# Cover Letter Attachments for Controlled Correspondences and ANDA Submissions

## Guidance for Industry

***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Nicole Park 240-402-7764.

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

**December 2021**
**Generics**

***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

# Cover Letter Attachments for Controlled Correspondences and ANDA Submissions

## Guidance for Industry

*Additional copies are available from:*
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https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

**December 2021**
**Generics**

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# Cover Letter Attachments for Controlled Correspondences and ANDA Submissions
# Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

This guidance is intended to assist prospective applicants, applicants, and holders of abbreviated new drug applications (ANDAs) with optional attachments that can be used when preparing cover letters that accompany controlled correspondence[2] to the Office of Generic Drugs (OGD), as well as original ANDAs, amendments to ANDAs, and supplements to approved ANDAs submitted to FDA. These attachments do not replace the recommendations for the content of cover letters provided in other FDA guidances.[3]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidance means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] *Controlled correspondence* is correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development. See GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter) available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf. See also the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (November 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[3] Recommended content of cover letters (or first page of submission) is provided in the following guidances for industry: *Controlled Correspondence Related to Generic Drug Development* (December 2020); *ANDA Submissions—Content and Format* (June 2019); *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018); and *ANDA Submissions–Prior Approval Supplements Under GDUFA* (October 2017). We update guidance periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

## II. BACKGROUND

A cover letter is generally included with controlled correspondence to OGD and submissions to an ANDA file. While a cover letter is not required content for an ANDA, the cover letter is a part of the electronic common technical document (eCTD) hierarchy and is included in Module 1 of an ANDA submission.[4]

The cover letter provides an overview of the submission and helps FDA ensure that the submission is properly triaged and assigned to the appropriate assessors. In an effort to ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments (GDUFA),[5] FDA has developed cover letter attachments to accompany, not replace, the applicant's cover letter for the following common submissions: controlled correspondence, original ANDAs and amendments to ANDAs, and supplements to approved ANDAs.

## III. USING THE COVER LETTER ATTACHMENTS

The cover letter attachments provided in this guidance have been developed by the disciplines that receive and respond to controlled correspondence and that assess ANDAs (including amendments and supplements). The cover letter attachments have been designed as a checklist to reflect common types of information applicants are expected to address in the cover letter for their submission. Please note that these checklists are not an exhaustive list of the information needed from applicants. There may be additional items that need to be submitted with the application, for example, information related to patents and exclusivities.

We recommend that prospective ANDA applicants, ANDA applicants, and ANDA holders complete and submit the appropriate attachment(s) along with their cover letter. Applicants are not required to submit an attachment with their cover letter; however, the optional checklist attachment can be a useful guide to help applicants prepare their cover letters. Completing a relevant checklist and attaching it to the cover letter submission is helpful to FDA in the triage of applications and management of submissions. The format of the checklist may be adapted by the applicant for their convenience. The main purpose of the cover letter attachment is to help applicants ensure that they are addressing relevant information outlined in the checklist in any cover letter submitted to FDA for the submissions covered in this guidance.

The attachment provided in Appendix 1 of this guidance is intended for use with controlled correspondence submitted to OGD. The attachment provided in Appendix 2 of this guidance is intended for original ANDA submissions, amendments to original ANDAs, and any correspondence associated with that original ANDA. The attachment provided in Appendix 3 of the guidance is for supplements to approved ANDAs, amendments to pending supplements,

[4] See *The Comprehensive Table of Contents Headings and Hierarchy*, available at https://www.fda.gov/media/76444/download.

[5] See Generic Drug User Fee Amendments of 2012 (Public Law 112-144, Title III) and FDA Reauthorization Act of 2017 (Public Law 115-52, Title III). See also GDUFA II Commitment Letter.

73 submissions to tentatively approved ANDAs under the President's Emergency Plan for AIDS
74 Relief (PEPFAR) program,[6] and any correspondence related to these submissions.
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[6] Under PEPFAR, certain antiretroviral products that have been granted a tentative approval may be distributed for use outside of the United States, even when there is still patent and/or exclusivity protection in the United States. See FDA's PEPFAR web page, available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar.

