ANDA Project Management Topics: PLAIR and Cover Letter Attachments

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Generic Drugs Forum 2024 – April 10, 2024

An Overview to the Pre-Launch Activities Importation Request (PLAIR)

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Generic Drugs Forum 2024 – April 10, 2024

Learning Objectives

- PLAIR overview and product eligibility
- Define when and how a PLAIR can be submitted
- List the information that should be submitted to FDA in a PLAIR
- Explain the circumstances under which FDA intends to grant a PLAIR and import process

Why PLAIR

- Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) prohibits the introduction into interstate commerce any new drug, unless an approval of an application is effective
- Section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)) states in part, that a drug being imported is subject to refusal of admission if it is in violation of section 505 of the FD&C Act
- PLAIR allows, under certain circumstances, product sponsors anticipating approval of a drug application to import unapproved finished drug products to prepare for market launch

What Products Are Eligible

- A finished dosage form drug product that is being imported to prepare for U.S. market launch based on anticipated approval of a pending NDA, ANDA or BLA regulated by CDER
- A finished dosage bulk product that may either require minimal further processing (such as final packaging and/or labeling) or be in final packaged form
- PLAIR **does not** apply to APIs (Active Pharmaceutical Ingredients) or drug products subject to a pending supplement

When to Submit a PLAIR

- A PLAIR should be submitted ***at least*** 30 days prior to the proposed entry date of the shipment to allow time to process the submission
- Additional timeframes:
  - NDA/ANDA/BLAs subject to **standard review** → no more than **60 days** before user fee goal date
  - NDAs and BLAs subject to **priority review** → up to **120 days** before user fee goal date
  - ANDAs subject to **priority review** → up to **80 days** before user fee goal date

How to Submit a PLAIR

- FDA has developed an electronic submission system through the CDER NexGen Portal
- CDER NexGen Portal permits an applicant, or authorized U.S. agent, to submit a PLAIR request to FDA electronically. It provides:
  - real-time communication with receipt confirmation
  - two-way communication
  - communication history in a centralized location
  - multi-factor authentication to ensure data security

What Must Be Included in a PLAIR

- Drug product name and how supplied
- Name of the CDER Office of New Drugs or Office of Generic Drugs regulatory project manager assigned to the pending application
- National Drug Code (NDC) number, if assigned
- Name, address, registration number, and telephone number of the foreign manufacturer of the finished dosage form drug product
- Name, address, registration number, and telephone number of the U.S. consignee
- Application number for the finished dosage form drug product pending FDA approval
- Letter from FDA officially documenting the user fee goal date
- Precise quantities to be imported (Only one import shipment will be allowed under a granted PLAIR)

What Must Be Included in a PLAIR

(cont'd)

- Name, address, facility identification number and telephone number of any facility where the finished dosage form drug product in final packaged form will be stored pending approval.
- When the finished dosage form drug product is imported for minimal further processing, information regarding the facility where minimal further processing activities will occur, including:
  (1) the name, address, and registration number of the facility; and
  (2) a description of the further processing activities.
- The authorized representative or applicant will also:
  - acknowledge that the product is an unapproved new drug
  - That the PLAIR represents the applicant's request to recondition the product, under section 801(b) of the FD&C Act and 21 CFR 1.95, by obtaining product approval within the specified timeframe.

What Actions FDA Will Take

- Once a complete PLAIR is submitted, the CDER PLAIR Program will confirm receipt of the submission through the CDER NexGen Portal
- CDER will review the submission and assess, completeness, timeliness, and among other things, the foreign facility's inspection history and conformity with applicable CGMP (e.g., 21 CFR parts 210 and 211)
- Following this review, the CDER PLAIR Program will notify the applicant whether the PLAIR has been granted or denied through the CDER NexGen Portal

