
POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

**Generic Drug Labeling Revisions Under
Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act**

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PURPOSE

This Manual of Policies and Procedures (MAPP) describes how the Office of Generic Drugs (OGD) will implement section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).¹

BACKGROUND

On March 23, 2010, the President signed into law H.R. 3590, the Patient Protection and Affordable Care Act. Section 10609 of that Act added section 505(j)(10) to the FD&C

¹ See 21 U.S.C. 355(j)(10)

Act. Section 505(j)(10) permits the Food and Drug Administration (FDA) to approve an abbreviated new drug application (ANDA), even if the ANDA approval coincides with certain changes approved by FDA to the labeling for the reference listed drug (RLD). FDA has implemented this provision by requesting that an applicant of an ANDA, which is otherwise eligible for approval, agree in a “Letter of Commitment” to submit revised labeling for its proposed generic drug product corresponding to the RLD labeling changes within a specified timeframe.

Specifically, FDA sends the applicant a General Advice Notification letter (referred to as General Advice letter in this MAPP) notifying the applicant of the RLD labeling changes and asks the applicant to commit, in a Letter of Commitment submitted to FDA, to submit the revised labeling within 60 calendar days of the date of the General Advice letter. By submitting a Letter of Commitment, the applicant agrees to the requirement in section 505(j)(10) of the FD&C Act to update its labeling no later than 60 calendar days after the date of the notification in the General Advice letter.

POLICY

- Under section 505(j)(10) of the FD&C Act, FDA may approve an ANDA, even though certain changes have been made to the labeling for the RLD and such changes are not included in the proposed labeling of the ANDA, if all the following criteria are met:
 - The ANDA was otherwise eligible for approval (1) but for expiration of a patent, exclusivity period, or of a delay of approval described in section 505(j)(5)(B)(iii) of the FD&C Act² (and (2) if FDA has approved the RLD’s labeling revision within 60 calendar days of such expiration or lifting of such delay (e.g., within 60 calendar days of expiration of the patent, exclusivity, statutory stay of approval or of court entry of judgment of non-infringement or invalidity).
 - The approved revisions to the labeling of the RLD did not include a change to the “Warnings” section of the labeling.³
 - The ANDA applicant has agreed, in a Letter of Commitment, to submit a “Supplement – Changes Being Effectuated” containing the revised labeling consistent with the changes made to the labeling for the RLD no later than 60 calendar days after the date of FDA’s General Advice letter.

² This clause in the FD&C Act describes a statutory stay of approval that generally extends for 30 months, but can be terminated early by a court entry of judgment of non-infringement or invalidity of the relevant patent(s).

³ Please note that the physician labeling rule (PLR) consolidates the “Warnings and Precautions” sections. For more information on PLR, please visit FDA’s website on Prescription Drug Labeling Resources at: <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>.

- FDA has determined that the applicant's continued use of the RLD labeling that was in effect before the RLD revision will not adversely impact the safe use of the proposed generic drug product.⁴
- FDA will not grant final approval of an ANDA until the applicant's Letter of Commitment is received.

RESPONSIBILITIES

- Any OGD staff member receiving a request by an ANDA applicant to determine whether the ANDA is eligible for approval, despite labeling changes approved for the RLD and the proposed ANDA labeling not including those labeling changes, will send that request to the appropriate Labeling Project Manager (LPM) in the Division of Labeling Review (DLR).
- DLR Labeling Assessor (LA):
 - Recommends whether the labeling changes approved for the RLD meet the criteria under section 505(j)(10) and requests approval of that recommendation from the DLR Team Leader (TL).
 - DLR LA will consult with Patent and Exclusivity Team (PET) within OGD Policy for assistance with issues such as determining when a delay of approval described in section 505(j)(5)(B)(iii) of the FD&C Act has ended, including whether there has been a court entry of judgment of non-infringement or invalidity that has terminated a statutory stay of approval.
 - With the assistance of the DLR LPM, completes a memorandum in the electronic archiving system used in the Center for Drug Evaluation and Research (CDER) documenting the section 505(j)(10) determination under the Labeling Review Task.
- DLR TL:
 - Verifies the recommendation of the DLR LA that the labeling changes approved for the RLD meet the criteria under section 505(j)(10) and the ANDA applicant is eligible for approval, notwithstanding the labeling considerations described under section 505(j)(10).

