NDA 219666

NDA APPROVAL

PTC Therapeutics, Inc.
Attention: Juliana Barbosa, BPharm, MBM
Director, Global Regulatory Leader
500 Warren Corporate Center Dr.
Warren, NJ 07059

Dear Juliana Barbosa:

Please refer to your new drug application (NDA) received July 29, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sephience (sepiapterin) oral powder.

This NDA provides for the use of Sephience (sepiapterin) oral powder for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients one month of age and older with sepiapterin-responsive phenylketonuria (PKU). Sephience is to be used in conjunction with a phenylalanine (Phe)-restricted diet.

APPROVAL & 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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. 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.

[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 https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, except with the minor revisions listed above [e.g., changes consistent with annual reportable changes under 314.70(d)], 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 219666**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Sephience (sepiapterin) oral powder shall be 24 months from the date of manufacture when stored at 20°C – 25°C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that your request for a rare pediatric disease priority review voucher is denied. This application is not eligible for a rare pediatric priority review voucher because the application did not meet the requirements to be a "rare pediatric disease product application" for the following reason:

> This application was not deemed eligible for priority review. See section 529(a)(4)(C) of the FDCA (21 U.S.C. 360ff(a)(4)(C)). An application may receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in the safety or effectiveness over available products indicated for the treatment, prevention, or diagnosis of a serious condition.[3,4] We agree that PKU is a serious disease. However, we have determined that the criterion of significant improvement in the safety or effectiveness of sepiapterin for treatment of PKU over available therapies (sapropterin and pegvaliase) has not been shown.

ADVISORY COMMITTEE

Your application for Sephience was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] See the FDA guidance for industry, Expedited Programs for Serious Conditions – Drugs and Biologics, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expeditedprograms-serious-conditions-drugs-and-biologics.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of carcinogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4857-1 A long-term (2-year) GLP-compliant carcinogenicity study with sepiapterin in rats to evaluate a signal for carcinogenic risk with sepiapterin administration.

The timetable you submitted on July 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	03/2026
Study Completion:	12/2028
Final Report Submission:	12/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4857-2 A clinical trial to assess the effect of renal impairment on the pharmacokinetics of sepiapterin and its metabolite BH4 designed and conducted in accordance with the FDA guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (March 2024).

The timetable you submitted on July 22, 2025, states that you will conduct this study according to the following schedule:

Trial Completion:	05/2026
Final Report Submission:	05/2027

4857-3 A clinical trial to assess the effect of hepatic impairment on the pharmacokinetics of sepiapterin and its metabolite BH4 designed and conducted in accordance with the FDA guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

The timetable you submitted on July 22, 2025, states that you will conduct this study according to the following schedule:

Trial Completion:	06/2026
Final Report Submission:	06/2027

Submit clinical protocols to your IND 143698 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.*[6]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Sephience you submit all serious domestic and foreign cases of hemorrhagic events as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 10th year following initial U.S. approval date.

We also request that you provide separate narrative summaries, including analyses, for both hemorrhagic events and gastrointestinal mucosal injury events as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 10th year following initial U.S. approval date. Your analysis should include interval and cumulative data relative to the date of approval of Sephience.

To identify reports of hemorrhagic events, we request you use the Standardised MedDRA Query (SMQ) *Haemorrhages*. The SMQ *Hemorrhages* includes two SMQs:

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

Haemorrhage Laboratory Terms (Broad) and *Haemorrhage Terms (Excluding Laboratory Terms)* (Broad).

To identify reports of gastrointestinal mucosal injury, we request you use both of the following High Level Group Terms (HLGT): *Gastrointestinal inflammatory conditions* and *Gastrointestinal ulcerations and perforation*.

Your narrative summary should provide the following information:

- Indication
- Sephience dose and frequency
- Duration of therapy
- Temporal association
- Associated signs and symptoms
- Concomitant medications
- Medical history
- Underlying risk factors
- Confounders
- Hospitalizations, testing, and treatment given for the event
- Outcome at the time of the report
- Dechallenge/rechallenge
- Assessment of causality

POST APPROVAL FEEDBACK MEETING

New molecular entities 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, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

[9] https://www.uspnf.com/

If you have any questions, contact Diego Diaz, Regulatory Project Manager, via email at Diego.Diaz@fda.hhs.gov or at (301) 796-7182.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drug
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- 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/

CHRISTINE P NGUYEN
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