BLA 761382/Original 1

BLA APPROVAL

Sandoz Inc.
Attention: Mark Kopulos
Associate Director, Regulatory Affairs
100 College Rd. West
Princeton, NJ 08540

Dear Mark Kopulos:

Please refer to your biologics license application (BLA) dated and received August 10, 2023, and your amendments, under section 351(k) of the Public Health Service Act for Enzeevu (aflibercept-abzv) injection.

This BLA provides for the licensure of Enzeevu (aflibercept-abzv) as follows:

- Enzeevu (aflibercept-abzv), 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a single-dose vial kit (vial kit) [redacted] (b) (4) US-Eylea (aflibercept) 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and single-dose pre-filled syringe (PFS), and

- Enzeevu (aflibercept-abzv), 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS [redacted] (b) (4) US-Eylea (aflibercept) 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS.

Enzeevu seeks licensure [redacted] (b) (4) US-Eylea for the following indication: Neovascular (wet) Age-Related Macular Degeneration (AMD).

For administrative purposes, we have split BLA 761382 into the following applications:

- BLA 761382/Original 1 – biosimilarity
    - Enzeevu, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS seeking biosimilarity to US-Eylea 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

[redacted] (b) (4)

(b) (4)

The subject of this action letter is BLA 761382/Original 1. (b) (4)

LICENSING

We have approved your BLA for Enzeevu (aflibercept-abzv) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Enzeevu under your existing Department of Health and Human Services U.S. License No. 2003. Enzeevu is indicated for neovascular (wet) age-related macular degeneration (AMD).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Enzeevu drug substance at (b) (4). The final formulated product for the PFS presentation will be manufactured, filled, labeled, and packaged at (b) (4). The final formulated product for the vial kit presentation will be manufactured and filled at (b) (4) final formulated product for the vial kit presentation will be labeled and packaged at (b) (4) You may label your product with the proprietary name, Enzeevu, and will market it as 2 mg (0.05 mL of 40 mg/mL) solution in a PFS or vial kit.

DATING PERIOD

The dating period for Enzeevu PFS presentation shall be 24 months from the date of manufacture when stored at 2 to 8°C protected from light. The dating period for Enzeevu vial kit presentation shall be 36 months from the date of manufacture when stored at 2 to 8°C protected from light. Prior to usage, the unopened blister or vial of Enzeevu may be stored at room temperature (below 30°C/86°F) for up to 14 days. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4). Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Enzeevu and each kit component to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Enzeevu, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761382/Original 1**." Approval of this submission by FDA is not required before the labeling is used.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We have determined that, at this time, no pediatric studies will be required under PREA for your BLA.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments and the timetables you submitted on August 2, 2024, with schedules for conducting the following studies:

PMC 4676-1: Include VEGF-A target binding as a potency assay in the release specifications for SOK 583 drug substance and drug product using a validated testing method and establish acceptance criteria with upper and lower limits. Submit the results of the method validation for the VEGF-A binding, the data used to set the acceptance criteria, and statistical analysis to support the acceptance criteria in a Prior Approval Supplement.

Final Report Submission: 08/2025

PMC 4676-2: Include a testing method that directly measures deamidation in the drug substance and drug product release and stability specifications as a limit test. Submit the results of the method validation for measuring deamidation, the data used to set the acceptance criteria, and statistical analysis to support the acceptance criteria in a Prior Approval Supplement.

Final Report Submission: 02/2026

PMC 4676-3: Perform additional validation of reduced CE-SDS assay to validate quantification of HP3 and set the specifications of HP3 for both drug substance (DS) and drug product (DP) release and stability testing after availability of at least 15 DS batches from at least 5 campaigns and at least 15 DP batches from at least 5 campaigns. Submit the results of the method validation for HP3 measurement, the data used to set the acceptance criteria, and statistical analysis to support the acceptance criteria in a Prior Approval Supplement.

Final Report Submission: 02/2026

PMC 4676-4: Re-evaluate the drug substance (DS) and drug product (DP) release and stability specifications for main peak and [redacted] by iCE after data for at least 30 representative DS batches and at least 30 representative DP batches analyzed using the advanced method becomes available. Submit the revised specifications with new available data and the statistical analysis used to support the acceptance criteria in a Prior Approval Supplement.

Final Report Submission: 08/2027

PMC 4676-5: Implement [redacted] Establish a critical process parameter for [redacted] based on the [redacted] study and update the BLA with supportive information for these changes.

Final Report Submission: 06/2025

PMC 4676-6: Provide method qualification data for a bacterial endotoxin test (BET) method that is suitable for reference standard endotoxin (RSE) or other control standard endotoxin (CSE) [redacted] and is not subject to Low Endotoxin Recovery. Method qualification should reflect three independent Drug Product (DP) batches tested at the intended commercial testing site(s).

Final Report Submission: 02/2026

Submit clinical protocols to your IND 142199 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, call Lois Almoza, MS, Senior Regulatory Health Project Manager, at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

William Boyd, MD
Deputy Director
Division of Ophthalmology
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
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