⁴ OGD may contact the Office of New Drugs to determine if the labeling revision impacts the safe use of the drug.

- Signs a General Advice letter to the ANDA applicant on behalf of the DLR Division Director, which is drafted by the DLR LPM.
- Asks the Division of Project Management (DPM) Regulatory Project Manager (RPM) or the Office of Regulatory Operations (ORO) Immediate Office (IO) to include language memorializing the post-approval labeling requirement (PALR) to submit revised labeling in the approval letter if it was not already added. This will be completed during the labeling endorsement stage when the ANDA is routing for final approval.
- DLR LPM:
 - Ensures appropriate DLR staff are aware that a request under section 505(j)(10) has been received.
 - Requests the DLR LA determine whether the labeling changes approved for the RLD meet the criteria under section 505(j)(10).
 - If the DLR staff determine that all criteria under section 505(j)(10) are met and the request is to be granted, creates and emails a General Advice letter via the electronic archiving system used in CDER and transmits that letter to the applicant after it is signed by the DLR TL.
 - When the request is to be denied, creates and emails a communication to ANDA applicants that have requested a 505(j)(10) determination from FDA that indicates FDA has determined that the labeling change(s) approved for the RLD do not meet the criteria under section 505(j)(10).
 - Communicates the section 505(j)(10) determination to the DPM RPM via CDER's electronic archiving system through an update under the Labeling Review Recommendation.
 - Verifies the Letter of Commitment has been received from the applicant and the memorandum has been completed in the electronic archiving system used in CDER.
 - Tracks status of PALRs monthly.
 - Ensures the required "Supplement – Changes Being Effectuated" is submitted within 60 calendar days of the date of the General Advice letter.
 - For supplements received within 60 calendar days:
 - Notifies the RPM of the applicant's timely revised labeling.

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- Within five calendar (5) days, issues a Post-Approval Labeling Requirement Released Letter at the program level.
 - When a supplement is not received within 60 calendar days:
 - Within five calendar (5) days, issues a Post-Approval Labeling Requirement Failure to Respond Letter to any ANDA applicant that fails to submit the labeling supplement within 60 calendar days from the date of the General Advice letter.
 - Notifies DPM RPM of the failure to submit the labeling supplement.
 - DPM RPM:
 - Triages requests to determine whether the ANDA is eligible for approval despite labeling changes approved for the RLD pursuant to section 505(j)(10) of the FD&C Act and forwards requests to the appropriate DLR LPM.
 - Ensures the language memorializing the PALR to submit revised labeling is included in the approval letter if it was not already added.
 - Triages and forwards incoming Letters of Commitment to the LPM as an Administrative Amendment.
 - Adds comments regarding receipt of the Letter of Commitment to the approval routing summary during the routing of the ANDA for final approval, thereby alerting the ORO IO of the applicant's commitment to submit revised labeling for its proposed generic drug product corresponding to the RLD labeling changes within the specified timeframe.
 - Informs the DLR LPM via email when the ANDA is approved.
 - Takes action to initiate withdrawal of approval of the application after notification from the DLR LPM if the applicant failed to submit the labeling supplement within 60 calendar days from the date of the *General Advice* letter.
 - ORO IO:
 - Confirms receipt of the Letter of Commitment from the applicant and documents, on the approval routing summary (ARS), the applicant's commitment to submit revised labeling through a "Supplement – Changes Being Effected" within 60 calendar days of the date of the General Advice letter.

- Ensures the final approval letter for the ANDA includes language requiring the applicant to revise, within 60 calendar days of the date of the General Advice letter, the labeling of its product to conform to the revisions approved for the RLD.
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PROCEDURES

