CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211875Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211875
Review #3

Drug Name/Dosage Form	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Strength	100 mg per vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	HBT Labs, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission#0028	02/07/2022	DP, OPMA, Micro,
Quality Amendment#0029	03/03/2020	OPMA

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Paresma Patel
Drug Product	Sheena Hailin Wang	Xiao Hong Chen
OPMA (Process & Facility)	Ke Ren	Feiyan Jin
Microbiology	Denise Miller	Bryan Riley
Biopharmaceutics	Mei Ou	
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
Refer to CMC review#1

B. Other Documents: *IND, RLD, or sister applications*
N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	129370	Initial IND to conduct BE study was submitted to OGD on 3/27/2013.
NDA	21660	LD NDA Abraxane
BLA	125154	Albumin

2. CONSULTS

N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 211875, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) 100 mg per vial, was issued an **Tentative Approval** letter on June 30, 2021. The current resubmission contains some minor CMC changes, which have been reviewed by product quality review team and found acceptable. All manufacturing and controls facilities for this NDA are deemed **Acceptable** by OPMA (Office of Pharmaceutical Manufacturing Assessment). The NDA is recommended for approval from the product quality perspective. Include the following statement in the action letter:

A 36-month expiry dating period is granted for the product stored in original carton at 20°C to 25°C (68°F to 77°F) (see USP controlled room temperature).

II. Summary of Quality Assessments

A. Product Overview

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). The applicant stated that the studies were conducted in accordance with FDA's Bioequivalence Recommendations for Specific Products, Draft Guidance on Paclitaxel (September 2012), using Abraxane as the LD. The proposed BE study was conducted under IND 129370, and was submitted in the NDA and reviewed by OCP (Office of Clinical Pharmacology) and found acceptable. Review of the original NDA resulted in the action of Complete Response (CR) letter based on product quality deficiencies, primarily in the drug product manufacturing and facilities. The resubmission dated April 24, 2022 has adequately addressed all product quality deficiencies and the NDA was issued a Tentative Approval letter on June 30, 2021. In the current resubmission, the applicant seeks full approval of the application. There are no substantial changes provided in the current Resubmission#0028. Based on product quality review team's assessment, we recommend **Approval** for the NDA.

Proposed Indication(s) including Intended Patient Population	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.
Duration of Treatment	Until disease progression or unacceptable toxicity occurs
Maximum Daily Dose	260 mg/m^2 intravenously over 30 minutes every 3 weeks
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance
As no new information for drug substance was submitted in the current submission, no drug substance was conducted. The drug substance reviewer entered NAI (no action indicated) for the NDA in Panorama. CMC information for drug substance remains **adequate**.

Drug Product
The information provided by the applicant in the resubmission and subsequent IR response is adequate from DP perspective. Drug product release and stability specifications have been revised based on registration batch release and stability data, and the related method validation has been updated as requested. Full term stability data along with in-use stability data at 36 months have been provided with testing of additional attributes as requested, which supports the proposed long-term and in-use storage condition described in the labeling. Particle size histograms provided for bulk samples and primary stability batches at various time points suppor (b) (4) the manufacturing process and physical stability of the nanoparticle upon long term and in-use storage. The applicant's responses to the deficiencies in the CR letter regarding drug product information is deemed **acceptable**.

OPMA: Process & Facility
The drug product is a sterile injectable suspension lyophilized powder. The manufacturing processes are divided into two phases. Performed by HBT Labs (b) (4) Critical process parameters were investigated and optimized. The exhibit batches were manufactured using the proposed commercial process. No scale up for commercial batch is proposed. The submission batches meet the established in-process control specifications. No reprocessing is employed to manufacture current exhibit as well as future commercial batches. Facilities responsible for manufacturing (b) (4) the final drug product are found acceptable based on 704(a)(4) assessment. The DS manufacturing facility is reviewed and found acceptable based on inspection history and district review recommendation. All the testing facilities have been found acceptable based on profile and OPMA evaluation.

Resubmission #0029 (seq. 0028 and 0029)

Both process and facility were adequate in the previous cycle (resub-17). In resub-29, there is no process change. There is one minor facility change (b) (4) (b) (4) There is no other change for facility. All the facilities are compliant. Both process and facility remain **adequate**.

Biopharmaceutics
As no new information for biopharmaceutics was submitted in the current submission, no biopharmaceutics was conducted. The biopharmaceutics reviewer entered **NAI** (no action indicated) for the NDA in Panorama.

Microbiology
The changes submitted in this resubmission were minor changes related to company name changes and method renumbering. The three microbiological methods, sterility, endotoxin, and container closure integrity had no changes to the methods or acceptance criteria. However, the company name wa (b) (4) for the container closure integrity method (b) (4) . The testing is still performed (b) (4) . CMC information for microbiology remains **adequate**.

Labeling
There are minor labeling updates as follows:
For Contain Carton labels, the applicant updated NDC number, barcode and company logo.
For Prescribing Information, the applicant updated NDC number and minor typographic corrections. These changes are deemed **acceptable**.