Importation of a PLAIR

- Importer uploads the granted PLAIR Letter into ITACS or emails the Import Division of the Office of Regulatory Affairs (ORA) where the entry will be presented
- Use the Affirmation of Compliance (PLR) and the associated drug application number in the Automated Commercial Environment (ACE)
- Ensure that the foreign manufacturer is registered, and include all known importers in their registration prior to importation
- Ensure that all entry information matches the information in the granted PLAIR such as the drug name, quantity of drugs, dosage and strength, NDC code, the consignee, and storage location

Importation of a PLAIR (cont'd)

- FDA will detain the product for 6 months as an unapproved new drug and to authorize the reconditioning in the manner and under conditions set forth in the PLAIR
- Securing release after detention:
  - When the application is approved
  - Upload the approval letter into ITACS and CDER Portal or email the FDA Import District where the product is detained to secure release of the entry
  - No FDA Form 766 is required; the PLAIR covers what will be done to bring the product into compliance.

Importation of a PLAIR (cont'd)

- FDA intends to refuse the unapproved drug if the application is not approved, or 6 months has passed since the detention.
  - The unapproved finished dosage form drug product must be exported or destroyed within 90 days if it is refused admission.

Resources

- PLAIR Guidance for Industry
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pre-launch-activities-importation-requests-plair
- Human Drug Imports
  https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-imports
- Automated Commercial Environment/International Trade Data System(ACE/ITDS)
  https://www.fda.gov/industry/import-systems/automated-commercial-environmentinternational-trade-data-system-aceitds
- Import Trade Auxiliary Communications System
  https://www.access.fda.gov/itacs/#/

Contacts

PLAIR Program
Imports Compliance Branch
Division of Global Drug Distribution and Policy
Office of Drug Security, Integrity and Response
Office of Compliance
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Main number: 301-796-3130

CDER-OC-PLAIR@fda.hhs.gov

Division of Import Operations
Office Of Import Operations
Office of Regulatory Affairs

Food and Drug Administration
12420 Parklawn Drive, Rm.3109
Rockville, MD
Main number: 301-796-0356

FDAImportsInquiry@fda.hhs.gov

Pre-Launch Activities Importation Request (PLAIR)
&
The Division of Project Management (DPM)

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Office of Regulatory Operations
Office of Generic Drugs | CDER | U.S. | FDA

Learning Objectives

- Describe OGD's PLAIR process for ANDAs
- Explain OGD's goal for PLAIR
- Tips for FDA to grant PLAIR

PLAIR Process

1. Office of Compliance (OC) evaluates the PLAIR request and assigns it to Deputy Director, Division of Project Management (DPM)
2. DPM's role is to decide if the PLAIR should be Granted or Denied
3. PLAIR guidance provides request submission timeframes
   - No less than 30 days
   - 60 days for standard
   - 80 days for priority

PLAIR Process (cont.)

4. Deputy Director (DD) checks database and if outcome is unclear, requests Regulatory Project Manager (RPM) evaluate on likelihood of disciplines being adequate (AD) or inadequate (IN)
5. RPM consults with discipline PMs and if outcome is IN, recommends denial
6. If pending discipline(s) likely AD (and other disciplines are AD), RPM recommends it be granted
7. DD communicates Grant/Deny decision to OC

PLAIR Goal

- OGD's goal is to maximize the usefulness of PLAIR program by granting in advance of the goal date, whilst avoiding a granted PLAIR that inaccurately indicates an upcoming action
- There will be more PLAIRs granted independent of a formal AD decision
- There will be more time required to grant the PLAIR

PLAIR for Original and Majors

- For PLAIRs submitted in a pending original ANDA or major amendment OGD will now delay its response to a PLAIR if OGD believes an assessment decision is coming soon. (Previously, OGD would immediately recommend denial in the absence of the ANDA assessments being complete and adequate for relevant portion(s) of the pending application.)
- By deferring decision-making on PLAIRs in this situation to later in the review cycle, the goal is to allow for more PLAIRs to be granted.

PLAIR for Minors

- For PLAIRs submitted in a pending minor amendment, if the discipline(s) have not yet completed their assessments when a PLAIR is received, OGD may now recommend granting the PLAIR absent a signal of a potential deficiency. (Previously a grant decision was only made when the disciplines had completed their assessments and found their portion of the application to be adequate.)

