CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211875Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader And Director Summary Review

Date	June 29, 2021
From	Xiao Hong Chen, Ph.D. (Team Lead, OPQ)
	Amna Ibrahim MD (Deputy Director, DO1)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	211875
Applicant	HBT Labs, Inc.
Date of Submission	April 24, 2020
PDUFA Goal Date	October 24, 2020
Proprietary Name / Established (USAN) names	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Dosage forms / Strength	100 mg per vial
Proposed Indication(s)	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a microtubule inhibitor indicated 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.
Recommended:	Tentative Approval

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment: in DARRTS and Panorama, dated 29-June-2021
  - Haripada Sarker, for drug substance dated 29-June-2018
  - Hailin Wang, for drug product dated 23-Sept-2020
  - Ke Ren, for process and facility dated 24-Sept-2020
  - Mei Ou, for biopharmaceutics dated 22-Sept-2020
  - Xiao Hong Chen, Ph.D. as Application Technical Lead dated 28-Sept-2020
- Clinical (Preeti Narayan); in DARRTS, dated 29-June-2021
- Clinical Pharmacology (Wentao Fu); in DARRTS, dated 29-June-2021
- Pharmacology/Toxicology (Wei Chen); in DARRTS, dated 29-June-2021
- Office of Study Integrity and Surveillance (Nicola M Fenty-Stewart); in DARRTS, dated 1-April-2019
- DMEPA Label and Labeling (Sarah Thomas) dated 9-Sept-2020
- Office of Medical Policy Initiatives Division of Medical Policy Program (Sarah Redwood) dated 9-Sept-2020

1. Background

This 505b2 NDA is submitted for the drug, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial. This application relies on the Agency's finding of safety and effectiveness for the listed drug (LD), Abraxane, NDA 21660, which was approved for marketing on January 7, 2005. The proposed drug is for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The proposed drug product for this NDA has the same active pharmaceutical ingredient, dosage form, strength, route of administration and indication as the LD; the formulation differs from the LD with respect to the pH adjusters, sodium hydroxide and hydrochloride, used in the proposed drug product's formulation. The clinical bridge that supports the reliance of safety and effectiveness of the LD is the *in vivo* and *in vitro* bioequivalence studies (BE) evaluated by the Office of Clinical Pharmacology and Biopharmaceutics in OPQ, and was deemed acceptable. Review of the original NDA resulted in the action of Complete Response (CR) due to the product quality deficiencies, primarily in the drug product manufacturing and facilities and some minor deficiencies in the drug product and biopharmaceutics. In the current resubmission, the applicant provides the responses to all deficiencies and comments in the CR letter.

2. Chemistry, Manufacturing and Controls (CMC)

Drug Substance: CMC information for Paclitaxel drug substance is provided in the cross referenced DMF (b) (4). DMF is deemed adequate with the amendment DMF (b) (4) reviewed on 4/23/2020 (Review#6). No new information was submitted in the NDA resubmission. The drug substance information to support the NDA is deemed **acceptable**.

Drug Product: The information provided by the applicant in the resubmission is adequate from drug product (DP) perspective. The applicant has addressed all DP deficiencies and comments in the CR letter. The drug product information is deemed **acceptable**.

OPMA: Process & Facility: From the previous review of the original NDA submission, there are manufacturing deficiencies and comments summarized listed below: 1) in process controls were missing or insufficient for some critical steps; 2) several in process parameters were open-ended or needed to be tightened; 3) (b) (4) (b) (4) were not properly monitored; 4) the development of (b) (4) was not sufficient; 5) the sampling plan was not considered statistically sound; 6) the characterization of paclitaxel amorphous state was missing after long term storage; 7) compliance documents for contacting instruments/materials were missing. In this resubmission, the applicant adequately addressed all deficiencies/comments in the CR letter. The applicant revised the process parameters, provided the in-process controls and missing data and documents, and provide additional process characterization results. The information for the drug product process is found to be **acceptable.**