C. Special Product Quality Labeling Recommendations (NDA only)
N/A

D. Final Risk Assessment
There is no substantial change provided in the current Resubmission#0028. Final risk assessment is provided in the IQA (Integrated Quality Assessment) filed in DARRTS dated June 29, 2021 for the Resubmission#0016 dated April 24, 2020

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
10-June-2022

Xiao
Chen

Digitally signed by Xiao Chen
Date: 6/10/2022 11:33:47AM
GUID: 508da7220002a138fcc70fbccbfd08bf

Office of New Drug Products
Division of New Drug Products I
Review of Chemistry, Manufacturing, and Controls

Product Information	The drug product is a white to off white lyophilized powder that is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP to form a suspension for injection.
NDA Number	211875
Assessment Cycle Number	3
Drug Product (DP) Name / Strength	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Route of Administration	Intravenous injection
Applicant Name	HBT Labs, Inc.
RLD Information (Brand Name of Product, Applicant)	Abraxane® by Abraxis Bioscience, LLC
RLD/RS Number	NDA 021660
Clinical Review Division	Division of Oncology I
Proposed Indication	Metastatic Breast Cancer
Subject	Review of Resubmission in SD29 on 02/07/2022 and SD30 on 03/03/2022

Assessment Recommendation: *Adequate*

Assessment Summary:

This is a review of the resubmission for NDA 211875 after FDA's tentative approval letter on 06/30/2021.

The information provided by the applicant in the resubmission and subsequent quality IR (facility) response are adequate from DP perspective. Drug product release and stability specifications remain the same as described in review #2 except for minor changes of manufacturer name and method numbering. The routine testing/acceptance criteria for all excipients at HBT, the manufacturer for drug produc [redacted] (b) (4) are considered fit-for-purpose and remain adequate. No new stability data was provided. The evaluation of the specification provided in 3.2. P.7 [redacted] (b) (4) used for storage of drug produc [redacted] (b) (4) is deferred to OPMA reviewer. The approval recommendation remains for this NDA from a DP perspective.

List Submissions being assessment (table):

Document(s) Assessed	Date Received
SD29 (eCTD 0028) Resubmission/Class 2	*02/07/2022*
SD30 (eCTD 0029) Quality/Response to IR	*03/03/2022*

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

(b) (4)

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	This is a lyophilized [redacted] frug product for the treatment of metastatic breast cancer. The active pharmaceutical ingredient i [redacted] bound to human albumin to form the drug produc [redacted]. Th [redacted] drug product is manufacture [redacted]
NDA Number	211-875
Assessment Cycle Number	3
Drug Product Name/ Strength	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) 100 mg/vial
Route of Administration	Intravenous
Applicant Name	HBT Labs Inc.
Therapeutic Classification/ OND Division	CDER/OOD/DO1
Manufacturing Site	[redacted]
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary: The changes submitted in this resubmission were minor changes related to company name changes and method renumbering. The three microbiological methods, sterility, endotoxin, and container closure integrity had no changes to the methods or acceptance criteria. However, the company name [redacted] for the container closure integrity method [redacted]. The testing is still performed [redacted]

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA-211875-ORIG-1-RESUB-29	**02/04/2022**

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: Review Cycle 1 was adequate from a DMA perspective however the NDA received a Complete Response for issues from other disciplines. The applicant responded in Cycle 2 and received a Tentative approval; DMA was NAI. This third cycle is for final approval and included some minor changes. These changes included updating the updating the numbering of the test methods to reflect current document ID numbering system at the testing facility and updating some acceptance criteria to match additional HBT specifications. None of the specifications that were updated included any microbiological tests.

Concise Description of Outstanding Issues: NA

Supporting Documents:
DMA review N211875MR01.pdf dated 04/03/2019, Adequate

P DRUG PRODUCT

There were no changes in the manufacturing process.

Assessment: NA

(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

No deficiencies were identified.

Primary Microbiology Assessor Name: Denise Miller
SPQA, OPQ/OPMA/DMAII/MAB5

Secondary Assessor Name: Bryan Riley, Ph.D.
Branch Chief, OPQ/OPMA/DMAII/MAB5

Denise Miller

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Bryan Riley

Digitally signed by Bryan Riley
Date: 5/23/2022 12:29:08PM
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/s/

XIAOHONG CHEN
06/10/2022 11:50:05 AM

Recommendation: Tentative Approval

NDA 211875
Review #2

Drug Name/Dosage Form	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Strength	100 mg per vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	HBT Labs, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	08/29/2018	API, DP, OPMA, Micro, Biopharm
Resubmission	04/24/2020	DP, OPMA, Micro, Biopharm
Quality Amendment 0017	06/02/2020	DP
Quality Amendment 0020	07/10/2020	Biopharm
Quality Amendment 0022	08/11/2020	DP, Biopharm
Quality Amendment 0023	08/24/2020	OPMA
Quality Amendment 0024	09/024/2020	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Ali Al Hakim
Drug Product	Hailin Wang	Anamitro Banerjee
OPMA (Process & Facility)	Ke Ren	Steve Rhieu
Biopharmaceutics	Mei Ou	Banu S. Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
Refer to CMC review#1

B. Other Documents: *IND, RLD, or sister applications*
N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	129370	Initial IND to conduct BE study was submitted to OGD on 3/27/2013.
NDA	21660	LD NDA Abraxane
BLA	125154	Albumin

2. CONSULTS

N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 211875, Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) 100 mg per vial, as resubmitted on April 24, 2020, is recommended for **Tentative Approval** from the product quality perspective. The resubmission satisfactorily addressed all product quality deficiencies and comments in the Complete Response letter dated . All manufacturing and controls facilities for this NDA are deemed **Acceptable** by OPMA (Office of Pharmaceutical Manufacturing Assessment). Include the following statement in the action letter:

A 36-month expiry dating period is granted for the product stored in original carton at 20°C to 25°C (68°F to 77°F) (see USP controlled room temperature).