PLAIR Note

- FDA's granting of a PLAIR does not represent an implicit or explicit statement of the approvability of the ANDA, and if FDA does not approve the application, the product is subject to refusal of admission into the United States.

Tips

1. Complete your Amendments
2. Address Information Requests/Discipline Review Letters (IR/DRLs) on time
3. Assure facilities are adequate
4. Assure Drug Master Files (DMFs) are adequate and aware of ANDA action timing
5. Work with your Regulatory Project Manager (RPM)
    - **Cannot** provide approval date
6. Subsequent PLAIR allowed

Challenge Question #1

When should a PLAIR NOT be submitted?

A. No more than 60 days before goal date for ANDAs subject to standard review

B. At least 30 days prior to proposed entry date of shipment

C. Up to 120 days before goal date for ANDAs subject to priority review

D. Up to 80 days before goal date for ANDAs subject to priority review.

Summary

Information to Include With a Cover Letter

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SBIA Generic Drugs Forum 2024 – April 10, 2024

Learning Objectives

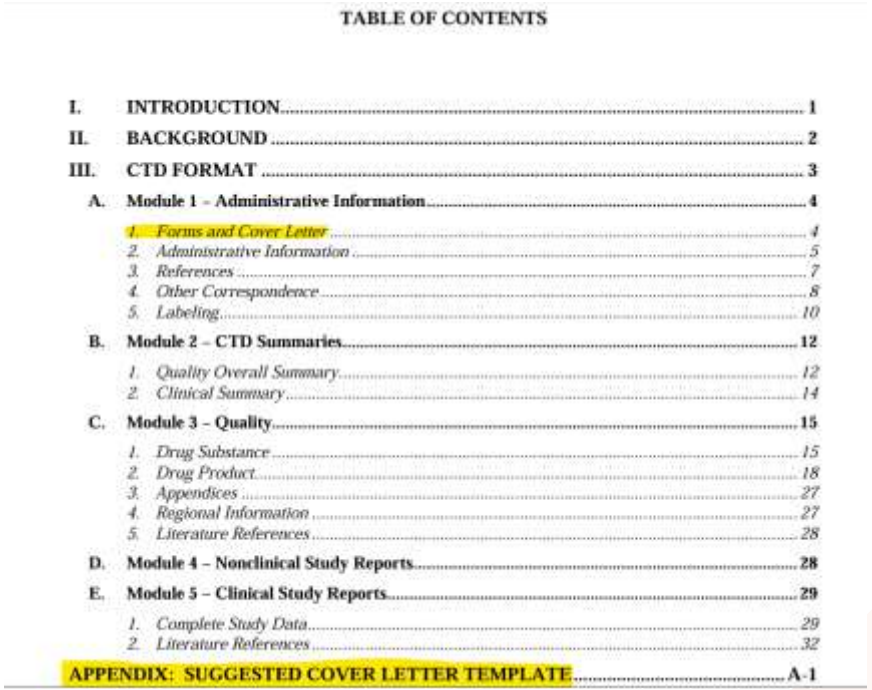
- Explain the purpose of a cover letter and the cover letter attachment
- Examine the FDA-issued guidances related to cover letters
- Evaluate pertinent information to include with a cover letter based on the submission type
- Discuss available resources for applicants to draft an effective cover letter

Purpose of a Cover Letter

- Summarize the contents and identify the purpose of the submission
- Highlight key elements of the submission
- Provide required regulatory statements
- **Help the FDA route and manage the submission effectively**

ANDA Submissions: Content and Format - Guidance

- **Current Final Version**: June 2019
- Recommendations on what should be included in the cover letter
- Provides a *Suggested Cover Letter Template* in the Appendix



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ANDA Submissions: Content and Format - Guidance

- Cover letter is included in Module 1 of the eCTD submission

- Cover letter **header** recommendation
  - Clearly state if any major changes to the original ANDA submission are proposed

