

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM S-8
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Upstream Bio, Inc.

(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	38-4187694 (I.R.S. employer identification no.)
890 Winter Street, Suite 200 Waltham, MA (Address of principal executive offices)	02451 (Zip Code)

Upstream Bio, Inc. 2024 Stock Option and Incentive Plan
(Full title of the plan)

E. Rand Sutherland, M.D.
Chief Executive Officer
Upstream Bio, Inc.
890 Winter Street, Suite 200
Waltham, MA 02451
(Name and address of agent for service)

(781) 208-2466
(Telephone number, including area code, of agent for service)

Copies to:
Gabriela Morales-Rivera
William D. Collins
Kathryn W. Clerici
Goodwin Procter LLP
100 Northern Avenue
Boston, Massachusetts 02210
(617) 570-1000

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

EXPLANATORY NOTE

Pursuant to General Instruction E of Form S-8, Upstream Bio, Inc. (the “Registrant”) is filing this registration statement with the U.S. Securities and Exchange Commission (the “Commission”) to register 2,680,169 additional shares of the Registrant’s common stock, par value \$0.001 per share (“Common Stock”), available for issuance under the Registrant’s 2024 Stock Option and Incentive Plan (the “Plan”), pursuant to the evergreen provisions of the Plan.

This Registration Statement incorporates by reference the contents of the Registrant’s Registration Statement on Form S-8 filed with the Securities and Exchange Commission on October 11, 2024 (File No. 333-282614) (the “Earlier Registration Statement”) related to the Plan, except to the extent supplemented, amended or superseded by the information set forth herein. Only those items of Form S-8 containing new information not contained in the Earlier Registration Statement are presented herein.

Part II INFORMATION REQUIRED IN THE REGISTRATION STATEMENT

Item 8. Exhibits.

The exhibits to this Registration Statement are listed in the Exhibit Index attached hereto and incorporated by reference herein.

EXHIBIT INDEX

Exhibit No.	Description
4.1	<u>Third Amended and Restated Certificate of Incorporation of Upstream Bio, Inc. (incorporated by reference to Exhibit 3.1 to the Registrant’s Current Report on Form 8-K (File No. 001-42366) filed on October 15, 2024).</u>
4.2	<u>Second Amended and Restated Bylaws of Upstream Bio, Inc. (incorporated by reference to Exhibit 3.2 to the Registrant’s Current Report on Form 8-K (File No. 001-42366) filed on October 15, 2024).</u>
4.3	<u>Amended and Restated Investors’ Rights Agreement, among the Registrant and certain of its stockholders, dated June 6, 2023 (incorporated by reference to Exhibit 4.2 to the Registrant’s Registration Statement on Form S-1 (File No. 333-282197) filed on September 18, 2024).</u>
5.1*	<u>Opinion of Goodwin Procter LLP.</u>
23.1*	<u>Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm.</u>
23.2*	<u>Consent of Goodwin Procter LLP (included in Exhibit 5.1).</u>
24.1*	<u>Power of Attorney (included on signature page).</u>
99.1	<u>Upstream Bio, Inc. 2024 Stock Option and Incentive Plan and form of award agreements thereunder (incorporated by reference to Exhibit 10.2 to Amendment No. 1 to the Registrant’s Registration Statement on Form S-1 (File No. 333-282197) filed on October 7, 2024).</u>
107*	<u>Filing Fee Table.</u>

* Filed herewith.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-8 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Waltham, Massachusetts, on this 12th day of March, 2025.

UPSTREAM BIO, INC.

By: /s/ E. Rand Sutherland
Name: E. Rand Sutherland, M.D.
Title: Chief Executive Officer

POWER OF ATTORNEY AND SIGNATURES

Each individual whose signature appears below hereby constitutes and appoints each of E. Rand Sutherland, M.D. and Michael Paul Gray, M.B.A. as such person's true and lawful attorney-in-fact and agent with full power of substitution and resubstitution, for such person in such person's name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Registration Statement on Form S-8, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange Commission granting unto each said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as such person might or could do in person, hereby ratifying and confirming all that any said attorney-in-fact and agent, or any substitute or substitutes of any of them, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the date indicated.