II. Summary of Quality Assessments

A. Product Overview

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). The applicant stated that the studies were conducted in accordance with FDA's Bioequivalence Recommendations for Specific Products, Draft Guidance on Paclitaxel (September 2012), using Abraxane as the LD. The proposed BE study was conducted under IND 129370, and was submitted in the NDA and reviewed by OCP (Office of Clinical Pharmacology) and found acceptable. Review of the original NDA resulted in the action of Complete Response (CR) letter based on product quality deficiencies, primarily in the drug product manufacturing and facilities. In the current resubmission, the applicant provides the responses to all deficiencies and comments in the CR letter.

Proposed Indication(s) including Intended Patient Population	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.
Duration of Treatment	Until disease progression or unacceptable toxicity occurs
Maximum Daily Dose	260 mg/m^2 intravenously over 30 minutes every 3 weeks
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

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 and subsequent IR response is adequate from DP perspective. Drug product release and stability specifications have been revised based on registration batch release and stability data, and the related method validation has been updated as requested. Full term stability data along with in-use stability data at 36 months have been provided with testing of additional attributes as requested, which supports the proposed long-term and in-use storage condition described in the labeling. Particle size histograms provided for bulk samples and primary stability batches at various time points support the (b) (4) manufacturing process and physical stability of the nanoparticle upon long term and in-use storage. The applicant's responses to the deficiencies in the CR letter regarding drug product information is deemed **acceptable**.

OPMA: Process

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); 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.**

OPMA: Facility

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 (b) (4). (b) (4) is responsible for the Stage 2 manufacturing, (b) (4) 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 (b) (4) 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. The OPMA reviewer recommends the following lifecycle managements:

A post approval inspection (#PoAI) is recommended for the following facilities (b) (4) HBT Labs, Inc./3011148804).

This application has a complicated manufacturing process. The (b) (4) is manufactured in HBT lab, and then transferred to (b) (4) (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) 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 [redacted] is recommended for post-approval inspection [redacted].

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 [redacted]. 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 [redacted] in HBT are provided. The qualifications haven't been performed at the time of review. Verification of complete qualification [redacted] is recommended for post-approval inspection of HBT.

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. Biopharmaceutics review for the current resubmission focuses on: (i) the proposed [redacted] method, (ii) the need of in vitro formulation bridging of the proposed drug product.

[redacted]

During the review of the data, the Biopharmaceutics review team along with Dr. Angelica Dorantes and Dr. Paul Seo decided that [redacted] test is not considered a meaningful quality control (QC) test for the proposed drug product for the following reasons:

1) [redacted]
2)

Division of Biopharmaceutics recommended removing the [redacted] method from the drug product specification table, which was agreed upon by the Applicant.

In Vitro Formulation Bridging:

There are no changes between the commercial formulation and the pivotal BE formulation (BE batch GPA005). Therefore, no additional in vitro or in vivo formulation bridging studies are needed for the proposed drug product.

From the Biopharmaceutics perspective, NDA 211875-ORIG-RESUB-17 for the proposed Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg per vial, is recommended for **APPROVAL.**

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

APPEARS THIS WAY IN ORIGINAL

D. Final Risk Assessment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Content uniformity (b) (4)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • **Container closure** • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Absence is demonstrated through the leachable studies performed during development
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place
Appearance (caking)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place
Physical stability (solid state) lyophilized small molecule products	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place
Osmolality	• Formulation • Container closure • Raw materials • Process parameters	L		Acceptable	Controls are in place

	• Scale/equipments • Site		(b) (4)		
Particle size distribution (b) (4)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place
Re-dispersability /reconstitution time	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place
Moisture content (lyophilized)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
29-September-2020

This review was written, finalized and ready to be signed off in DARRTS on September 29, 2020, prior to the PDUFA goal date of October 24, 2020. All manufacturing facilities have been verified to be acceptable by the facility reviewer since the review was finalized about 9 months ago. This review will be uploaded into Panorama and the IQA will be filed in DARRTS on June 29, 2021. The delay past the PDUFA goal date was per ORP's instruction, 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.

Xiao Chen

Digitally signed by Xiao Chen
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/s/

XIAOHONG CHEN
06/29/2021 03:47:50 PM

Recommendation: Complete Response

NDA 211875
Review #1

Drug Name/Dosage Form	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Strength	100 mg per vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	HBT Labs, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	08/29/2018	All
Quality Amendment 0002	09/24/2018	DP
Quality Amendment 0004	11/16/2018	Facility
Quality Amendment 0005	12/28/2018	Facility
Quality Amendment 0006	01/25/2019	DP/Biopharm/Micro
Quality Amendment 0007	02/14/2019	Facility
Quality Amendment 0008	03/11/2019	DP/Process/Facility

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Ben Zhang	Suong T. Tran
Drug Product	William Adams	Anamitro Banerjee
Process	Ke Ren	Steve Rhieu
Facility	Ke Ren	Steve Rhieu
Microbiology	Denise Miller	Bryan Riley
Biopharmaceutics	Akm Khairuzzaman	Banu S. Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	N/A	
ORA Lead	N/A	

Environmental	Mike Adams	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	6/3/2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1)
	Type V			Adequate	10/3/2018	DMF has been reviewed and found adequate.
	Type III			Adequate	6/3/2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
	Type V			Adequate	11/14/2018	DMF has been reviewed and found adequate.
	Type V			Adequate	10/1/2016	DMF has been reviewed and found adequate.
	Type II			Adequate	3/15/2019	DMF has been reviewed and found adequate.