A. Module 1 – Administrative Information

1. Forms and Cover Letter

Section 1.1 contains the following forms:[15]

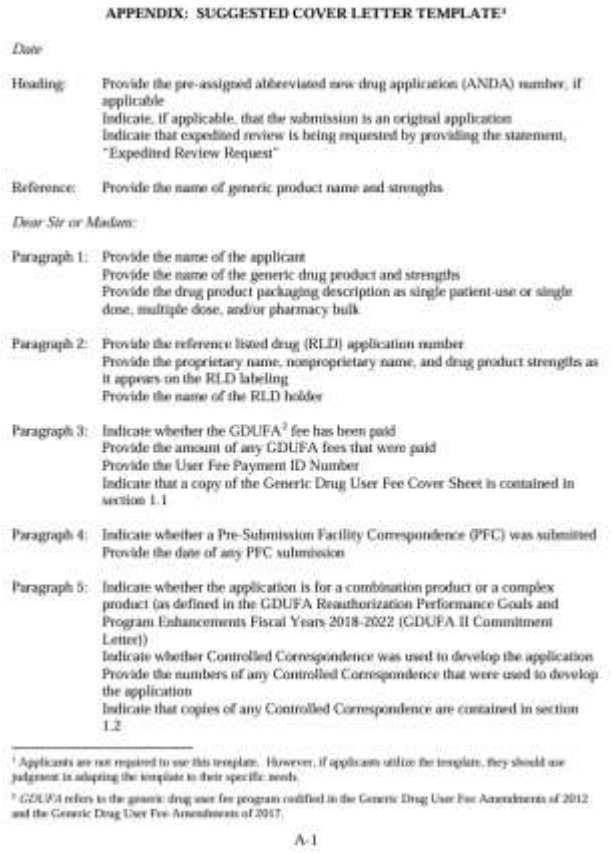
- Form FDA 356h (Form 356h) – Application to Market a New or Abbreviated New Drug or Biologic for Human Use, which ANDA applicants must fully complete and sign for their submissions[16]
- Form FDA 3794 – Generic Drug User Fee Cover Sheet[17]
- Form 3674 – Certification of Compliance Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

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]
- 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)

ANDA Submissions: Content and Format - Guidance

- Applicants are encouraged to use the template
- Applicants should adapt the cover letter to meet the specific needs and submission type
  - Choose applicable paragraphs listed in the Appendix



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.

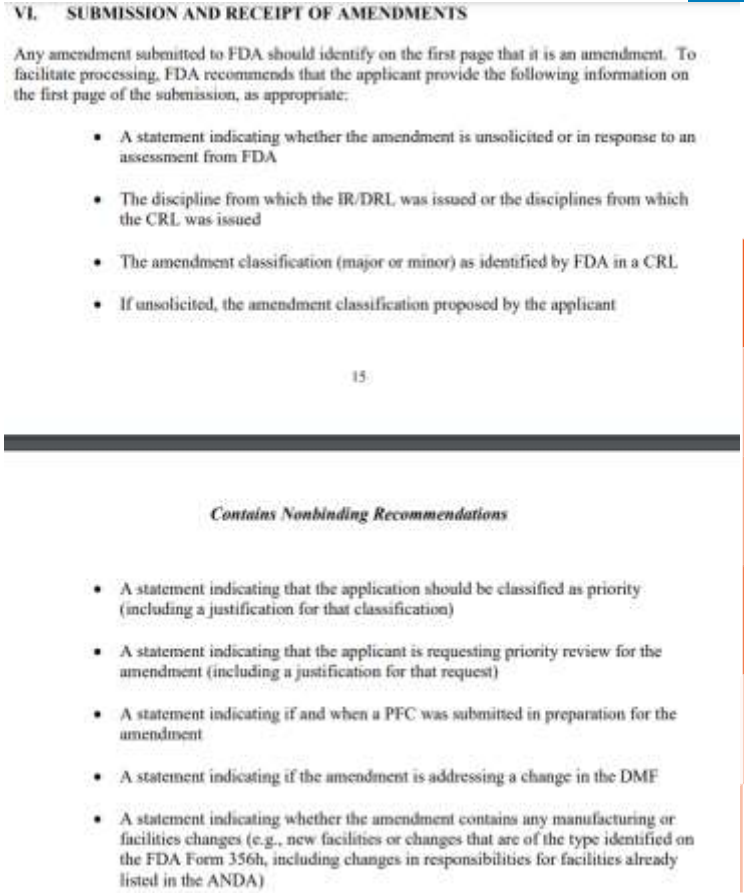
[2] *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

