CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211875Orig1s000

OTHER ACTION LETTERS

NDA 211875

TENTATIVE APPROVAL

HBT Labs, Inc.
Attention: Donald Hodgson, PhD
President
536 Vanguard Way
Brea, CA 92821

Dear Dr. Hodgson:

Please refer to your new drug application (NDA) dated and received August 29, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), lyophilized powder for reconstitution, 100 mg/vial.

We acknowledge receipt of your amendment dated April 24, 2020, which constituted a complete response to our June 14, 2019, action letter.

This NDA provides for the use of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), lyophilized powder for reconstitution, for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information, text for the Patient Package Insert, and carton and container labeling**)**. This determination is based upon information available to FDA at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

Please note that this drug product may not be marketed in the United States without final FDA approval under section 505 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 501 of the FD&C Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*[1] and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)

[1] 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.

If you have any questions, contact Jessica Kim, Regulatory Project Manager, at 240-402-0883 or Jessica.Kim1@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

AMNA IBRAHIM
06/30/2021 12:48:14 PM

NDA 211875

COMPLETE RESPONSE

HBT Labs, Inc.
Attention: Donald Hodgson, PhD
President
536 Vanguard Way
Bren, CA 92821

Dear Dr. Hodgson,

Please refer to your new drug application (NDA) dated August 29, 2018, received August 29, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), lyophilized powder for reconstitution, 100 mg/vial.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Drug Product

1. Control of the drug product is not adequate. Update the drug product specifications to reflect the changes in acceptance criteria, methods, and validation data per your commitment in the amendments dated January 25, 2019 (SD007) and March 11, 2019 (SD009). The proposed changes include:

    a. Addition of an identity test for human serum albumin with appropriate criterion, method description and method validation.

    b. Revised acceptance criterion and methods along with appropriate validation data for paclitaxel assay, (b) (4), reconstitution time, pH, (b) (4), total degradants, (b) (4), particle size distribution, (b) (4), and albumin aggregates.

    c. Updated method validation studies for identity, assay and content uniformity, related substances, (b) (4), (b) (4), and albumin aggregates.

2. The HBT stability report RPT-PS-013.00 (Module 3.2.P.8) which addresses the effect of long-term storage (b) (4) on finished product stability is not adequate. Revise the protocol to include sample evaluation at 12 and 24 month intervals along with 6 and 36 month intervals. In addition, revise the post approval stability protocol to address long term storage (b) (4).

Process

(b) (4)

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(b) (4)

Biopharmaceutics

1. Your plans to use the (b) (4) method to assess the in vitro drug release of your proposed product at release and stability is not acceptable. Develop an in vitro drug release method utilizing appropriate equipment/ apparatus (e.g., dialysis/microdialysis) and medium that is capable of directly measuring drug release from the albumin bound paclitaxel formulation. The selected in vitro drug release method should demonstrate discriminating ability of the in vitro drug release profiles of the target product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical formulation, process, and manufacturing variables that can impact the drug release kinetics. The testing conditions used for each test should be clearly specified. The release profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3

consecutive time-points) is reached. We recommend the use of at least twelve samples per testing variable.

REGULATORY

In your August 29, 2018, NDA 211875 you submitted Paragraph IV (PIV) certifications pursuant to section 505(b)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR 314.50(i)(1)(i)(A)(4), certifying that "the following patents related to ABRAXANE® (NDA 021660) are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of HBT's Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial, for which this 505(b)(2) application is submitted:"

U.S. Patent Number	Patent Expiration Date	Patent Use Code*	Claims DP
7,758,891 ('891 patent)	Feb 21, 2026	U-1434	
7,820,788 ('788 patent)	Oct 27, 2024	U-1092 U-1290 U-1434	DP
7,923,536 ('536 patent)	Dec 9, 2023	U-1117 U-1290 U-1434	
8,034,375 ('375 patent)	Aug 13, 2026	U-1290	
8,138,229 ('229 patent)	Dec 9, 2023	U-1092 U-1290 U-1434	DP
8,268,348 ('348 patent)	Feb 21, 2026	U-1290	
8,314,156 ('156 patent)	Dec 9, 2023	U-1290 U-1434	
8,853,260 ('260 patent)	Oct 10, 2020	U-1092 U-1290 U-1434	DP
9,101,543 ('543 patent)	Feb 21, 2026	U-1434	
9,393,318 ('318 patent)	Mar 4, 2032	U-1290	
9,511,046 ('046 patent)	Jan 12, 2034	U-1434	
9,597,409 ('409 patent)	Mar 4, 2032	U-1290	

* Patent Use Codes:
U-1434 Treatment of Pancreatic Cancer
U-1092 Treatment of Breast Cancer
U-1290 Treatment of Lung Cancer
U-1117 Treatment of Breast Cancer

The agency notes that these patents are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) as method of use patents, meaning that the listed drug (LD) application holder has represented that the patents claim one or more methods of using the drug product. Three of these patents also claim

the drug product (i.e., the ‘788, ‘229, and ‘260 patents). The patent information listed for Abraxane in the Orange Book is shown above. Your August 29, 2018, application also included a statement pursuant to section 505(b)(2)(B) of the Act and 21 CFR 314.50(i)(1)(iii) (a “method of use statement”) referencing the same patents shown above, while also stating that “HBT’s proposed labelling does not include any indication or other information for the uses set forth in use codes that our labeling for this drug product for which the present NDA is seeking approval does not include any indications that are covered by use codes U-1434 (Treatment of Pancreatic Cancer) and U-1290 (Treatment of Lung Cancer) listed for these patents.” We are unsure of the meaning of this statement.