B. Other Documents: *IND, RLD, or sister applications*
N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	129370	Initial IND to conduct BE study was submitted to OGD on 3/27/2013.
NDA	21660	LD NDA Abraxane
BLA	125154	Albumin

2. CONSULTS
N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
OBP	Complete	Acceptable	5/23/19	Mills, Frederick; Tao Wang
CBER	Complete	Acceptable	4/29/19	Karnaukhova, Elena

Executive Summary

I. Recommendations and Conclusion on Approvability

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. Refer to the deficiency comments provided below.

Facility Inspections

During a recent inspection of the NAME manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Drug Product

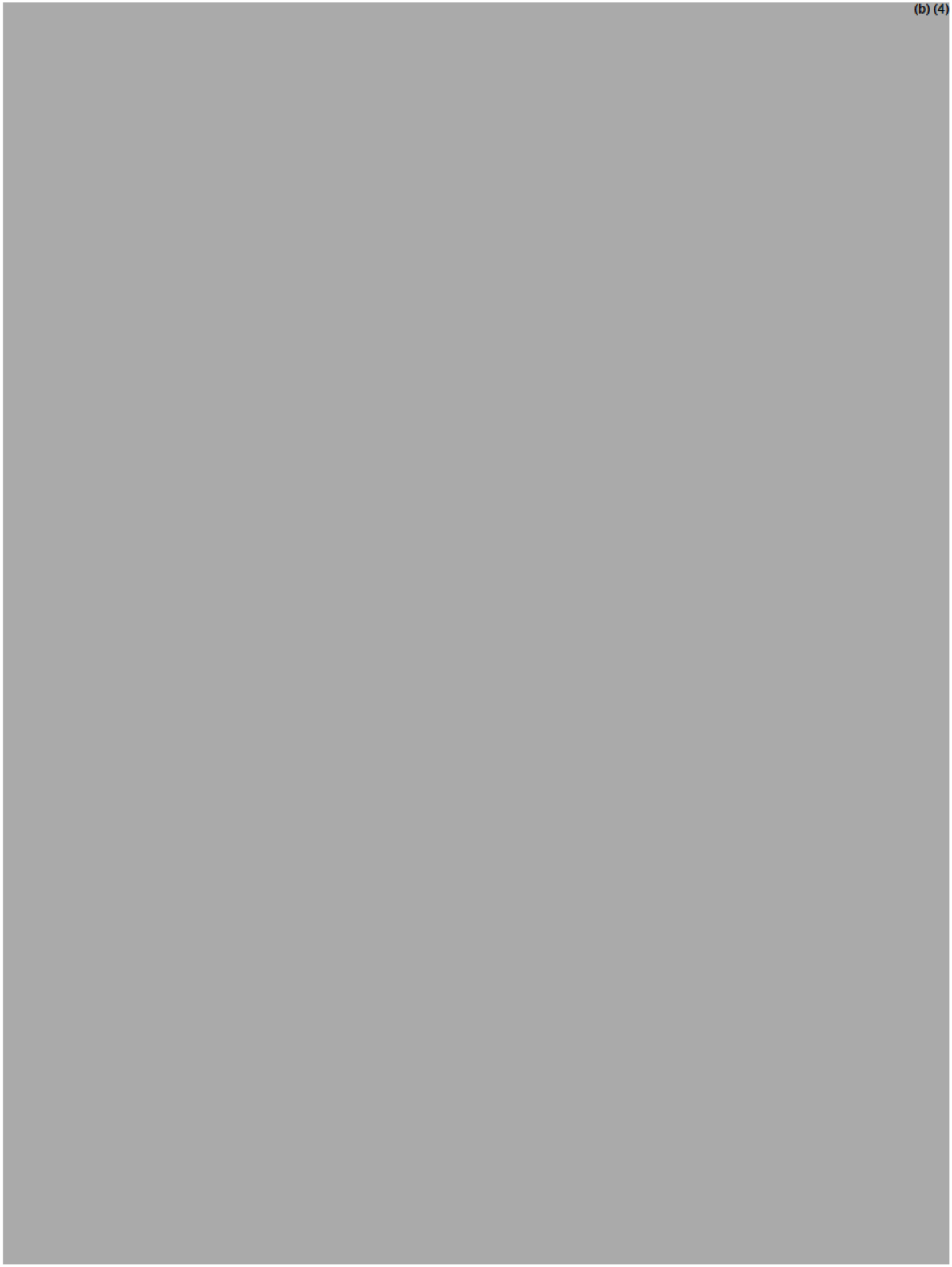
1. Control of the drug product is not adequate. Update the drug product specifications to reflect the changes in acceptance criteria, methods, and validation data per your commitment in the amendments dated January 25, 2019 (SD007) and March 11, 2019 (SD009). The proposed changes include:
   a. Addition 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. HBT stability report RPT-PS-013.00 (modules 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

Address the following deficiencies related to your response submitted on 3/11/2019. The same goes for additional product quality comments listed below.

(b) (4)

(b) (4)



Biopharmaceutics

12. Your plans to use the [redacted] (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 [redacted] (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.

Additional Product Quality Comments:

Drug Product

1. Provide updated stability data 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

[redacted] (b) (4)

Biopharmaceutics

11. 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.).
12. In vitro drug release acceptance criterion: For the selection of the acceptance criterion of the product, consider the following points:
    a. FDA recommends 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.

II. Summary of Quality Assessments

A. Product Overview

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 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 API, 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). The applicant stated that the studies were conducted in accordance with FDA's Bioequivalence Recommendations for Specific Products, Draft Guidance on Paclitaxel (September 2012), using Abraxane as the LD. The proposed BE study was conducted under IND 129370, and was reviewed by OGD and OLDP. The 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.