A-1

ANDA Submissions: Amendments to ANDAs under GDUFA - Guidance

- **Current Final Version:** July 2018

- Recommendations for content to include in a cover letter for ANDA **amendments**



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

15

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)

Cover Letter Components

- Company letterhead
- Submission Type
- Submission Date
- Heading and Reference
  - ANDA #, name of generic product and strength(s), eCTD sequence #

Cover Letter Components

Heading Example

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

Reference Example

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

Cover Letter Components

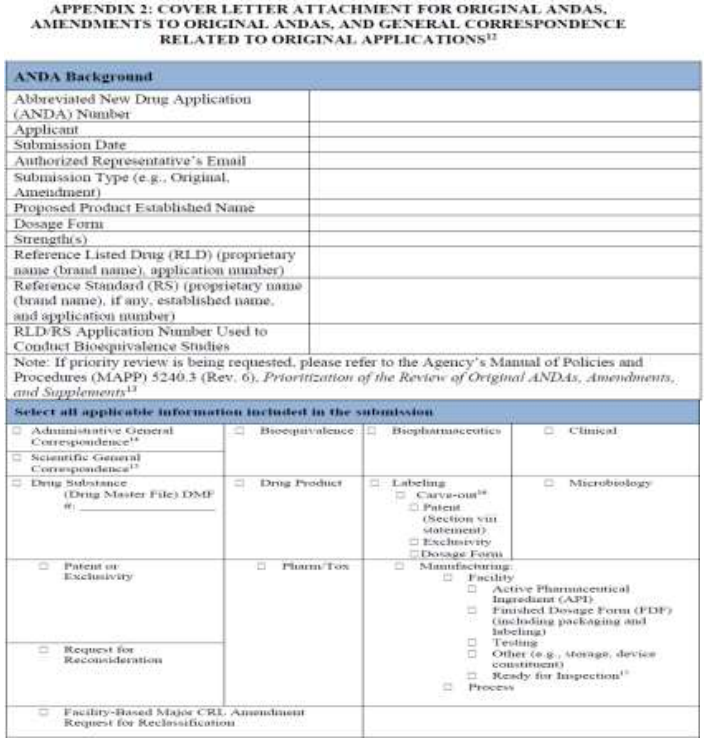
- Statement of how documents were submitted and file structure
- Name, signature, and contact information of person submitting information
- A responsible official or U.S. Agent for the submission, including email address
- Reference, if any, to relevant FDA action letters, emails, or correspondences

Cover Letter Components

- MMA/verification statement [21 CFR 314.96(d)]
- Regulatory description of the submission, including:
  - appropriate regulatory information
  - hyperlinks to submitted information
- 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

Purpose of a Cover Letter Attachment

- Serve as a guide/checklist to prepare the cover letter
  - Facilitates accurate processing of the submission
- Ensure all relevant information outlined in the checklist is addressed in the cover letter
- Help FDA triage and manage submissions



