



ANDA 210154

ANDA APPROVAL/TENTATIVE APPROVAL

Zydus Pharmaceuticals (USA) Inc.
73-B, Route 31 North
Pennington, NJ 08534
Attention: Srinivas Gurram
Senior Vice President - Head of Regulatory Affairs and CQA Lead - Americas

Dear Srinivas Gurram:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 30, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lenalidomide Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

Reference is also made to the tentative approval letter issued by this office on August 16, 2021, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. We have determined your Lenalidomide Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Revlimid Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg, of Celgene Corporation (Celgene).

However, we are unable to grant final approval to your Lenalidomide Capsules, 2.5 mg and 20 mg, at this time because of the exclusivity issue noted below. Therefore, your ANDA is **approved** insofar as it pertains to Lenalidomide Capsules, 5 mg, 10 mg, 15 mg, and 25 mg. Your Lenalidomide Capsules, 2.5 mg and 20 mg, are **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The RLD upon which you have based your ANDA, Revlimid Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg, of Celgene, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
7,189,740 (the '740 patent)	April 11, 2023
7,465,800 (the '800 patent)	April 27, 2027
7,468,363 (the '363 patent)	October 7, 2023
7,855,217 (the '217 patent)	November 24, 2024
7,968,569 (the '569 patent)	October 7, 2023
8,404,717 (the '717 patent)	April 11, 2023
8,492,406 (the '406 patent)	October 7, 2023
8,530,498 (the '498 patent)	May 15, 2023
8,648,095 (the '095 patent)	May 15, 2023
8,741,929 (the '929 patent)	March 8, 2028
9,056,120 (the '120 patent)	April 11, 2023
9,101,621 (the '621 patent)	May 15, 2023
9,101,622 (the '622 patent)	May 15, 2023
9,155,730 (the '730 patent)	May 15, 2023
9,393,238 (the '238 patent)	May 15, 2023

Your ANDA contains paragraph IV certifications to the '800, '217, '569, '498, '095, and '622 patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Lenalidomide Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg, under this ANDA. You have notified the Agency that Zydus Pharmaceuticals (USA) Inc. (Zydus) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Zydus for infringement of the '800, '217, '569, '498, '095 and '622 patents in the United States District Court for the District of New Jersey [Celgene Corporation v. Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Limited, Civil Action No. 17-2528] You have also notified the Agency that this case was dismissed.

With respect to the '740, '363, '717, '406, '929, '120, '621, '730 and '238 patents¹, your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication for which you are seeking approval under your ANDA.

The RLD upon which you have based your ANDA, Celgene's Revlimid Capsules, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg, is also subject to periods of exclusivity. As noted in the Orange Book, the ODE-131, ODE-241 and ODE-245 exclusivities are scheduled to expire on February 22, 2024, May 28, 2026 and May 28, 2026, respectively. You have provided a copy of a letter from Celgene that waives the unexpired ODE-131, ODE-241, and ODE-245 exclusivity periods associated with the RLD, with respect to ANDA 210154.

However, we are unable to grant final approval to your ANDA, with respect to the Lenalidomide Capsules, 2.5 mg and 20 mg, products at this time. Prior to the submission of your ANDA, another applicant or applicants submitted a substantially complete ANDA providing for Lenalidomide Capsules, 2.5 mg and 20 mg, and containing a paragraph IV certification. Your ANDA for these strengths will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

Upon the foregoing, your ANDA is **approved** insofar as it pertains to the Lenalidomide Capsules, 5 mg, 10 mg, 15 mg, and 25 mg products. Your Lenalidomide Capsules, 2.5 mg and 20 mg products, are **tentatively approved**.

Approval of Lenalidomide Capsules, 5 mg, 10 mg, 15 mg, and 25 mg

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is

necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a) of the FD&C Act]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated February 21, 2017.

Your final proposed REMS, referenced in Drug Master File (DMF) # (b) (4); is approved, and will be posted on the FDA REMS website: <http://www.fda.gov/rem>s. Other products may be added in the future if additional NDAs or ANDAs are approved.

The Lenalidomide REMS consists of Elements to Assure Safe Use (ETASU) and an implementation system.

Your REMS must be fully operational before you introduce Lenalidomide into interstate commerce.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**ANDA 210154 REMS ASSESSMENT
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 210154/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 210154/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF**

or

**NEW SUPPLEMENT FOR ANDA 210154/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX
CROSS REFERENCE TO THE REMS DMF**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR ANDA 210154
CROSS REFERENCE TO THE REMS DMF**

The Lenalidomide REMS uses a Type V DMF for shared system REMS submissions. Please refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,² for instructions on how to submit and reference the shared system REMS DMF.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter

requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <https://www.fda.gov/media/128163/download>)

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <https://www.fda.gov/media/73013/download>. Information and Instructions for completing the form can be found at <https://www.fda.gov/media/132152/download>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions³ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <https://www.fda.gov/media/71211/download>. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug’s labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled “Changes to an Approved NDA or ANDA” at <https://www.fda.gov/media/71846/download>.

Tentative Approval of Lenalidomide Capsules, 2.5 mg and 20 mg

Our decision to tentatively approve your Lenalidomide Capsules, 2.5 mg and 20 mg, is based upon information currently available to the agency (i.e., data in your ANDA and the status of current good manufacturing practice (cGMP) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

RESUBMISSION

To request final approval, please submit an amendment titled “FINAL APPROVAL REQUESTED” with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 3 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 3 months prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities’ compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available Agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. As part of this consideration, applicants should monitor any changes to the RLD that occur after tentative approval, including changes in labeling, patent or exclusivity information, or marketing status. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a “MINOR/MAJOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED.”

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions³ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee.

Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection

prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ The Agency notes that the '406, '730, and '238 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

³ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Sarah
Kurtz

Digitally signed by Sarah Kurtz

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