In the previous review for the original NDA submission, all three API manufacturing facilities are deemed acceptable based on previous history and district review recommendation. They are still in acceptable status. The drug product is manufactured in two Stages. HBT Labs, Inc. (FEI: 3011148804) is responsible for the Stage 1 manufacturing which involves manufacturing

[redacted] is responsible for the Stage 2 manufacturing, [redacted]. Pre-Approval Inspections (PAIs) conducted for both facilities during review of the original NDA resulted in 483 Observations and both facilities were in OAI (Official Action Indicated) status. In the resubmission, facilities responsible for manufacturing [redacted] the final drug product are found acceptable based on 704(a)(4) assessment. All the testing facilities have been found acceptable based on profile and OPMA evaluation. The facility review recommends **Acceptable** for the NDA.

Biopharmaceutics: The Biopharmaceutics review for the original NDA has concluded inadequate due to the deficiencies for the proposed [redacted] method used as a quality control tool. Based on the new available data, the Biopharmaceutics review team along with Dr. Angelica Dorantes and Dr. Paul Seo concluded that [redacted] is not a meaningful quality control (QC) test for the DP for the following reasons:

[redacted]

Division of Biopharmaceutics recommended removing the [redacted] method from the drug product specification table, which was agreed upon by the Applicant. The Biopharmaceutics information in the NDA was deemed acceptable.

Microbiology: Microbiology information was found **acceptable** in the original NDA review. No change was proposed in the resubmission.

3. Nonclinical Pharmacology/Toxicology

No nonclinical deficiencies were identified from the original NDA submission and no additional nonclinical study reports were submitted in this resubmission. The Applicant's proposed labeling in the nonclinical sections was reviewed; the recommendations were made by the DHOT Pharmacology/Toxicology team to comply with PLLR content and formatting and to be consistent with the label for Abraxane.

4. Clinical Pharmacology

No clinical pharmacology deficiencies were identified from the original NDA submission and no additional clinical pharmacology information was submitted in this resubmission.

5. Clinical/Safety

No new clinical data was included with this resubmission. This 505(b)(2) application is relying upon FDA's finding of safety and effectiveness for Abraxane (NDA 021660) The applicant has submitted a bioequivalence (BE) study (HBT001-BE-01) to demonstrate that the proposed drug product is bioequivalent to Abraxane. Refer to the clinical review memo dated May 15, 2019 in DARRTs for the review of safety data from the BE study. In the original review, no

new safety signals were noted. From a clinical perspective the recommendation for this application is **approval**.

6. Pediatrics

Not applicable.

7. Other Relevant Regulatory Issues

Not applicable.

8. Labeling

Proposed labeling has been discussed in the labeling meeting and the FDA comments/revisions have been accepted by the applicant.

9. Other

This review was written, finalized and ready to be signed off in DARRTS on October 8, 2020, prior to the PDUFA goal date of October 24, 2020. This review will be filed into DARRTS on June 29, 2021. The delay past the PDUFA goal date was per ORP's instruction; notwithstanding, we note only a Tentative Approval action can be made at this time because of exclusivity and/or patent issues.

10. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Tentative Approval

Tentative approval is the recommended regulatory action because final approval of the NDA is subject to expiration of a period of patent protection and/or exclusivity.

- **Risk Benefit Assessment**

The NDA 211875, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) 100 mg per vial, is recommended for **Approval** based on the Acceptable recommendation from all disciplines in the review team. No PMC or PMR has been recommended from the review team. Due to the current COVID19 pandemic, pre-approval inspection of manufacturing facilities cannot be performed. The Product quality review team recommends the following lifecycle managements:

A post approval inspection (#PoAI) is recommended for the following facilities (b) (4) .

This application has a complicated manufacturing process. The (b) (4) suspension is manufactured in HBT lab, and then transferred to (b) (4). In the original application, PAI was conducted for both facilities. The EI outcome of both facilities was recommended for a withhold. In resubmission 17, 704 records reviewing was performed for both facilities due to travel restriction. A total of 37 requests for HBT Labs and 29 requests (b) (4) were sent. The responses were reviewed and found adequate. However, there are still several remaining issues that are recommended to be verified during post-approval inspection.