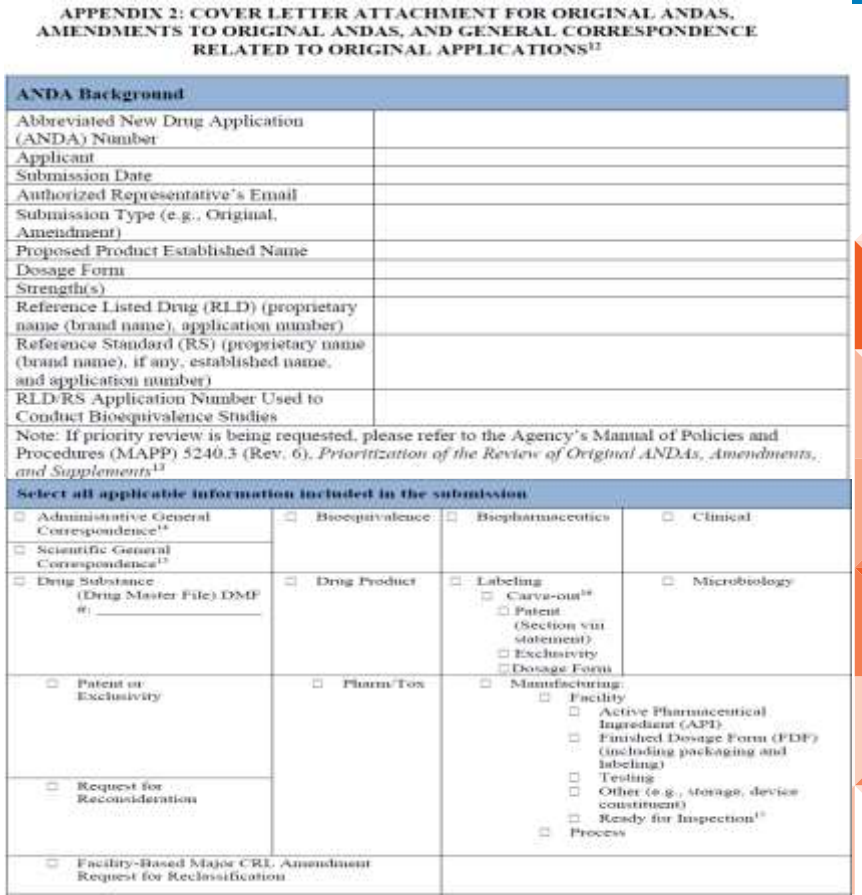
APPENDIX 2: COVER LETTER ATTACHMENT FOR ORIGINAL ANDAS, AMENDMENTS TO ORIGINAL ANDAS, AND GENERAL CORRESPONDENCE RELATED TO ORIGINAL APPLICATIONS[12]

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. 6), *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*[13]	

Select all applicable information included in the submission			
☐ Administrative General Correspondence[14] ☐ Scientific General Correspondence[15]	☐ Bioequivalence	☐ Biopharmaceutics	☐ Clinical
☐ Drug Substance (Drug Master File) DMF #: _____	☐ Drug Product	☐ Labeling ☐ Carve-out[16] ☐ Patent (Section viii Statement) ☐ Exclusivity ☐ Dosage Form	☐ 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) ☐ Ready for Inspection[17] ☐ Process	
☐ Request for Reconsideration			
☐ Facility-Based Major CRL Amendment Request for Reclassification			

Cover Letter Attachments for Controlled Correspondence and ANDA Submissions - Guidance

- **Current Final Version:** June 2023
- Cover Letter Attachment Templates for
  - Controlled correspondences
  - Originals
  - Amendments
  - Supplements
- Applicants can modify the cover letter attachment templates



