



Our STN: BLA 125825/0

ACCELERATED BLA APPROVAL

October 30, 2026

Inovio Pharmaceuticals, Inc.
Attention: Stephanie Bekker
660 W. Germantown Pike, Suite 110
Plymouth Meeting, PA 19462

Dear Stephanie Bekker:

Please refer to your Biologics License Application (BLA) received October 30, 2025, under section 351(a) of the Public Health Service Act (PHS Act) for doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2358 to Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA , under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products and pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd, which is indicated to reduce the frequency of surgical papilloma excisions in adults with recurrent respiratory papillomatosis.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT04398433

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled studies establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these statutory provisions and regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as durable elimination of surgical papilloma excisions and symptomatic improvement.

Accelerated Approval Required Study

We remind you of the following postmarketing requirement:

1. Conduct an adequate and well-controlled clinical study to verify and describe the clinical benefit of doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxhd (VOCERYQ) in patients with recurrent respiratory papillomatosis (RRP). The study should enroll at least 50 adult and pediatric patients with RRP requiring 3 or more surgical interventions for papilloma management in the 12 months prior to treatment with the product. The study should evaluate the number of surgical interventions needed for papilloma management over at least 3 years following completion of treatment with the product and compare this to an appropriate external control group or scientifically justified threshold. Product redosing may be explored in patients without sustained “complete response” (no surgical interventions over the assessment period) to doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxhd beyond 36 months.

Draft Protocol Submission: December 30, 2026

Final Protocol Submission: June 30, 2027

Study completion: December 30, 2031

Final Study Report Submission: August 30, 2032

We expect you to complete design, initiation, accrual, completion, and reporting of this study within the framework described in your letter of October 27, 2026.

Please submit the protocol to your IND 19508, with a cross-reference letter to this BLA, STN BL 125825, explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study and the submission number as shown in this letter.

You must conduct this study with due diligence. If required postmarketing study fails to verify that clinical benefit is conferred by doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxhd, or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval.

You must submit reports of the progress of the study listed above as required under section 506(c) of the FDCA to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c) of the FDCA. The initial report will be a standalone submission and the subsequent report will be combined with your application’s annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application’s annual status report. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.

Your 180-day report must include the information listed in 21 CFR 601.70(b). FDA recommends that you use form FDA 3989 PMR/PMC Annual Status Report for Drugs and Biologics, to submit your 180-day reports. Form FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at <https://www.fda.gov/about-fda/reports-manuals-forms/forms>.

Your 180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval and the 180-day report submitted with your annual status report, must be clearly designated as **180-Day AA PMR Progress Report**.

FDA will consider the submission of your annual status report under section 506B(a)(1) of the FDCA and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2) of the FDCA. You are also required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) of the FDCA until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Postmarketing Requirements and 506B Commitments are fulfilled or released.

Please submit the final study report as a supplement to this BLA, STN BL 125825. For administrative purposes, all submissions related to this postmarketing study

requirement must be clearly designated as “**Subpart E Postmarketing Study Requirements.**”

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture doruxapapogene ralaplasamid and lalikinogene sifuplasamid drug substance (b) (4)

The doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxhd drug product will be manufactured at Alliance Medical Products Inc. dba Siegfried (AMP), 9342 and 9292, Jeronimo Road, Irvine, CA 92618-1903. The final drug product will be labeled and packaged at (b) (4)

The CELLECTRA 5PSP device will be manufactured, labeled, and packaged at Inovio Pharmaceuticals, Inc., 6769 Mesa Ridge Road, San Diego, CA 92121-2995.

You may label your product with the proprietary name VOCERYQ and market it in single-dose, pre-filled clear glass cartridges containing 1 mL (6.25 mg/ml).

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from an advisory committee discussion.

DATING PERIOD

The dating period for doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxhd drug product shall be 36 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of aseptic filling of the (b) (4)

The dating period for doruxapapogene ralaplasamid and lalikinogene sifuplasamid (b) (4)

The dating period of doruxapapogene ralaplasamid and lalikinogene sifuplasamid drug substance shall be (b) (4)

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12. The shelf-life for the array of CELLECTRA 5PSP device is 12 months from the date of device manufacture.

FDA LOT RELEASE

You are required to submit protocols showing results of all applicable release tests for future lots of doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxfd to the Center for Biologics Evaluation and Research (CBER). You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, 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 the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at <https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations>.

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of doruxapapogene ralaplasamid and lalikinogene sifuplasamid-gxfd, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft content of labeling including Package Insert submitted under amendment 96, dated October 29, 2026, and the draft carton and container labels submitted under amendment 94, dated October 27, 2026.