1. The applicant committed itself to revising (b) (4) Master Batch Record: (b) (4) (b) (4) (b) (4). It is required that the updated (b) (4) Master Batch Record be verified during post-approval inspection (b) (4).
2. The applicant provided 3-month compatibility study data of Paclitaxel Albumin Bound Suspension (b) (4) in report RPT-20-035. The 6-month compatibility data is not available at the time of review. Review of the 6-month compatibility data is recommended for post-approval inspection (b) (4).
3. Regarding (b) (4) 704 request 5 and 6, the microbiology method validation and bioburden method validation have not been performed at the time of review. The completion of the validation should be verified during post-approval inspection (b) (4).
4. The applicant plans to replace (b) (4) for commercial production. Regarding (b) (4) 704 request 8, the applicant plans to conduct additional studies to verify the data (b) (4) based on this planned change. Review of additional support data (b) (4) is recommended for post-approval inspection (b) (4).
5. Regarding HBT 704 request 15, the applicant plans to conduct an additional study pertaining to seasonal climatic variations of the year in shipping and distribution of (b) (4) . Verification of the study and review of the study data is recommended for post-approval inspection of HBT.
6. Regarding HBT 704 request 37, the IQ/OQ/PQ protocols (b) (4) (b) (4) (b) (4) in HBT are provided. The qualifications haven't been performed at the time of review. Verification of complete qualification (b) (4) is recommended for post-approval inspection of HBT.

- **Recommendation for Postmarketing Risk Management Activities**

Not applicable.

- **Recommendation for other Postmarketing Study Commitments**

Not applicable.

- **Recommended Comments to Applicant**

None

11. Division Director (Clinical)

See my previous review from 2019. All deficiencies have been resolved and all disciplines recommend approval from their discipline's perspective. Consultant recommendations have been incorporated. There are no PMCs or PMRs. I agree with a Tentative Approval as recommended for this NDA.

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/

XIAOHONG CHEN
06/29/2021 08:12:55 PM

AMNA IBRAHIM
06/30/2021 10:10:18 AM

Cross-Discipline Team Leader Review

Date	June 13, 2019
From	Xiao Hong Chen, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	211875
Applicant	HBT Labs, Inc.
Date of Submission	August 29, 2018
PDUFA Goal Date	June 28, 2019
Proprietary Name / Established (USAN) names	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Dosage forms / Strength	100 mg per vial
Proposed Indication(s)	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a microtubule inhibitor indicated 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.
Recommended:	Complete Response

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Product Integrated Quality Assessment; in Panorama, dated 14-June-2018
  - Ben Zhang, for drug substance
  - William Adams, for drug product
  - Ke Ren, for process and facility
  - Denise Miller, for microbiology
  - Akm Khairuzzaman, for biopharmaceutics
  - Xiao Hong Chen, Ph.D. as Application Technical Lead
- Clinical (Preeti Narayan); in DARRTS, dated 15-May-2019
- Clinical Pharmacology (Wentao Fu); in DARRTS, dated 21-May-2019
- Pharmacology/Toxicology (Wei Chen); in DARRTS, dated 21-May-2019
- Office of Biotechnology Products (Tao Wang); in DARRTS, dated 6-June-2019
- Office of Study Integrity and Surveillance (Nicola M Fenty-Stewart); in DARRTS, dated 1-April-2019

1. Background

This 505b2 NDA is submitted for the drug, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial. This application relies on the Agency's determination of safety and efficacy for the listed drug (LD), Abraxane®, NDA 21660, which was approved for marketing under NDA 21660 on January 7, 2005. The drug is for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The proposed drug product for this NDA has the same active pharmaceutical ingredient, dosage form, strength, route of administration and indication as the LD except the pH adjusters, sodium hydroxide and hydrochloride, used in the drug product formulation. The clinical bridge that supports the reliance of safety and effectiveness of the LD is the *in vivo* and *in vitro* bioequivalence studies (BE) evaluated by the Office of Clinical Pharmacology and Biopharmaceutics in OPQ. The proposed BE study described in IND 129370 was reviewed by OGD and OLDP.