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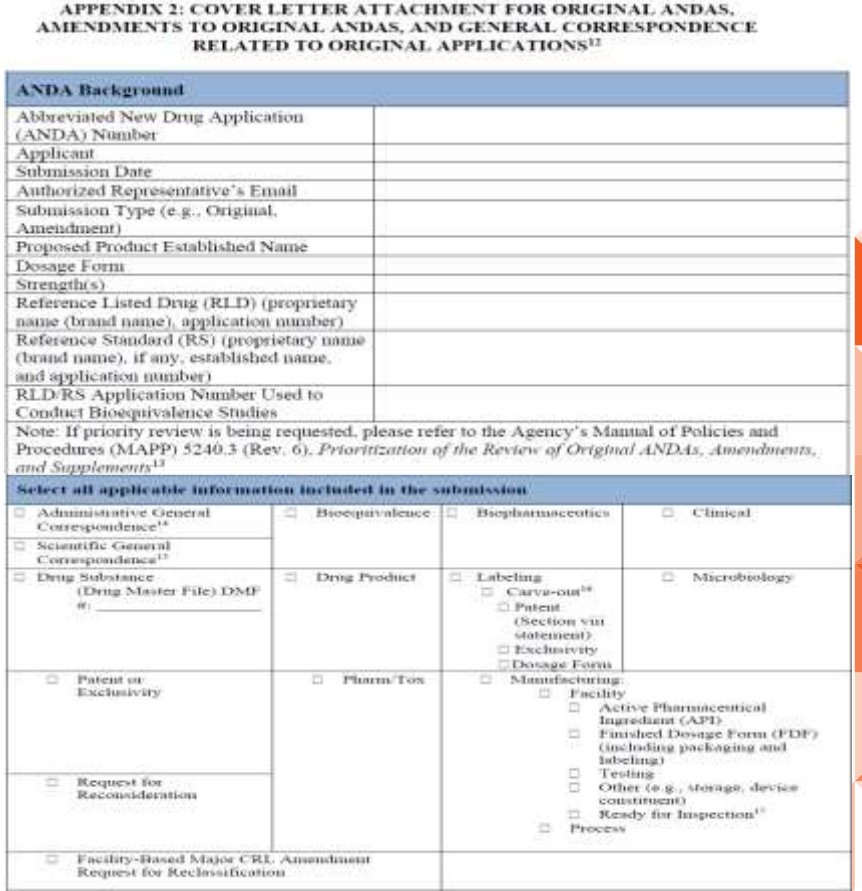
☐ Facility-Based Major CRL Amendment Request for Reclassification			

Cover Letter Attachments for Controlled Correspondence and ANDA Submissions - Guidance

- Does not replace cover letter contents but intended as an Add On
- **Assists FDA in identifying and routing submissions correctly**
  - Highly recommended to prevent delays in review time
  - Example: Request for Reconsiderations and Facility-Based Request for Reclassifications are especially difficult to differentiate and will benefit with the use of a cover letter attachment



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☐ Facility-Based Major CRL Amendment Request for Reclassification			

Information Commonly Omitted in a Cover Letter

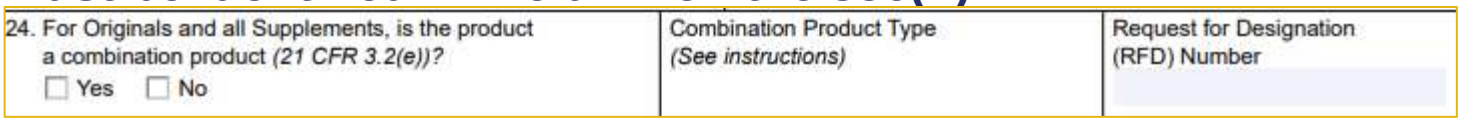
- MMA/Verification Statement [21 CFR 314.96(d)]
- Priority requests on **every** resubmission after priority was previously granted
- Unsolicited (gratuitous) information
- New or revised patent certification, litigation, or carve out updates
- Facility Based Major to Minor Reclassification Requests:
  - cGMP Downgrade letter or Withdrawn Facility Statement WITH additional statement stating the facility did not manufacture batches and conduct analyses to support approval of application (MAPP 5021.5 [Rev. 1])

Information Commonly Omitted in a Cover Letter

- Major Amendment information
  - New batch/studies
  - Changes in manufacturing sites
  - Reformulations
  - Changes to DMF
  - Changes that would require an additional filing review

Information Commonly Omitted in a Cover Letter

- Identification of a Combination Product
  - Under section 503(g)(8)(C)(v), sponsors are required to identify their products as combination products in seeking Agency action with respect to the product
  - Can be identified in a Cover Letter Attachment
  - **Must be identified in Field 24 on the 356(h)**