This is a reminder that as of September 24, 2014, device constituents of combination products may be subject to certain provisions of the final Unique Device Identifier (UDI) rule. These provisions include the requirement to provide a UDI on the device constituent label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18 and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, please identify each device identifier implemented for the subject device constituent, and the device identifiers that have been discontinued for the subject device constituent as a labeling change in an annual report consistent with 21 CFR 601.12(f)(3). For more information on these requirements, please see the UDI website at <http://www.fda.gov/udi>.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the : Package Insert submitted on October 29, 2026. 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* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package and container labels and CELLECTRA® User Manual submitted on October 27, 2026 according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125825 at the time of use and include implementation information on Form FDA 356h.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA

at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying FORM FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports> and FDA's Adverse Event reporting System website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

AGREED UPON POSTMARKETING COMMITMENTS:

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

We acknowledge your written commitments as described in your correspondence of October 27, 2026, as outlined below:

2. Inovio commits to conducting additional linearity studies using a minimum of (b) (4) concentrations for the IL-12 bioassay and HPV11 (b) (4) assay in accordance with ICH Q2(R1), Section 2. The results of these studies will be submitted as a Postmarketing Commitment - Final Study Report on or before June 30, 2027.

Final Study Report submission: June 30, 2027

3. Inovio commits to conducting an additional robustness assessment of the HPV11 (b) (4) assay by varying some of the detection components, e.g., different lots of primary and secondary antibodies and different (b) (4). The results of these assessments will be submitted as a Postmarketing Commitment - Final Study Report on or before June 30, 2027.

Final Study Report submission: June 30, 2027

4. Inovio commits to conducting a total of (b) (4) assay runs for the HPV11 (b) (4) and the IL-12 Bioactivity assays to bridge clinical lots with the current reference standard. The results of these assessments will be submitted as a Postmarketing Commitment - Final Study Report on or before January 31, 2027.

Final Study Report submission: January 31, 2027

5. Inovio commits to reevaluating the acceptance criterion for quantity of plasmid of (b) (4) of the target dose (b) (4) using data from a minimum of (b) (4) additional manufactured lots (b) (4) lots total). The results of the reevaluation will be submitted as a Postmarketing Commitment - Final Study Report on or before October 31, 2031.

Final Study Report submission: October 31, 2031

6. Inovio commits to reevaluating the acceptance criterion for potency of (b) (4) using data from a minimum of (b) (4) additional manufactured lots (b) (4) lots total). The results of the reevaluation will be submitted as a Postmarketing Commitment - Final Study Report on or before October 31, 2031.

Final Study Report submission: October 31, 2031

7. Inovio commits to conducting a comprehensive re-evaluation of the human factors (HF) validation study for the CELLECTRA™ 5PSP device. This re-evaluation will consist of a complete data reanalysis using (b) (4) categories aligned with FDA's human factors guidance (separating close calls from difficulties) and a consolidated root cause and clinical risk analysis for all observed use errors, difficulties, and close calls. Based on this re-evaluation, Inovio will determine if risk-mitigation modifications (design, labeling, or training) are necessary.
 - a. If no device modifications are warranted based on the re-evaluation, Inovio will submit the final report containing the reanalysis and risk evaluation as a Postmarketing Commitment - Final Study Report before June 30, 2027.

If device modification is not required:

Final Study Report Submission: June 30, 2027

- b. If device modifications are necessary, Inovio will submit the proposed device modifications and supplemental validation testing protocol on or before June 30, 2027, as a product correspondence for FDA review. Inovio will then conduct supplemental human factors validation testing on the modified interface to demonstrate that the changes effectively mitigate risks without introducing new hazards. The final report containing the reanalysis, risk evaluation, proposed revision of the device, and any subsequent validation testing results of the revised device will be submitted as a Prior Approval Supplement to the BLA on or before December 30, 2027.

If device modification is required:

Product correspondence submission: June 30, 2027

Prior Approval Supplement: December 30, 2027

8. Inovio Pharmaceuticals Inc. commits to perform and provide results of a container closure integrity testing (CCIT) study for the INO-3107 drug product 1.5mL glass cartridges using a positive control with an established sensitivity [i.e., minimum critical leak defect (size) that can be reliably detected] in accordance with (b) (4) and that correlates to risk and detection of microbial ingress. The final study report will be submitted as a Postmarketing Commitment - Final Study Report submission by April 30, 2027.

Final Study Report Submission: April 30, 2027.

9. Inovio commits to conducting comprehensive verification and validation testing of the sharps injury prevention feature for the CELLECTRA™ 5PSP device in accordance with (b) (4) and FDA guidance “Medical Devices with Sharps Injury Prevention Features - Guidance for Industry and FDA Staff”. This testing will consist of (b) (4)



Based on this testing, Inovio will determine if risk-mitigation modifications (design, labeling, or training) to the sharps injury prevention feature are necessary.

- a. If no device modifications are warranted based on the testing (i.e., all acceptance criteria are met), Inovio will submit the final report containing the verification and validation testing results as a Postmarketing Study Commitment - Final Study Report before June 30, 2027.

If device modification is not required:

Final Study Report Submission: June 30, 2027

- b. If device modifications are necessary, Inovio will submit the proposed device modifications and supplemental validation testing protocol on or before June 30, 2027, as product correspondence for FDA review. Inovio will then conduct supplemental testing on the modified device to demonstrate that the changes effectively mitigate risks without introducing new hazards. The final report containing the proposed revision of the device and any subsequent validation testing results of the revised device will be submitted as a Prior Approval Supplement to the BLA on or before December 30, 2027.

If device modification is required:

Product correspondence submission: June 30, 2027

Prior Approval Supplement: December 30, 2027

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125825. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Study Commitment – Correspondence Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Vincent Amatrudo
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

Rosa Sherafat, MD
Acting Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and
Research