2. Chemistry, Manufacturing and Controls (CMC)

The drug substance (DS) is manufactured (b) (4). CMC information for DS is provided in the Type II DMF # (b) (4). The DMF has been reviewed and deemed **adequate**.

The drug product, Paclitaxel Protein-Bound Particles for Injectable Suspension, 100 mg/vial, is an albumin bound particle form of paclitaxel with a mean particle size of approximately 130 nm. The drug product is supplied as a white to off-white, sterile, lyophilized powder in a single-dose 50 mL glass vial, which is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous injection. The proposed drug product and the listed drug (LD), Abraxis Bioscience's Abraxane®, NDA 21600, have the same formulation except that the sodium hydroxide and hydrochloride acid are used as pH adjusters in the proposed drug product formulation. (b) (4) Drug product review has identified and conveyed deficiencies regarding the specifications and the stability studies, which are still unresolved. There were disagreements between the primary DP reviewer, William Adams, and the secondary reviewer, Dr. Anamitro Banerjee, regarding the two comments. Dr. Banerjee wrote a memo providing the justification of not conveying the following two comments:

1. *Submit the acceptance specifications for the proposed packaging components.* (Justification of deletion: the applicant provided adequate specifications and corresponding Certificates of Analysis for the proposed packaging that are consistent with the FDA expectations)

2. *The in-use stability study for compatibility of syringes, infusion bags, primary sets and catheters with reconstituted suspension should be submitted.* (Justification of deletion: The applicant provided a compatibility study for infusion bag and lines used for this type of product in clinical setting. The drug product has very low residence time in the syringes and catheters, hence presents low risk.)

Manufacturing of drug product consist of two stages (phases). [redacted]

The identified deficiencies are related to the in-process controls and sampling plan for [redacted] testing. This NDA is **inadequate** from drug product and process perspective.

The API manufacturing facilities are found to be acceptable based on previous history. The drug product is manufactured in two Stages. HBT Labs, Inc. (FEI: 3011148804) is responsible for the Stage 1 manufacturing [redacted]. [redacted] is responsible for the Stage 2 manufacturing, [redacted] Pre-Approval Inspection (PAI) were conducted for both facilities. 483 Observations were issued to both facilities and the current status is OAI (official action indicated). There are significant manufacturing risks associated with the facilities, therefore, the drug product facilities are inadequate. It is recommended **withhold** for the approval of the NDA.

The microbiology review of the [redacted] process for the final drug product. This includes a review of the [redacted] validation, equipment [redacted] validation and the container closure [redacted] and container integrity. The review also assessed the microbial contamination risk for the infusion solution over the maximum proposed storage limit. The microbiology review found the information provided in the NDA as well as in the referenced DMFs (#[redacted]) **adequate** to support the approval of the NDA.

The Biopharmaceutics review evaluated the adequacy of the overall information/data supporting [redacted] method as a quality control tool. Biopharmaceutics found the proposed [redacted] method **inadequate**. Biopharmaceutics recommends that the applicant develop an in vitro drug release method utilizing appropriate equipment/apparatus 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.

3. Nonclinical Pharmacology/Toxicology

The applicant is relying on FDA's previous findings of safety and publicly available information on nonclinical properties of Taxol and Abraxane to support this NDA. No additional nonclinical pharmacology/toxicology data on paclitaxel were submitted with this application or warranted to support the approval of the application. The CMC review team requested a Pharmacology/Toxicology consult on the acceptability of the toxicological evaluation and risk assessment on extractables/leachables from the contact with the drug

product manufacturing equipment during the drug product manufacturing. Study submitted and reviewed are the following:

1) Evaluation of three extractables-paclitaxel injectable suspension drug product
2) Evaluation of two extractables [redacted] (b) (4) - paclitaxel injectable suspension drug product

The pharm/tox reviewer found the justification using the published toxicologic data on the listed 5 extractables, the genotoxic feature and proposed indication of the proposed drug product, are acceptable. The nonclinical recommendation for this application is **approval**.