- **Determination**

- Once the ANDA applicant becomes aware that a revision to the RLD labeling has been approved that meets the statutory criteria under section 505(j)(10), as described in the Policy section, the applicant may request a determination whether to invoke section 505(j)(10).
 - Upon receipt of a request from an ANDA applicant via the electronic gateway for a determination of eligibility for approval under section 505(j)(10), any OGD staff member receiving that request will triage the request to the DLR LPM as an administrative amendment. The DLR LPM will ensure all parties are aware of the submission and request a determination of eligibility from the DLR LA.
 - The DLR LA determines whether the criteria under section 505(j)(10) are met, and with the assistance of the DLR LPM, both (1) completes a memorandum in CDER's electronic archiving system documenting that recommendation under the Labeling Review Task (see Attachment D) and (2) requests concurrence from the DLR TL with that determination.
 - The DLR TL verifies whether the DLR LA's recommendation regarding the determination of eligibility is appropriate. If the DLR TL agrees with the DLR LA's recommendation, then the DLR TL signs the memorandum documenting concurrence (see Attachment D). If the DLR LA and DLR TL are not in agreement about that determination, they will consult the DLR Supervisor for resolution. Documentation of the final determination is archived in CDER's electronic archiving system.
 - The DLR LPM will notify the RPM of the determination.

- **Processing**

- If the DLR staff determine that all criteria under section 505(j)(10) are met, the DLR LPM will issue a General Advice letter signed by the DLR TL to the applicant or its authorized agent(s) via email through the electronic archiving system used in CDER (see Attachment A). The General Advice letter will

request that the applicant submit a Letter of Commitment to FDA, in which the applicant agrees to submit a “Supplement – Changes Being Effected” within 60 calendar days of the date of the General Advice letter.

- If the DLR staff determine the criteria under section 505(j)(10) are not met and the request should therefore be denied, the DLR LPM will create and email a communication to ANDA applicants that have requested a section 505(j)(10) determination from FDA that indicates FDA has determined that the labeling change(s) approved for the RLD do not meet the criteria under section 505(j)(10) (see Attachment A).
- After the Letter of Commitment is received from the applicant, the LPM will update the memorandum under the Labeling Review Task with the PALR information.
- At the time of labeling endorsement for final approval of the ANDA, the DLR TL will:
 - Verify the Letter of Commitment has been received and the memorandum under the Labeling Review Task has been completed.
 - Ask the DPM RPM or the ORO IO to include language memorializing the PALR to submit revised labeling in the approval letter if it was not already added (see Attachment B).
- Once FDA receives the applicant’s Letter of Commitment, the DPM RPM and/or the ORO IO staff will include language memorializing the PALR to submit revised labeling in the approval letter (see Attachment A) and document the PALR on the OGD Approval Routing Summary form.
- **Tracking Commitment**
 - The DLR LPM will use CDER’s electronic archiving system to track the applicant’s fulfillment of the PALR to submit revised labeling as a Supplement – Changes Being Affected within 60 calendar days of the date of the General Advice letter.
 - The DPM RPM informs the DLR LPM via email when the ANDA is approved.
 - The DLR LPM tracks status of PALRs monthly.
 - Based on the date of the General Advice letter, the DLR LPM will track the required submission date for revised labeling (which is due within 60 calendar days of the date of the General Advice letter).

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- Once the applicant submits a timely “Supplement – Changes Being Effected” with the revised labeling, the DLR LPM will notify the DPM RPM of the revised labeling and issue a Post-Approval Labeling Requirement Released Letter at the program level (see Attachment C).

 - Failure to Respond
 - The DLR LPM issues a Post-Approval Labeling Requirement Failure to Respond Letter to any ANDA applicant that fails to submit the labeling supplement within 60 calendar days from the date of the General Advice letter (see Attachment E). The Post-Approval Labeling Requirement Failure to Respond Letter will state that timely changes to the labeling were required as a condition of approval and, if necessary, FDA will begin withdrawal of approval of the application.
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REFERENCE

- Patient Protection and Affordable Care Act (Public Law 111-148) (<http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf>).
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EFFECTIVE DATE

- This MAPP is effective upon date of publication.
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CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
2/12/2013	N/A	Initial
7/27/2021	1	Procedures updated

**ATTACHMENT A – Sample Letter - General Notification Template
(Denied/Granted)**

ANDA #####

GENERAL ADVICE NOTIFICATION

Applicant or US Agent Name
U.S. Agent for: Applicant Name
Applicant or US Agent Address 1
Applicant or US Agent Address 2
Applicant or US Agent Address 3

Attention: CONTACT NAME
TITLE

Dear CONTACT:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on DATE, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for TRADE NAME.