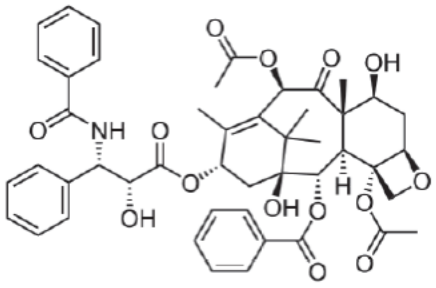
Proposed Indication(s) including Intended Patient Population	Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a microtubule inhibitor indicated for the treatment of metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
Duration of Treatment	Until disease progression or unacceptable toxicity occurs
Maximum Daily Dose	260 mg/m^2 intravenously over 30 minutes every 3 weeks
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

CMC information for Paclitaxel drug substance is provided in DMF (b) (4). The applicant makes reference to the DMF for all CMC information for paclitaxel drug substance. The drug substance specification and batch analysis data for drug substance lots used to make the three registration drug product batches are provided in the NDA. The DMF has been reviewed and found adequate.

Paclitaxel is a white to off-white, crystalline powder. (b) (4)



The applicant references DMF [redacted] (b) (4) for all the related information for drug substance paclitaxel. The drug substance specification and batch analysis data for drug substance lots used to make the three-registration drug product lots are provided in the NDA. The DMF has been reviewed and found **adequate**.

Drug Product

HBT Labs, Inc.'s (HBT) proposed drug product, Paclitaxel Protein-Bound Particles for Injectable Suspension, 100 mg/vial, is an albumin bound particle 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. [redacted] (b) (4)

To bridge the proposed drug product and the LD, the applicant performed in vitro characterization study and a BE study to be evaluated by clinical pharmacology reviewer. The physicochemical comparative studies showed that the proposed formulation has the same properties for the most attributes tested: appearance, pH, assay, albumin content, related compounds, [redacted] (b) (4), mean particle size, particles size distribution (Span), [redacted] (b) (4), particle morphology, crystallinity, fraction of free/bound paclitaxel in reconstituted suspension, nature of paclitaxel/albumin bonding, and *in vitro* release rate. Insignificant differences are observed for particle surface potential and fraction of free/bound albumin. Abraxane showed [redacted] (b) (4) stated to be due to the raw materials and process controls for the HBT product.

There are outstanding deficiencies/comments for 1) the drug product specifications related to adding the identity test for human serum albumin and revising the acceptance criteria methods for the tests of paclitaxel assay, [redacted] (b) (4), reconstitution time, pH, [redacted] (b) (4), total degradants, [redacted] (b) (4), particle size distribution, [redacted] (b) (4), and albumin aggregates; 2) the stability studies to include sample evaluation at 12 and 24 month intervals along with 6 and 36 month intervals and to provide updated stability data to support the proposed shelf life at the proposed label storage condition.

Therefore, the drug product information provided in the NDA has been found **inadequate** to support the approval of the NDA.

Process

Manufacturing of drug product consist of two stages (phases). (b) (4) [redacted]. There are outstanding manufacturing deficiencies summarized 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; (b) (4) [redacted] 4) the development (b) (4) [redacted] 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.

The information for the drug product process is found to be **inadequate** the outstanding deficiencies.

Facility

There are three facilities involved in API manufacturing. All three API manufacturing facilities are deemed 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 (b) (4) [redacted] is responsible for the Stage 2 manufacturing, (b) (4) [redacted]. Pre-Approval Inspection (PAI) were conducted for both facilities. 483 Observations were issued to both facilities and the current status is OAI. There are significant manufacturing risks associated with both facilities. Therefore, the manufacturing facility information in the NDA is deemed to be **inadequate**. In addition, there are three other drug product manufacturing facilities that are involved in release and stability testing and container/closure testing. They are deemed acceptable based on previous history. The facility review recommends **withhold** of the approval of the NDA.

Microbiology

The microbiology review concentrated on the (b) (4) [redacted] process for the final drug product. This includes a review of the (b) (4) [redacted] validation, equipment (b) (4) [redacted] validation and the container closure (b) (4) [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.

Biopharmaceutics

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting [redacted] method as a quality control tool. Based on the review of the provided information/data, Biopharmaceutics found the proposed [redacted] method **inadequate**. The Applicant has proposed to use [redacted] study which is not considered as an appropriate [redacted] method [redacted]. 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.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

N/A

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D.
13-June-2019

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 03, 2019

FROM: OPQ/ONDP/DNDP1/Branch 2

SUBJECT: NDA 211875/Branch Chief Memo for Expiration Dating Period of the Drug Product

APPLICATION/DRUG: NDA 211875 Paclitaxel Protein-Bound Particles for Injectable suspension (Albumin-Bound), 100 mg/vial, single-dose vial

Memo:
The drug product secondary reviewer disagrees with the drug product primary reviewer reading some of the comments to be sent out to the applicant in the action letter. The comments as proposed by the primary reviewer are:

The CMC information for drug product is not adequate to support NDA approval for the following reasons:

1. 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) and albumin aggregates*

2. Submit the acceptance specifications for the proposed packaging components (module 3.2.P.7) per your commitment in the amendment dated March 11, 2019 (SD009).

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

In addition, we have the following comments.

4. The in-use stability study for compatibility of syringes, infusion bags, primary sets and catheters with reconstituted suspension should be submitted per your commitment in the amendment dated March 11, 2019 (SD009).