4. Clinical Pharmacology

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211875 submission. This NDA is approvable from a clinical pharmacology perspective pending on the scheduled OSIS clinical sites inspection results. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Evidence of PK Similarity of HBT-001 and ABRAXANE under Overnight Fasted Conditions	A Phase 1 trial provides evidence establishing PK bioequivalent (BE) between HBT-001 and ABRAXANE when 260 mg/m^2 administrated intravenously over 30 minutes under overnight fasting conditions.
General dosing instructions	HBT-001 is 260 mg/m^2 intravenously over 30 minutes every 3 weeks

The proposed commercial formulation of HBT001 was used in the study. The study was a Phase 1, multicenter, randomized, open-label, 2-period, 2-sequence, crossover, 2-stage group sequential design study assessing the BE of a single dose of HBT001 versus ABRAXANE. Based on the results of the BE study, the clinical pharmacology reviewer has determined that bioequivalence (BE) has been demonstrated between HBT-001 and ABRAXANE. This NDA is **approvable** from a clinical pharmacology perspective pending the conclusion of scheduled Office of Study Integrity and Surveillance clinical sites inspection. The clinical site inspection is still ongoing with the requested review goal date of 9/11/2019.

Based on OSIS memorandum dated 4/1/2019, the clinical site inspection is still pending. The request for analytical site inspection has been declined based on the OSIS inspection dated [redacted] (b) (4), and the final classification for that inspection was No Action Indicated (NAI).

5. Clinical/ Safety

The applicant is relying on FDA's previous findings of safety and efficacy for the LD Abraxane NDA 21660 to support this NDA. The Abraxane application was approved via the 505(b)(2) pathway using Taxol as the LD. The applicant has submitted a bioequivalence (BE) study (HBT001-BE-01) to demonstrate that the proposed drug product is bioequivalent to

Abraxane. The clinical study report (CSR) prepared by the applicant was reviewed. Twenty-two patients received a single IV infusion of Abraxane, and 21 of these patients also received a single IV infusion of HBT001. No deaths occurred during the study. No severe adverse events (SAEs) were reported. Two treatment-emergent adverse events (TEAEs) leading to study drug discontinuation were reported during the study. The BE stud is evaluated by the clinical pharmacology reviewer.

6. Immunogenicity

OBP (Office of Biotechnology Products) was consulted for immunogenicity due to the drug product contains human serum albumin (HAS). The HAS used in the drug product formulation is the CBER approved human serum albumin (BLA 125154). There are no immunogenicity issues raised during the review process, as well as after approval. Albumin is the most abundant protein in human serum, and should be immunologically inert. Extensive literature searches have provided no evidence for human anti-human albumin antibodies. The first FDA approved albumin coated Paclitaxel, ABRAXANE® has been in clinical use for more than 12 years (NDA 21660). There are no reports that ABRAXANETM has any safety issue related to Albumin immunogenicity. The impurity profile and aggregates are similar between the HBT proposed drug product and Abraxane®. No novel impurity is found in the proposed HBT drug product. The conclusion is that Albumin is unlikely to increase immunogenicity related risk.

7. Pediatrics

Not applicable.

8. Other Relevant Regulatory Issues

Not applicable.

9. Labeling

DMEPA did not write a review for the NDA since the application will be recommended for Complete Response.

10. 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.

11. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Complete Response

- **Risk Benefit Assessment**

The NDA 211875, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) 100 mg per vial, is recommended for **Complete Response** from the product quality perspective. The product quality team reviewed full CMC information in the NDA including the manufacturing facilities, and they are found to be inadequate. Specifically, the drug product manufacturing facilities are currently at OAI status, and CMC deficiencies for Drug Product, Process, Biopharmaceutics have been identified, conveyed and not resolved.