24. For Originals and all Supplements, is the product a combination product *(21 CFR 3.2(e))?* ☐ Yes ☐ No	Combination Product Type *(See instructions)*	Request for Designation (RFD) Number

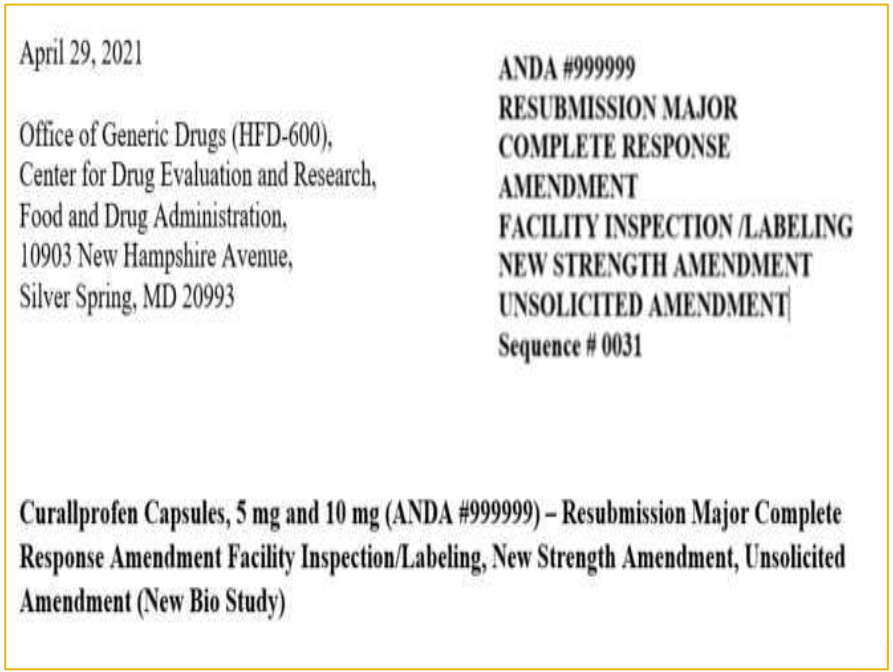
    - Current GMP manufacturing practice requirements
    - Postmarketing safety reporting requirements at 21 CFR Part 4 Subpart B

What is a Combination Product?

- A product comprised of two or more different types of medical products (e.g., a drug/device, drug/biologic, device/biologic, or all three together).
  - For a more exhaustive list of what constitutes a combination product, see *21 CFR 3.2(e)*
  - For any questions, please contact Office of Combination Products at combination@fda.gov

Best Practices

- Include all new or major change information 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

- Although not required, it is highly recommended to include a cover letter attachment with your cover letter
- Highlight significant elements of your submission in the beginning of your cover letter
- Prominently identify/bold if there's a labeling carve-out
- Separate each item in its own paragraph
- Use key words vs. vague or lengthy descriptions
  - e.g., "reformulation" vs. "changes to composition of product"

Challenge Question

What are the commonly omitted information that should be included in a cover letter? (choose all that apply):

A. New batches/studies

B. Changes in manufacturing sites

C. Mention of unsolicited information in submission

D. Priority requests on all submissions, if applicable

Summary

- Cover Letter:
  - Should be used to help the FDA identify the purpose and route the content of the submission
  - Should clearly state any significant changes to the application in the heading/reference and body of the cover letter
- Cover letter attachment:
  - Assists FDA in identifying and routing submissions correctly and is highly recommended to prevent delays in review time

Resources

- Guidance for Industry: ANDA Submissions – Content and Format
- Guidance for Industry: Cover Letter Attachments for Controlled Correspondence 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
- GDUFA Guidances and MAPPs
- eCTD Technical Conformance Guide
- Code of Federal Regulations Title 21
- 21 CFR 3.2(e) on Combination Products
- Combination Product Definition and Combination Product Types

Questions?

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Generic Drugs Forum 2024 – April 10, 2024


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