Reference is also made to your request to invoke section 505(j)(10) of the FD&C Act.

FDA approved new labeling for the reference listed drug (RLD), insert name of RLD, on insert date. The (specify '~~###~~ patent, pediatric exclusivity period attached to the '~~###~~ patent, 3-year exclusivity period under section 505(j)(5)(F)(iii)-(iv) of the FD&C Act, 180-day exclusivity period under section 505(j)(5)(B)(iv) or (v) of the FD&C Act, orphan exclusivity period under section 527 of the FD&C Act, or 30-month stay of approval) is scheduled to expire on add expiration date. Section 505(j)(10) of the FD&C Act permits FDA to approve an ANDA with labeling that differs from that of the RLD provided: (1) the application is otherwise eligible for approval but for expiration of a patent, an exclusivity period, or a delay in approval described under section 505(j)(5)(B)(iii) of the FD&C Act, and FDA has approved a revision to the labeling of the RLD within 60 days of such expiration, (2) the labeling changes do not include a change to the "Warnings" section, (3) FDA has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug, and (4) the applicant agrees to submit revised drug labeling no later than 60 days after being notified via FDA correspondence of the required changes.

OPTION A:

We have determined that the drug under your ANDA meets the criteria under section 505(j)(10), provided that you agree to supplement your application with updated labeling reflecting the change to the insert name of RLD labeling within 60 days of the date of this letter of notification. Your commitment in writing should be identified as a "Letter

of Commitment to Submit Revised Labeling Pursuant to 505(j)(10)” and submitted via the Electronic Submissions Gateway (ESG), faxed followed by a hardcopy, or mailed to:

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research Food and Drug Central
Document Room (CDR)
5901B Ammendale Road
Beltsville, MD 20705-1266

Please note that this commitment letter must be received before approval of your application can be granted.

When submitting your supplement with updated labeling to reflect the change to the *insert name of RLD* labeling, identify your supplement as:

**CBE SUPPLEMENT
LABELING
POST-APPROVAL COMMITMENT – MET**

Your supplement must be submitted in Electronic Common Technical Document (eCTD) format. The eCTD is CDER’s standard format for electronic regulatory submissions. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

OPTION B:

We have determined that the drug under your ANDA does not qualify under section 505(j)(10), due to (list reason).

You are required to amend your pending application to align your labeling with the recent NDA supplement approval prior to approval of your application. This submission will receive a minor amendment GDUFA date of three months from date of receipt.

Your amendment must be submitted in Electronic Common Technical Document (eCTD) format. The eCTD is CDER’s standard format for electronic regulatory submissions. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission.

**MINOR AMENDMENT
LABELING**

If you have questions, please contact (LPM) via email at (email address).

Sincerely Yours,

{See appended electronic signature page}

For xx
Director
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ATTACHMENT B - Standard Language for Approval Letter**POST-APPROVAL LABELING REQUIREMENT UNDER SECTION 505(j)(10)**

We remind you of your post-approval labeling requirement (PALR).

FDA approved a revision to the labeling of the RLD within 60 days of the expiration of the *insert '### patent, pediatric exclusivity period attached to the '### patent, 3-year exclusivity period under section 505(j)(5)(F)(iii)-(iv) of the FD&C Act, 180-day exclusivity period under section 505(j)(5)(B)(iv) or (v) of the FD&C Act, orphan exclusivity period under section 527 of the FD&C Act, or 30-month stay of approval*__. This revision to the labeling of the RLD does not include a change to the “Warnings” section, and the agency has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug.

The agency has also determined that your ANDA meets the applicable standards for approval under section 505(j) of the FD&C Act, and was otherwise eligible for approval but for expiration of the *insert '### patent, pediatric exclusivity period attached to the '### patent, 3-year exclusivity period under section 505(j)(5)(F)(iii)-(iv) of the FD&C Act, 180-day exclusivity period under section 505(j)(5)(B)(iv) or (v) of the FD&C Act, orphan exclusivity period under section 527 of the FD&C Act, or 30-month stay of approval*. Therefore, under section 505(j)(10) of the FD&C Act, your ANDA is eligible for approval with labeling that differs from that of the RLD. As indicated in the General Advice Notification letter dated xx/xx/xxxx, you are required to submit revised labeling for your product to conform to the revision that was approved on _____ *insert date for the RLD* _____ for _____ *insert RLD's name* _____. Acceptance of this letter constitutes your agreement to submit a “Supplement – Changes Being Effected” containing such revised labeling no later than 60 days after the date of the General Advice Notification Letter.