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

- **Recommendation for Postmarketing Risk Management Activities**

Not applicable.

- **Recommendation for other Postmarketing Study Commitments**

Not applicable.

- **Recommended Comments to Applicant**

The deficiencies and comments provided in the IQA (Integrated Quality Assessment) for NDA 211875 should be included in the Complete Response letter for this NDA application.

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/

XIAOHONG CHEN
06/14/2019 02:42:02 PM

Division Director Summary Review for Regulatory Action

Date	6/14/2019
From	Amna Ibrahim MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	211875
Applicant	HBT LABS INC
Date of Submission	8/29/2018
PDUFA Goal Date	6/29/2019
Proprietary Name	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Dosage Form(s)	Lyophilized Powder
Applicant Proposed Indication(s)/Population(s)	• 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.
Action or Recommended Action:	Complete Response
Approved/Recommended Indication(s)/Population(s) (if applicable)	NA

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Narayan, Preeti
Biopharmaceutics Reviewer	Khairuzzaman, Akm
Pharmacology Toxicology Review	Chen, Wei
OPQ Review	Adams, William M.
Microbiology Review	Miller, Denise
Clinical Pharmacology Review	Fu, Wentao
CDTL Review	Chen Xiao Hong

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
CDTL=Cross-Discipline Team Leader

1. Background

This NDA 211875 for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) was submitted under section 505b2 of the FD&C Act and relies on the safety and efficacy of the Listed Drug Taxol (NDA 20262). Abraxane was approved under section 505b2, with Taxol as the LD for the nonclinical information. Abraxane has the advantage of lacking cremophor which is present in Taxol and causes hypersensitivity reactions requiring premedication. However, hypersensitivity reactions, including fatal ones have been reported and there may be cross hypersensitivity with other taxanes.

The proposed drug product (DP) and Abraxane have the same active ingredient. The dosage form, route and strength are the same as Abraxane. The proposed DP, however, uses HCL and NaOH for PH adjustment (b) (4), making it suitable for a 505b2 pathway, instead of 505j. To support the application, the applicant has submitted the following:

A. CMC information
B. Bioequivalence (BE) Studies with the intent to demonstrate the bioequivalence to Abraxane
C. Published literature, to support the approval of the NDA to include

- NDA 021660 (Abraxane): Previous finding of safety and effectiveness for metastatic breast cancer (labeling sections 1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 17)
- NDA 020262 (Taxol) Previous finding of safety with respect to:
    - Postmarketing experience (labeling section 6.2)
    - Accidental exposure (labeling section 6.3)
    - Mechanism of Action (labeling section 12.1)
- Published literature (Taxol)
    - Metabolism (labeling section 12.3)
    - Carcinogenesis, Mutagenesis, Impairment of Fertility (labeling section 13.1)
- Published literature (Abraxane):
  Pharmacokinetics in Hepatic Impairment, Renal Impairment and Population pharmacokinetic analyses (labeling section 12.3)

A Complete Response letter will be issued as there are multiple product quality issues as outlined below and in the CDTL review. In addition, there are unresolved patent infringement issues and an ongoing citizen petition. The citizen petition submitted on behalf of Celgene Corporation and Abraxis Bioscience LLC, requests that 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. This review of this petition is ongoing.

2. Product Quality

Paclitaxel is a white to off-white, crystalline powder for injectable suspension.

DMF and API information was adequate for this application.

Per the CDTL review, the drug product, Paclitaxel Protein-Bound Particles for Injectable Suspension, 100 mg/vial, is an albumin bound particle form of paclitaxel with a mean particle size of approximately 130 nm. The drug product is supplied as a white to off-white, sterile, lyophilized powder in a single-dose 50 mL glass vial, which is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous injection. The proposed DP, however, uses HCL and NaOH for PH adjustment. (b) (4) .

Multiple product quality deficiencies were identified for DP, DP process, biopharmaceutics and DP manufacturing facilities. Per the biopharmaceutics reviewer, the applicant has proposed to use (b) (4) study which is not considered as an in vitro drug release test and the methodology associated with such test is not acceptable (b) (4) (b) (4) .