5. Provide updated stability data to support the proposed shelf life at the proposed label storage condition.

6. The label storage statement should be updated to reflect the current definition of USP controlled room temperature.

The comments indicated in red colored fonts (indicated above) is not needed as per the secondary reviewer for the following reasons:

Comment 2:

Submit the acceptance specifications for the proposed packaging components (module 3.2.P.7) per your commitment in the amendment dated March 11, 2019 (SD009).

Justification for deleting this comment:

The applicant provided adequate specifications and corresponding Certificates of Analysis for the proposed packaging that are consistent with the FDA expectations (ID, dimensions, and compliance to appropriate USP and CFRs). The applicant has also provided Letters of Authorization to the DMFs of each vendor for the packaging components. The bulk packaging is evaluated by the process reviewer and is beyond the scope of the drug product review.

In the amendment dated March 11, 2019, the applicant indicated that the current specifications were created by the applicant, while the contract facility (b) (4) will create and/or revise these specifications for "future commercial production" when (b) (4) assumes the responsibility of direct purchase and acceptance testing of these materials. As these are post approval changes, the changes to vendors, and hence specifications, will be handled as per the post approval changes guidance if the proposed product is approved.

Comment 4:

The in-use stability study for compatibility of syringes, infusion bags, primary sets and catheters with reconstituted suspension should be submitted per your commitment in the amendment dated March 11, 2019 (SD009).

Justification for deleting this comment:

The applicant provided a compatibility study for infusion bag and lines that were used in clinical study in the report titles "RPT-PHARMDEV-013." The information provided by the applicant include in-use testing of the product with the infusion bags and infusion 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. The data provided by the applicant indicates that the drug product is compatible with the infusion bags and catheters.

Recommendation:

The applicant has satisfactorily responded to the comments 2 and 4 during the review cycle.

These comments are not to be sent as deficiencies to the applicant.

Anamitro Banerjee, Ph.D.
Branch Chief, Branch 2
Division of New Drug Product I (DNDPI)
Office of New Drugs Products (ONDP)
Office of Pharmaceutical Quality (OPQ)/CDER/FDA

Final list of comments from drug product perspective to be conveyed to the applicant in the action letter:

1. 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) and albumin aggregates*

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

3. Provide updated stability data to support the proposed shelf life at the proposed label storage condition.

4. The label storage statement should be updated to reflect the current definition of USP controlled room temperature.

MICROBIOLOGY

Product Background: This is a lyophilized [redacted] drug product for treatment of metastatic breast cancer. The active pharmaceutical ingredient is [redacted] bound to human albumin to form the drug product [redacted]. The [redacted] drug product is manufactured [redacted] and is shipped [redacted].

NDA/ANDA: 211-875

Drug Product Name / Strength: Paclitaxel Protein - Bound Particles for Injectable Suspension / 100 mg/vial

Route of Administration: Intravenous

Applicant Name: HBT Inc.

Manufacturing Sites:
Drug Substance: [redacted]

Drug Product: **HBT Labs, Inc** [redacted]
Brea, Ca
[redacted]

Method of Sterilization: [redacted]

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: The review concentrated on 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.

List Submissions Being Reviewed:
Original Application dated 08/29/2018
Response of information request dated 01/18/2019

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: None

Concise Description Outstanding Issues Remaining:

Supporting Documents:
DMF (b) (4) *Paclitaxel Produced* (b) (4) *USP as Manufactured* (b) (4). LOA dated April 07, 2016

DMF (b) (4) *Contract Testing for Packaging Components for the Pharmaceutical Industry* (b) (4). Letter of Authorization dated 30April 2018. DMA review for the (b) (4) test method dated 10/01/2016 was acceptable. There have been recent updates to the testing SOP with minor documentation changes that did not require revalidation of the method or an updated DMA review. The DMF is adequate.

BLA 125154 Human albumin manufacture (b) (4) LOA dated 05/18/2016. The human albumin is a FDA approved product.

DMF (b) (4) LOA dated 04/25/2018. The DMF was reviewed on 14 November 2018 and was adequate and supports the (b) (4) process for the proposed (b) (4) in the current application.

DMF (b) (4). LOA dated 02/09/2016. The DMF was reviewed by DMA on 01 October 2018; the review covered only the buildings and facilities. All other elements of the (b) (4) manufacturing process are covered in the NDA application. The DMF was adequate. This is acceptable for the current NDA application as the (b) (4) process validation is supplied in the NDA application.

DMA review (b) (4) dated 06/13/2017 for (b) (4) manufacturing facility (b) (4).

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance – NA; drug substance (b) (4) though the following was noted:

Drug Substance Manufactures:
(b) (4)

(b) (4)

The drug substance is manufactured (b) (4). The process is described under DMF (b) (4). A quality microbiology review of the DMF was not needed (b) (4). The NDA application provided the drug substance release specifications that included the following:

Bacterial Endotoxin: (b) (4) EU/mg
TAMC: (b) (4) cfu/gram
Absence of:
S. aureus
P. aeruginosa
Salmonella species
E. coli

P Drug Product

Reviewer note: The manufacture of the drug product is a two part process that is as follows:

(b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The finished drug product is a white to off-white sterile, lyophilized powder for reconstitution. Each vial is a single dose.
- **Drug product composition –** The composition of the drug product is copied below from submission Table 3.2.P.1-1

Ingredient	Function	Quality Standard	Weight/unit (mg/vial)	Reconstituted[9] (%w/v)
Paclitaxel[1]	Active ingredient	USP	(b) (4)	
Albumin Human[1, 6]	(b) (4)	USP		
Sodium Hydroxide[2]	pH adjustment	NF		
Hydrochloric Acid[2]	pH adjustment	NF		

(b) (4)

(b) (4)

- **Description of container closure system –**
  - **Vial:** 50 mL 20 mm (b) (4) Vial (b) (4)
  - **Stopper:** (b) (4) 20 mm (b) (4) Gray (b) (4)

P.2 Pharmaceutical Development

(b) (4)

(b) (4)

[redacted]

R Regional Information

Executed Batch Records

Batch records for the [redacted] (b) (4) process was provided for lots GPA0002, GPA0004, and GPA0005. These were the three registration batches that were also placed on stability.