Your proposed labeling (which purports to omit certain protected information) and certain associated PIV certifications are incongruent with each other. Specifically, you submitted PIV certifications to the ‘891, ‘375, ‘348, ‘156, ‘543, ‘318, ‘046, and ‘409 patents that are associated with use codes U-1434 (treatment of pancreatic cancer) and U-1290 (treatment of lung cancer). Your proposed labeling does not include indications for pancreatic cancer (U-1434) or lung cancer (U-1290).

Additionally, we are uncertain whether you intended to submit split certifications to the ‘788, ‘536, ‘229, and ‘260 patents. As FDA has noted, “a 505(b)(2) applicant may submit a statement under section 505(b)(2)(B) of the FD&C Act for a method-of-use patent that does not claim a use for which the applicant is seeking approval and a paragraph IV certification for any remaining drug substance, drug product, or other method-of-use claims covered by the same patent. This approach is sometimes described as a ‘split certification’ to the patent.” 80 FR 6802, 6819 (February 6, 2015).

If you seek to maintain your proposed labeling, please submit a revised patent amendment to withdraw the PIV certifications to the ‘891, ‘375, ‘348, ‘156, ‘543, ‘318, ‘046, and ‘409 patents that are associated with use codes for uses for which you are not seeking approval (i.e., pancreatic cancer and lung cancer). Please also include more specific method of use statements addressing each method of use and indicating that you are not seeking approval for information protected under the use codes listed for the associated patents (i.e., U-1434 and U-1290 assigned to the ‘891, ‘375, ‘348, ‘156, ‘543, ‘318, ‘046, and ‘409 patents). Please clarify that you have submitted split certifications to the ‘788, ‘536, ‘229, and ‘260 patents to address each of the method of use claims associated with each patent and to address the drug product claims for the ‘788, ‘229, and ‘260 patents. For example, the ‘788 patent has a drug product claim and three use codes listed. One of the use codes (U-1117) describes a use that you are seeking approval for, and two use codes (U-1434 and U-1290) describe uses for which you are not seeking approval in your proposed labeling. Thus, your certification would be a PIV for the drug product claim and U-1117 and a method of use statement for each of the U-1434 and U-1290 use codes.

Conversely, if you seek to maintain all PIV certifications and include the protected information in your proposed labeling (i.e., information about the treatment of pancreatic

cancer and lung cancer), please submit an amendment with revised labeling that includes information about these uses consistent with the labeling for Abraxane. If you seek to maintain the PIV certifications and include the protected information in your proposed labeling, then the amendment should also withdraw the method of use statement.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

FACILITY INSPECTIONS

During recent inspections of HBT Labs, Inc. (FEI 3011148804) (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) resent a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Drug Product

1. Provide available updated stability data of the current registration lots, and that of any new drug product batch(es) manufactured, to support the proposed shelf life at the proposed label storage condition.

2. Update the label storage statement to reflect the current definition of USP controlled room temperature.

Process

(b) (4)

(b) (4)

Biopharmaceutics

1. Provide the complete in vitro release profile data (individual, mean, SD, profiles) for your product. The data should be reported as the cumulative percentage of drug released with time (the percentage is based on the product's label claim at 5 min, 10 min, 15 min, etc.).

2. In vitro drug release acceptance criterion: For the selection of the acceptance criterion of the product, consider the following points:

    a. We recommend use of the in vitro drug release profile data (i.e., 5 min, 10 min, 15 min, etc.) from the clinical batches and primary (registration) batches (throughout the stability program) for setting the acceptance criterion.

    b. The in vitro drug release profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete drug release occurs.

    c. The in vitro drug release acceptance criterion should be based on average in vitro drug release data (n=12).

    d. The selection of the specification time point should be where Q= (b) (4) % drug release occurs.

    e. Include a detailed discussion of the justification of the proposed acceptance criterion in the appropriate section of the CTD.

OTHER

On March 6, 2015, Arnold & Porter, LLP submitted a citizen petition to FDA (Docket No. FDA-2015-P-0732) on behalf of Celgene Corporation and Abraxis Bioscience LLC, requesting, among other things, that FDA refrain from approving any application submitted pursuant to section 505(b)(2) of the FD&C Act that relies upon FDA's finding of safety and/or effectiveness for Abraxane or "any other paclitaxel-based formulation" unless certain data requirements are met. The issues raised by this petition are currently under review by the agency, and FDA has not made a final decision on these

issues. The deficiency comments included in this communication reflect only our current thinking and this communication does not represent a final decision by the agency on the issues raised in the pending citizen petition.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call LT Mitchell Chan, PharmD, BCPS, Regulatory Project Manager, at (301) 796-9105.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/

AMNA IBRAHIM
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