Name	Title	Date
<u>/s/ E. Rand Sutherland</u> E. Rand Sutherland, M.D.	Chief Executive Officer and Director (Principal Executive Officer)	March 12, 2025
<u>/s/ Michael Paul Gray</u> Michael Paul Gray, M.B.A.	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	March 12, 2025
<u>/s/ Ronald C. Renaud, Jr.</u> Ronald C. Renaud, Jr., M.B.A.	Director and Chairman	March 12, 2025
<u>/s/ Daniella Beckman</u> Daniella Beckman	Director	March 12, 2025
<u>/s/ Erez Chimovits</u> Erez Chimovits, M.B.A., M.Sc.	Director	March 12, 2025
<u>/s/ H. Edward Fleming, Jr.</u> H. Edward Fleming, Jr., M.D.	Director	March 12, 2025
<u>/s/ Liam Ratcliffe</u> Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A.	Director	March 12, 2025
<u>/s/ Marcella Kuhlman Ruddy</u> Marcella Kuhlman Ruddy, M.D., M.S.	Director	March 12, 2025

March 12, 2025

Upstream Bio, Inc.
890 Winter Street, Suite 200
Waltham, Massachusetts 02451

Re: Securities Being Registered under Registration Statement on Form S-8

We have acted as your counsel in connection with your filing of a Registration Statement on Form S-8 (the "Registration Statement") pursuant to the Securities Act of 1933, as amended (the "Securities Act"), on or about the date hereof relating to an aggregate of 2,680,169 shares (the "Shares") of Common Stock, par value \$0.001 per share ("Common Stock"), of Upstream Bio, Inc., a Delaware corporation (the "Company"), that may be issued pursuant to the Company's 2024 Stock Option and Incentive Plan (the "Plan").

We have reviewed such documents and made such examination of law as we have deemed appropriate to give the opinion set forth below. We have relied, without independent verification, on certificates of public officials and, as to matters of fact material to the opinion set forth below, on certificates of officers of the Company.

For purposes of the opinion set forth below, we have assumed that, at the time Shares are issued, the total number of then unissued Shares, when added to the number of shares of Common Stock issued, subscribed for, or otherwise committed to be issued, does not exceed the number of shares of Common Stock authorized by the Company's certificate of incorporation.

The opinion set forth below is limited to the Delaware General Corporation Law.

Based on the foregoing, we are of the opinion that the Shares have been duly authorized and, when delivered against payment therefor in accordance with the terms of the Plan, will be validly issued, fully paid and nonassessable.

This opinion letter and the opinion it contains shall be interpreted in accordance with the Core Opinion Principles as published in *74 Business Lawyer* 815 (Summer 2019).

We hereby consent to the inclusion of this opinion as Exhibit 5.1 to the Registration Statement. In giving our consent, we do not admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations thereunder.

Very truly yours,

/s/ Goodwin Procter LLP
GOODWIN PROCTER LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-8 of Upstream Bio, Inc. of our report dated March 12, 2025 relating to the financial statements, which appears in Upstream Bio, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2024.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 12, 2025

Calculation of Filing Fee Table

Form S-8
(Form Type)

Upstream Bio, Inc.
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered Securities

Security Type	Security Class Title	Fee Calculation Rule	Amount to be Registered ⁽¹⁾	Proposed Maximum Offering Price Per Share ⁽²⁾	Maximum Aggregate Offering Price ⁽²⁾	Fee Rate	Amount of Registration Fee
Equity	Common Stock, par value \$0.001 per share	457(c) and 457(h)	2,680,169 shares	\$8.26	\$22,138,195.94	0.00015310	\$3,389.36
Total Offering Amounts					\$22,138,195.94		\$3,389.36
Total Fee Offsets							—
Net Fee Due							\$3,389.36

- (1) Pursuant to Rule 416(a) under the Securities Act of 1933, as amended (the “Securities Act”), this Registration Statement shall also cover any additional shares of the Registrant’s common stock, par value \$0.001 per share (“Common Stock”), that become issuable under the Registrant’s 2024 Stock Option and Incentive Plan (the “Plan”) by reason of any stock dividend, stock split, recapitalization or any other similar transaction effected without the receipt of consideration which results in an increase in the number of our outstanding shares of Common Stock.
- (2) Estimated solely for the purpose of calculating the registration fee pursuant to Rules 457(c) and 457(h) of the Securities Act, and based on \$8.26, the average of the high and low price of the Registrant’s Common Stock, as reported on the Nasdaq Global Select Market, on March 5, 2025.
- (3) Consists of 2,680,169 additional shares issuable under the Plan, which represents an automatic annual increase to the number of shares available for issuance under the Plan effective as of January 1, 2025. Pursuant to such provision, an additional number of shares will automatically be added to the shares authorized for issuance under the Plan on January 1 of each year. Shares available for issuance under the Plan were previously registered on a registration statement on Form S-8 filed with the Securities and Exchange Commission on October 11, 2024 (File No. 333-282614).