## APPENDIX 1: COVER LETTER ATTACHMENT FOR CONTROLLED CORRESPONDENCES

| **Controlled Correspondence (CC) Background** | |
|---|---|
| Submission Date | |
| Subject | |
| **Person submitting the CC** | |
| Name | |
| Title | |
| Entity (e.g., corporate affiliation)<br>Note here if this is a U.S. Agent or the Prospective Applicant | |
| Address | |
| Phone number | |
| Email | |
| **Relevant Reference Listed Drug (RLD)/Reference Standard (RS) information** | |
| Application number | |
| Proprietary (brand) name | |
| Manufacturer | |
| Established Name | |
| Dosage form | |
| Strength(s) | |
| **CC Information** | |
| Concise statement of the inquiry | |
| Prospective applicant's recommendation of the appropriate FDA review discipline | |

| **Additional Background** | **Yes** | **No or N/A** |
|---|---|---|
| Are copies of relevant prior research, background information, and supporting materials included with the CC submission? | | |

**Previous CC History**

- **If this is related to a previous CC that was accepted for substantive review and response, provide the FDA-assigned CC number and submission date.**
- **Include copies of all previous, related CC(s) accepted for substantive review and response and the Agency's response.**

| **Previous CC Number** | **Submission Date** | **Concise Statement of Inquiry** | **Concise Statement of Agency's Response** |
|---|---|---|---|
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| **Related Submissions**<br>• **If this is related to a submitted abbreviated new drug application (ANDA) or a pre-assigned ANDA, provide the information below.** | | |
|---|---|---|
| **ANDA Number** | **Submission Date** | **Submission Status** |
| | | |
| | | |
| | | |
| | | |
| | | |

List of attachments provided:

1.
2.
3.

88 **APPENDIX 2: COVER LETTER ATTACHMENT FOR ORIGINAL ANDAS,**
89 **AMENDMENTS TO ORIGINAL ANDAS, AND CORRESPONDENCE RELATED TO**
90 **ORIGINAL APPLICATIONS**
91

| **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*[7] | |

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

[7] FDA's MAPP 5240.3 (Rev. 5) is available at https://www.fda.gov/media/89061/download.

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| Additional background | Yes | No or N/A |
|---|---|---|
| 1. Is the email secure?<br>If no, apply for a secure email with the FDA by contacting secureemail@fda.hhs.gov | | |
| 2. Was a Pre-Submission Facility Correspondence (PFC) submitted? | | |
| 3. If a PFC was submitted, have any changes been made to the pre-submitted facility information? | | |
| 4. Does the submission contain any technology that has been accepted into or may qualify for the Emerging Technology Program[8]? | | |
| 5. For all submissions: Was a Competitive Generic Therapy (CGT) designation granted for a drug product or drug products under this ANDA? | | |
| 6. For original ANDAs: Is a CGT designation request being made concurrently with the original ANDA submission?<br>If yes, please refer to the guidance for industry *Competitive Generic Therapies* (March 2020) for additional information on what to include in the cover letter.[9] | | |
| **Drug-device combination product** | **Yes** | **No or N/A** |
| 7. Is the proposed product a drug-device combination product?<br>If yes, answer questions #8 and #9<br><br>Note: If this is a combination product, mark the corresponding box to identify it as such on line #24 of the FDA Form 356h | | |
| 8. Does the submission include comparative analyses for a drug-device combination product?<br>If yes, then specify location in the submission: | | |
| 9. Does the submission include additional data and/or information, such as data from a comparative use human factors study, to support differences in user interface?<br>If yes, then specify location(s) in the submission: | | |

[8] See guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2017).

[9] This guidance recommends including a statement supporting the request for designation and information supporting the assertion that there is inadequate generic competition for the drug product under section 506H of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356h).

| Study Information | Yes | No or N/A |
|---|---|---|
| 10. Does the submission include an alternate method for demonstrating bioequivalence (BE) (e.g., modeling, in vitro testing) that deviates from the current recommendations in a Product-Specific Guidance? | | |
| 11. Does your submission include a request for a waiver under 21 CFR 320.22?<br>If yes and referencing a BE study submitted under a different application, then include the original BE study's ANDA number, submission date, and the module for the BE study referenced in support of the waiver request in the current submission: | | |
| 12. Are there any additional data and/or information from comparative studies (e.g., in-vitro studies, failed BE studies) included in other modules besides module 5?<br>If yes, then specify study type and location in the submission: | | |
| 13. Does the submission include a Pharmacology/Toxicology (safety) justification, for example, nonclinical studies as defined in 21 CFR 58.3(d)?<br>If yes, then specify justification/study type and location in the submission: | | |

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| **Proposed product development history**<br>• **For original ANDAs: ensure that copies of all related pre-ANDA communications accepted for substantive review and the Agency's response (e.g., controlled correspondence, pre-ANDA meeting written responses) are included in your submission**<br>• **For subsequent amendments: only include updates or new information since last submission, as applicable** | | |
|---|---|---|
| **Complete this section to document any prior FDA communications for this ANDA, as appropriate** | **Yes** | **No or N/A** |
| 1. Controlled correspondence(s)<br>If yes, include #(s) and date(s): | | |
| 2. Protocol review(s)<br>If yes, include #(s) and date(s): | | |
| 3. Bio-investigational new drug (Bio-IND) protocol review(s)<br>If yes, include #(s) and date(s): | | |
| 4. Approved suitability petition for the basis of submission, as per 21 CFR 314.94(a)(3)(iii)<br>If yes, include docket number and a copy of FDA's correspondence approving the petition: | | |

| | | |
|---|---|---|
| 5. Approved citizen petition requesting a specific basis of submission<br>If yes, include docket number: | | |
| 6. Pre-ANDA meeting(s)<br>If yes, include #(s) and date(s): | | |
| 7. Scientific General Correspondence(s)[10] after complete response letter (CRL) response (for amendments only)<br>If yes, include #(s) and date(s): | | |
| 8. Device related communication(s) (for drug-device combination product only)<br>If yes, include #(s) and date(s): | | |

