    - Changes made on 356h or in Quality Section but not noted on cover letter
  - Changes to DMF
  - Changes that would require an additional filing review

Best Practices

Best Practices

- Include all new or major changes including labeling updates in header/reference if combining submissions



April 29, 2021

Office of Generic Drugs (HFD-600),
Center for Drug Evaluation and Research,
Food and Drug Administration,
10903 New Hampshire Avenue,
Silver Spring, MD 20993

ANDA #999999
RESUBMISSION MAJOR
COMPLETE RESPONSE
AMENDMENT
FACILITY INSPECTION /LABELING
NEW STRENGTH AMENDMENT
UNSOLICITED AMENDMENT
Sequence # 0031

Curallprofen Capsules, 5 mg and 10 mg (ANDA #999999) – Resubmission Major Complete Response Amendment Facility Inspection/Labeling, New Strength Amendment, Unsolicited Amendment (New Bio Study)

Best Practices

- Create a Cover Letter and Cover Letter Attachment template to include all the information typically included
  - Reduce chances of leaving out information that will require another submission (i.e., MMA/verification statement)
  - Inapplicable information can be removed as needed

- Highlight significant elements of your submission in the beginning of your cover letter
  - Order the major changes first to increase visibility

Best Practices

- Prominently identify/bold in the cover letter if a labeling carve-out is part of the submission
- Separate each item in its own paragraph
- Be concise, especially if more detail is provided within other Modules
- Use key words rather than vague and lengthy descriptions of content
  - “reformulation” vs. “changes to composition of product”

Best Practices

- Get familiar with the types of changes/information that can affect your review process and ensure those changes are always noted on your cover letter body and header
  - i.e., NSA, Facilities not ready for inspection
- Bold the text of any administrative requests that are combined with data submitted for review
  - i.e., Request for Reconsideration submitted along with CR letter response
- Use a cover letter and cover letter attachment when combining submission types and to avoid long cover letters
  - Use cover letters for responses to IRs, DRLs, and CRs rather than putting the information in the body of the cover letter

Best Practices

- For Facilities Major to Minor Requests
  - Key Word: “Facility only/based Reclassification”
  - Recommend including in the header and the body of the letter
  - Is applicable only to CR responses and should be included with CR response to be considered

Test Your Knowledge

Challenge Question 1

Which module of the eCTD submission is the Cover letter contained in?

A. Module B

B. Module 2

C. Module A

D. Module 1

Challenge Question 2

True or False: The FDA cover letter template provides information that is required for each submission.

A. True

B. False

Challenge Question 3

True or False: The FDA cover letter attachment can be used instead of the cover letter for submissions.

A. True

B. False

Summary

- Applicant should use cover letters to help the FDA identify the content and purpose of the submission
- While FDA provides some guidance for cover letters and cover letter attachments, the applicant should tailor their cover letter to meet their specific needs and regulatory requirements
- The cover letter should help guide the FDA on how to route your submission for appropriate review
- The cover letter should clearly state any significant changes to the application (i.e., formulation change, new strength amendment, etc.) in the heading and body of the cover letter
- Cover letter attachment is an excellent tool to ensure all pertinent information is addressed in the cover letter and submission

Resources

- GDUFA Guidances and MAPPS
- eCTD Technical Conformance Guide
- Code of Federal Regulations Title 21

Resources

- **Guidance for Industry**: ANDA Submissions — Content and Format of Abbreviated New Drug Applications
- **Guidance for Industry** (*Draft*): Cover Letter Attachments for Controlled Correspondences and ANDA Submissions
- **Guidance for Industry**: ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA
- **MAPP**: ANDA Amendments and Supplements Reviewed by the Division of Filing Review

For additional questions, please contact the Regulatory Project Manager (RPM) assigned to the respective ANDA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ADMINISTRATION