Reviewer's Assessment: ***Adequate***

Comparability Protocols: NA

Reviewer's Assessment: ***NA***

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

As listed in the Package Insert:

Reconstitution directions are to reconstitute each vial with 20 mL of 0.9% sodium chloride into the vial such that the product is at 5 mg/mL. [redacted] (b) (4)

Stability of Reconstituted Suspension in the Vial: the vial should be used immediately but may be refrigerated at 2-8°C for a maximum of 24 hours if necessary.

Stability of Reconstituted Suspension in the Infusion Bag: The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be refrigerated at 2-8°C for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature for a maximum of 4 hours.

Note: this is the same language as in the Reference Listed Drug package insert.

Post-dilution/constitution Study PRTL-VALQCM-023.01 (*In-Use Stability Protocol of Reconstituted Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bounds) Finished Drug Product*) was provided to support the proposed hold times. The study used two lots of product that were reconstituted and inoculated with NMT [redacted] (b) (4) cfu/mL of the USP indicator organisms plus S. epidermidis. The inoculated product was then stored at 2-8°C for 48 hours followed by storage at ambient temperature for 12 hours (proposed limits is 2-8°C for NMT 24 hours followed by ambient storage for NMT 4 hours). The diluent was 0.9% sodium chloride USP.

- Sampling and counts were performed at 0, 12, 24, and 48 hours for the refrigerated hold and at 2, 4, 8, and 12 hours for the ambient temperature hold for a total hold time of 60 hours.
- Acceptance criterion was for each sampled time point there shall be "no increase" in counts (defined as no more than [redacted] (b) (4) increase from the initial time point)

Summary of bacterial counts at each time point:

(b) (4)

The acceptance criterion was met; none of the timepoints demonstrated any microbial growth for the two product lots.

Reviewer's Assessment: ***Adequate***. The microbial data provided support the proposed reconstitution maximum hold time is acceptable.
It was noted in the report that the inoculation level for the solutions did not always meet the <(b) (4) cfu/mL requirement (range was (b) (4) cfu/mL). The impact assessment was that though the inoculation/challenge was higher than expected, the cfu counts remained constant throughout each time point and still provides documentation of the inability of low level microbial contamination to proliferate in the product over the proposed maximum storage times and temperatures. The assessment is acceptable.

Post-Approval Commitments: NA

Reviewer's Assessment: ***NA***

List of Deficiencies: None identified in the information provided.

Primary Microbiology Reviewer Name: Denise Miller
Sr. Microbiologist, OPF/DMA/Branch II

Secondary Reviewer Name: Bryan Riley, Ph.D.
Branch Chief, OPF/DMA/Branch II

Denise Miller

Digitally signed by Denise Miller
Date: 4/03/2019 01:05:11PM
GUID: 508da7280002a5d546459b998253d1aa

Bryan Riley

Digitally signed by Bryan Riley
Date: 4/03/2019 01:08:18PM
GUID: 503450f200004f5816a1d3ae902b5e91

BIOPHARMACEUTICS

Application No: NDA 211875
Drug Product Name/Strength: Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound)
Route of Administration: Intravenous
Applicant Name: HBT Labs LLC.
Date of Submission: 08/29/2018
Date of Review: 5/20/2019
Primary Biopharmaceutics Reviewer:
Akm Khairuzzaman, PhD
Secondary Biopharmaceutics Reviewer:
Banu Zolnik, PhD

Submission & Background: [redacted] (b) (4) is seeking approval for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial under the 505 (b)(2) regulatory path referencing the Listed Drug Product, Abraxane® (NDA # 021660). The dosage form is an injectable lyophilized powder which is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous injection. The Applicant has conducted a in vivo and in vitro BE study as per the Paclitaxel Product specific guidance.

REVIEW SUMMARY
The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting [redacted] (b) (4) method as a quality control tool. Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) **In Vitro Drug Release Method**
Currently there is no in vitro drug release test in the specification. The Applicant has proposed to use [redacted] (b) (4) study which is not considered as an in vitro drug release test and the methodology associated with such test is not acceptable [redacted] (b) (4) [redacted] (b) (4). ***Not acceptable.***

RECOMMENDATION: From a Biopharmaceutics perspective, the recommendation for Paclitaxel Protein-Bound Particles for Injectable Suspension, is **NOT ADEQUATE** and the following deficiencies need to be captured as a part of the **Complete Response Letter** from the CMC team.

Biopharmaceutics Deficiencies: Based on the information you have provided, we do not agree with your plans to use the [redacted] (b) (4) method to assess [redacted] (b) (4) your proposed product at release and stability. [redacted]

Therefore, the FDA recommends developing 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. This may include, but is not limited to, changes in pH and ionic strength of the dissolution medium, temperature, oligomeric nature of albumin, particle size, polymorphic state of the drug substance and other critical physicochemical properties of the drug product can impact the drug release kinetics

BIOPHARMACEUTICS ASSESSMENT

The drug product is a Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial. The drug product contains injectable lyophilized powder of Paclitaxel Protein-Bound particles at nano scale (~130 nm). The dosage form is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous injection.