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| **For Amendments Only** | | | |
|---|---|---|---|
| **Type of amendment** | **Date of FDA correspondence or action that elicited the amendment (e.g., CRL, discipline review letter (DRL), information request (IR), or tentative approval (TA)** | **Is this a response to a CRL?** | |
| | | **Yes** | **No or N/A** |
| Unsolicited | | | |
| Solicited | | | |
| Post-TA amendment | | | |
| Post-TA Request for Final Approval | | | |
| **Patent Certification/Statement** | | **Yes** | **No or N/A** |
| 1. Does the submission contain any of the following changes?<br><br>(i) To add a new indication or other condition of use;<br>(ii) To add a new strength;<br>(iii) To make other than minor changes in product formulation; or<br>(iv) To change the physical form or crystalline structure of the active ingredient<br><br>If yes, please address this according to 21 CFR 314.96(d)(1)<br><br>If no, please provide a statement according to 21 CFR 314.96(d)(2) within the cover letter | | | |
| **Does the amendment submission include any of the following?** | | **Yes** | **No or N/A** |
| 2. New strength (including new fill volume for parenteral products) | | | |
| 3. Modified formulation | | | |

[10] A *scientific general correspondence* is a general correspondence from an applicant to FDA requesting scientific advice after a complete response letter has been issued by the Agency.

| | | |
|---|---|---|
| 4. New batch | | |
| 5. Specification change(s) | | |
| 6. New container closure system | | |
| 7. Active Pharmaceutical Ingredient (API) source change<br>If yes, then include Drug Master File (DMF) #: | | |
| 8. Changes or additions to the manufacturing/quality facilities? | | |
| 9. For a request for final approval, is new data being submitted? | | |
| 10. New bioequivalence (BE) study/studies<br>If yes, then specify the following for each new BE study:<br>a. Select study type:<br>in vivo or in vitro, including failed study<br>b. Study number:<br>c. Study site (clinical, analytical, in-vitro testing)<br>Name and address:<br>d. Location of new BE study in the submission: | | |
| 11. Updated labeling due to a new or revised patent or exclusivity currently listed in the Orange Book[11] | | |

[11] The publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) identifies drug products approved on the basis of safety and effectiveness by FDA under the FD&C Act and related patent and exclusivity information. For more information on the Orange Book, see the Agency's web page https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

## APPENDIX 3: COVER LETTER ATTACHMENT FOR SUPPLEMENTS TO APPROVED ANDAS, AMENDMENTS TO PENDING SUPPLEMENTS, AMENDMENTS TO TENTATIVELY APPROVED PEPFAR ANDAS, AND CORRESPONDENCE RELATED TO THESE SUBMISSIONS

| **ANDA background** | |
|---|---|
| Abbreviated new drug application (ANDA) number | |
| Applicant | |
| Submission Date | |
| Email | |
| Established Name | |
| Dosage Form | |
| Strength(s) | |
| Reference Listed Drug (RLD) (proprietary name (brand name) and application number) | |
| Reference Standard (RS) (proprietary name (brand name), if any, established name, and application number) | |
| If priority review is being requested, please refer to FDA's Manual of Policies and Procedures (MAPP) 5240.3 (Rev. 5) *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*[12] | |

| **Select all applicable information included in the submission** | | | |
|---|---|---|---|
| ☐ Administrative General Correspondence | ☐ Bioequivalence | ☐ Biopharmaceutics | ☐ Clinical |
| ☐ Scientific General Correspondence | | | |
| ☐ Drug Substance DMF #: | ☐ Drug Product | ☐ Labeling | ☐ Microbiology |
| ☐ Patent or Exclusivity | ☐ Pharm/Tox | ☐ Manufacturing:<br>☐ Facility<br>☐ Active Pharmaceutical Ingredient (API)<br>☐ Finished Dosage Form (FDF) (including packaging/labeling)<br>☐ Testing<br>☐ Other (e.g., storage warehouse, device constituent parts)<br>☐ Process | |
| ☐ Notice of Commercial Marketing | | | |

[12] FDA's MAPP 5240.3 (Rev. 5) is available at https://www.fda.gov/media/89061/download.