DP deficiencies include those regarding specifications and stability studies. There was disagreement between the primary reviewer for DP, Dr Adams and Branch Chief, Dr Banerjee regarding two deficiencies. Dr Banerjee detailed in his memo the reasons for removing these as deficiencies, specifications for the packaging components and in-use stability studies for syringes and associated devices with the reconstituted suspension. Per Dr Banerjee, the changes to vendors, and hence specifications, will be handled as per the post approval changes guidance if the proposed product is approved. In addition, his memo states that the drug product has very low residence time in the syringes and catheters, hence presents low risk. The data provided by the applicant indicates that the drug product is compatible with the infusion bags and catheters. As a result, these comments will not be sent as deficiencies in the CR letter. Manufacturing deficiencies were identified related to the in-process controls and sampling plan (b) (4) testing. (b) (4) suspension manufacture and in-process testing, and final drug manufacture facilities were found to be inadequate.

API manufacturing facilities were found acceptable based on previous history, but significant manufacturing risks are associated with the DP facilities, and the drug product facilities are inadequate.

3. Nonclinical Pharmacology/Toxicology

Nonclinical reviewers were consulted by the CMC team regarding 5 extractables (b) (4) . Given the published toxicologic data on the listed 5 extractables, the genotoxic feature and proposed indication of the proposed drug product, there were no safety concerns for these 5 extractables at the estimated concentrations from the Pharmacology/ toxicology perspective. The nonclinical recommendation for this application is approval.

4. Clinical Pharmacology

In a Phase 1, multicenter, randomized, open-label, 2-period, 2-sequence, crossover, 2-stage group sequential design study (N=22), the BE of a single dose of HBT001 versus ABRAXANE was assessed. Period 1 in Cycle 1 (Period 1 and washout period of three weeks) and Period 2 in Cycle 2 (Period 2 and follow-up period) evaluated the pharmacokinetics (PK) of paclitaxel following dosing with commercial formulation of the DP or Abraxane. After a single-dose IV infusion of the two study treatments unbound paclitaxel total and free PK profiles were similar on the two arms. BE was demonstrated under overnight fasted conditions, and a dosage of 260 mg/m^2 intravenously over 30 minutes every 3 weeks is recommended. This NDA is approvable from a clinical pharmacology perspective pending on the scheduled OSIS clinical sites inspection results. These sites will be inspected with the goal date of 9/11/2019, after the PDUFA date for this NDA.

5. Clinical Microbiology

NA

6. Clinical/Statistical-Efficacy

Given that BE was demonstrated, this NDA relies on the safety and efficacy of Abraxane.

7. Safety

Given that BE was demonstrated, this NDA relies on the safety and efficacy of Abraxane. In the BE study, adverse reactions were similar in both arms

Per the clinical review, “this 505(b)(2) NDA application references the findings, safety and effectiveness for Abraxane as well as referenced published literature for Taxol, and the BE study did not reveal any new safety signals. Therefore, from a clinical perspective the recommendation for this application is approval.”

8. Advisory Committee Meeting

NA

9. Pediatrics

NA

10. Other Relevant Regulatory Issues

- *Exclusivity or patent issues of concern:* While the applicant acknowledged multiple unexpired patents and provided paragraph IV certification. However, the proposed labeling (which purports to omit certain protected information) and certain associated PIV certifications are incongruent with each other. In addition, it is not clear whether the applicant intended to submit split certifications. See CR letter for more detail.

- *Office of Scientific Investigations (OSI) Audits:* OSIS inspection will be completed with the goal date of 9/11/2019

- *Financial Disclosure:* The applicant certified that there was no financial disclosure whereby the investigator could be affected by the outcome of the study.

- *Deficiencies:* See CR letter for the deficiencies and recommendations to resolve them

11. Labeling

Due to the expected CR action, labeling was not reviewed.

12. Postmarketing

NA

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
06/14/2019 02:47:09 PM