ATTACHMENT C - Standard Language for Release from Post-Approval Labeling Requirement

POST-APPROVAL LABELING REQUIREMENT UNDER SECTION 505(j)(10)

We acknowledge receipt of your “Supplement – Changes Being Effected” on insert date. As indicated in the General Advice Notification letter dated xx/xx/xxxx, you were required to change the labeling of your product to conform to the revisions that were approved on ____ insert date for the RLD ____ for ____ insert RLD’s name ____ . You agreed to submit a “Supplement – Changes Being Effected” containing revised labeling no later than 60 days after the date of the General Advice Notification Letter, which constituted a Post-Approval Labeling Requirement (PALR).

As you have now submitted a “Supplement – Changes Being Effected” containing revised labeling, you are hereby released from your PALR as of the date of this letter.

ATTACHMENT D – Memorandum to File – Documenting Decision

Determination whether an ANDA meets the criteria described in section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Background information

Section 505(j)(10) of the FD&C Act (added by section 10609 of the Patient Protection and Affordable Care Act) permits FDA to approve an ANDA with labeling that differs from that of the RLD provided: (1) the application is otherwise eligible for approval but for the expiration of a patent, an exclusivity period, or a delay of approval described under section 505(j)(5)(B)(iii) of the FD&C Act, and FDA has approved a revision to the labeling of the RLD within 60 days of such expiration, (2) the labeling changes do not include a change to the “Warnings” section, (3) the ANDA applicant(s) agrees to submit revised labeling no later than 60 days after notification that such changes to labeling are required, and (4) FDA has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug.

NDA Number	
Product Name	
Applicant Name	
Approval of the revision of the labeling for the RLD has been made within 60 days before the expiration of a listed patent, an exclusivity period, or a statutory stay of approval: 1. Date RLD labeling was approved: 2. Expiration date of listed patent, exclusivity period, or stay of approval. <i>(This could be an ANDA exclusivity)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
Has DLR verified the approved revisions to the RLD labeling do not included a change to the “Warnings” section?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Has the applicant committed to submit revised labeling to reflect the change in the labeling of the RLD no later than 60 days after the date of the General Advice Notification letter?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Has FDA determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug?	<input type="checkbox"/> Yes <input type="checkbox"/> No Please explain:
FINAL DECISION: Can this ANDA be approved with certain labeling differences from that of the RLD as described in section 505(j)(10) of the FD&C Act?	<input type="checkbox"/> Yes <input type="checkbox"/> No

{ See appended electronic signature }

Labeling Reviewer

Supervisory Comment/Concurrence:

{ See appended electronic signature }
Team Leader

ATTACHMENT E – Sample Letter Template – Failure to Respond to Supplement Request

ANDA #####

**REQUEST RESPONSE TO
SUPPLEMENT REQUEST**

APPLICANT NAME

Attention: NAME OF CONTACT PERSON

TITLE

APPLICANT ADDRESS

Dear CONTACT:

Please refer to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME.

A CHANGES BEING EFFECTED LABELING SUPPLEMENT IS REQUIRED

As indicated in the General Advice Notification letter dated xx/xx/xxxx, you were required to change the labeling of your product to conform to the revisions that were approved on _____ *insert date for the RLD* _____ for _____ *insert RLD's name* _____. You agreed to submit a “Supplement – Changes Being Effected” containing revised labeling no later than 60 days after the date of the General Advice Notification Letter, which constituted a Post-Approval Labeling Requirement (PALR).

To date we have not received a “Supplement – Changes Being Effected” containing revised labeling. If you do not submit the required supplement, this drug product may be considered misbranded, and, if necessary, FDA will begin withdrawal of approval of the application.

If you have questions, please contact (LPM) via email at (email address).

Sincerely,

{See appended electronic signature page}

For xx
Director
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research