| **Additional background** | **Yes** | **No or N/A** |
|---|---|---|
| 1. Is the email secure?<br>If no, apply for a secure email with the FDA by contacting secureemail@fda.hhs.gov. | | |
| 2. Was a Pre-Submission Facility Correspondence (PFC) submitted? | | |
| 3. If a PFC was submitted, have any changes been made to the pre-submitted facility information? | | |
| 4. Does the submission contain any technology that has been accepted into or may qualify for the Emerging Technology Program[13]? | | |
| **Drug-device combination product** | **Yes** | **No or N/A** |
| 5. Is the proposed product a drug-device combination product?<br>If yes, answer questions #6 through #9. | | |
| 6. Does the supplement propose a change to the drug-device combination product that may impact quality or labeling"? | | |
| 7. Does the supplement propose a change to the drug-device combination product that may impact the user interface? | | |
| 8. Does the submission include comparative analyses for a drug-device combination product?<br>If yes, then specify location in the submission: | | |
| 9. Does the submission include additional data and/or information, such as data from a comparative use human factors study, to support differences in user interface?<br>If yes, then specify location(s) in the submission: | | |
| **Does the submission (supplement or amendment to the supplement) include any of the following?** | **Yes** | **No or N/A** |
| 10. New strength (including new fill volume for parenteral products) | | |
| 11. Modified formulation | | |
| 12. Specification change(s) | | |
| 13. New container closure system | | |
| 14. Request for an Rx-to-over the counter (OTC) switch | | |

[13] See guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2017).

| | | |
|---|---|---|
| 15. A reactivation/reintroduction request as noted in MAPP 5200.7 (Rev. 1)[14] | | |
| 16. Revised and/or new patent certification and/or exclusivity statement | | |
| 17. Updated labeling due to a new or revised patent or exclusivity currently listed in the Orange Book | | |
| 18. A new facility that has never been inspected for similar operations to those proposed in the supplement | | |
| 19. Removal of a facility | | |
| 20. Active Pharmaceutical Ingredient (API) source change<br>If yes, then include Drug Master File (DMF) #: | | |
| 21. A Pharmacology/Toxicology (safety) justification for example nonclinical studies as defined in 21 CFR 58.3(d)<br>If yes, then specify justification/study type and location in the submission: | | |
| 22. New bioequivalence (BE) study/studies<br>If yes, then specify the following for each new BE study:<br>a. Select Study type: in vivo or in vitro, including failed study<br>b. Study Number<br>c. Study Site (clinical, analytical, in-vitro testing) Name and Address<br>d. Location of new BE study in the submission | | |
| 23. An alternate method for demonstrating BE (e.g., modeling, in vitro testing) that deviates from the current recommendations in a Product-Specific Guidance | | |
| 24. A waiver request under 21 CFR 320.22?<br><br>If yes, include the module where your waiver is located: | | |

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| **Select one filing category corresponding to the highest risk of all proposed supplemental changes, ranked by supplement filing category (PAS, CBE-30, CBE-0) per 21 CFR 314.70** | | |
|---|---|---|
| ☐ PAS | ☐ CBE-30 | ☐ CBE-0 |

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| **For Amendments Only** | | | |
|---|---|---|---|
| **Type of amendment** | **Supplement #** | **Date of FDA correspondence or action that elicited the amendment (e.g., Complete Response Letter** | **Is this a response to a CRL?** |

[14] FDA's MAPP 5200.7 (Rev. 1) is available at https://www.fda.gov/media/94417/download.

| | | (CRL), discipline review letter (DRL), information request (IR), or tentative approval (TA)): | | |
|---|---|---|---|---|
| | | | **Yes** | **No or N/A** |
| Unsolicited | | | | |
| Solicited | | | | |
| President's Emergency Plan for AIDS Relief Program (PEPFAR) Post-TA[15] | | | | |

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| **Proposed changes** | | | | |
|---|---|---|---|---|
| • **For all supplemental changes proposed, populate the table below, ranked by supplement filing category (PAS, CBE-30, CBE-0) per 21 CFR 314.70** | | | | |
| **#** | **Change description** | **Filing category** | **Scale-Up and Post Approval Changes (SUPAC) level (1, 2 or 3), as applicable[16]** | **Justification for filing category based on current guidances and/or risk assessment**<br><br>**If the same change has been previously approved, include ANDA # and approval date for the same change.** |
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |

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[15] Under PEPFAR, certain antiretroviral products that have been granted a tentative approval may be distributed for use outside of the United States, even when there is still patent and/or exclusivity protection in the United States. See FDA's PEPFAR web page, available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar.

[16] SUPAC guidances are available for modified-release solid oral dosage forms, immediate-release solid oral dosage forms, and nonsterile semisolid dosage form products (see the guidances for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (October 1997); *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995); and *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)). These guidances define levels of change (i.e., SUPAC levels 1, 2, and 3) for the covered products, along with recommended tests and documentation that should support the change.