The biopharmaceutics review on this application captured the following information:

1) **Formulation Bridging Study:** Since the formulation composition is different than that of the listed product and the drug product is submitted through 505b(2) regulatory path, the Applicant's approach to establish a bridge between these two formulation was based on the evaluation of *in vivo* BE study, as well as in vitro BE study that includes particle population as per the applicant's cited FDA's product specific guidance[1]. The comparative composition of this new formation and the listed drug product along with comparative physicochemical characteristics are copied from the application and pasted below:

Table 1. Formulation composition of the proposed drug product

Ingredient	Function	Quality Standard	Weight/unit (mg/vial)	Reconstituted[9] (%w/v)
Paclitaxel[1]	Active ingredient	USP	(b) (4)	(b) (4)
Albumin Human[1, 6]	(b) (4)	USP		
Sodium Hydroxide[2]	pH adjustment	NF		
Hydrochloric Acid[2]	pH adjustment	NF		
(b) (4)				

The formulation composition differs from that of the Listed Drug Product as follows:

Table 1. Compositional Differences Between Abraxane and HBT's Proposed Drug Product (Each Single-Dose Vial)

[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320015.pdf

Abraxis Bioscience's Abraxane®	HBT's Proposed Drug Product	Function
900 mg Paclitaxel, USP	900 mg Paclitaxel, USP	Active ingredient
100 mg Albumin Human, USP	100 mg Albumin Human, USP	(b) (4)
Not in label	Sodium Hydroxide, NF	pH adjustment
Not in label	Hydrochloric Acid, NF	pH adjustment

Additionally, the following comparative physicochemical attributes between the two formulation was provided:

Table 2. Comparative and physicochemical characterization between the Proposed and LD

TEST	SPECIFICATIONS	HBT001				Abraxane®			
		TEST METHOD	GPA002	GPA004	GPA005	TEST METHOD	6009848	6009892	6200363
Appearance	(i) The powder or cake is white to off-white (ii) Container/closure: No visible leak or damage to the seal	TM.04622	Conforms	Conforms	Conforms	TM-QCC-007	Conforms	Conforms	Conforms
pH	(b) (4)	Current USP <791>	(b) (4)			Current USP <791>			(b) (4)
Assay		TM.04444				TM-QCC-012			
Albumin Content		TM.04439				TM-QCC-019			
Related Compounds		TM.04420				TM-QCC-022			
Residual Solvent		TM.04561				TM-QCC-017			
(b) (4)		(b) (4)				(b) (4)			
Mean Particle Size		TM.04462				TM-QCC-018			
Particle Size Distribution (Span)		TM.04462				TM-QCC-018			
(b) (4)		(b) (4)				(b) (4)			

Table 3. Comparison of particle size and particle size distribution between HBT001 and Abraxane®

Test	HBT001				Abraxane®			
	GPA002	GPA004	GPA005	Mean ±95% CI	6009848	6009892	6200363	Mean ±95% CI
D10 (nm)	(b) (4)							
D50 (nm)								
D90 (nm)								
Mean Diameter (nm)								
PSD (Span)								

Reviewer's Assessment on Formulation Bridging:

From Biopharmaceutics perspective the data provided to demonstrate the comparative physicochemical characteristics appears to be reasonable except for that there is no comparative in vitro drug release profile. Please note that the OCP will determine whether this product has sufficiently demonstrated BE.

2) In Vitro Drug release Characteristics

Currently, there is no in vitro drug release method in the proposed drug product specification. Instead a test (b) (4) is included in the drug product specification with a limit of (b) (4)%. (b) (4)

(b) (4)

On 12/21/2018, an IR was issued asking for the following information:

In vitro drug release test is not included in the list of Specifications being proposed for your drug product. We recommend that you develop an appropriate in vitro drug release method capable of measuring paclitaxel release from paclitaxel albumin bound nanoparticles. In general, the in vitro drug release method development and validation report, should include, but not limited to, the following information:
1. A detailed description of the in vitro drug release method being proposed for the evaluation of your drug product and development parameters (selection of the equipment/apparatus, such as dialysis, in vitro release medium, agitation, pH, sink condition, etc.) used to select the most

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appropriate in vitro release method as the optimum method for your product. 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.

2. Complete in vitro drug release profile data (individual, mean, SD, profiles) for your drug 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 different time points).

3. Data to support the discriminating ability of the selected in vitro drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare 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 and manufacturing variables (e.g., different albumin source, different paclitaxel to albumin ratio).

4. The in vitro drug release method report including appropriate method validation data.

Applicant's Response: The Applicant has responded to this IR and provided justification why an in vitro drug release test is not included in the drug product specification. In summary, the Applicant's justification includes the following reasons:

(i) drug product is comprised of paclitaxel nanoparticles (b) (4) associated with paclitaxel (b) (4)

(ii) (b) (4)

(iii) Instead of in vitro drug release, the Applicant proposed to conduct (b) (4) test in the drug product specification. (b) (4)

Reviewer's Assessment: **Not Acceptable**

Applicant's response was not satisfactory (b) (4) (b) (4) (b) (4). Therefore, the biopharmaceutics deficiencies as captured on page 1 under review summary need to be communicated to the Applicant as a part of the CR letter from the CMC Team.

- **OVERALL RECOMMENDATION:** From a Biopharmaceutics perspective, the recommendation for Paclitaxel Protein-Bound Particles for Injectable Suspension, is **NOT ADEQUATE**. Please see deficiencies on page 1 of this review.

Akm Khairuzzaman

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