

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211875Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 18, 2022
Requesting Office or Division: Division of Oncology 1 (DO1)
Application Type and Number: NDA 211875
Product Name and Strength: Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound), 100 mg/vial
Applicant/Sponsor Name: HBT Labs, Inc.
OSE RCM #: 2018-1967-2
DMEPA 2 Safety Evaluator: Sarah Thomas, PharmD
DMEPA 2 Team Leader: Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

HBT Labs, Inc. submitted final container label, carton labeling, prescribing information (PI), and patient information received on February 7, 2022 for Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound) in preparation for final approval of NDA 211875. Of note, NDA 211875 received tentative approval on June 30, 2021 due to outstanding patent litigation and exclusivity issues. The Division of Oncology 1 (DO1) requested in their June 15, 2022 consult that we review the revised container label, carton labeling, prescribing information (PI), and patient information for Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound) (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

Per the February 7, 2022 cover letter, HBT Labs, Inc. updated the proposed container label, carton labeling, and PI with the correct NDC number (70534-001-00). In addition, the company logo was updated, and the expiration date format was revised from "YYYY-MMM-DD" to "YYYY MMM DD" on the container label and carton labeling. Upon review of the proposed label and labeling, we find the proposed edits acceptable. However, we have an additional edit for the label and labeling (b) (4).

3 RECOMMENDATIONS FOR HBT LABS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Prescribing Information (PI), Sections 2.7 and 16

- a. We recommend revising the statement [REDACTED] (b) (4) [REDACTED] to the following: "Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is a hazardous drug. Follow applicable special handling and disposal procedures."¹

B. Container Label and Carton Labeling

- a. We recommend revising the statement [REDACTED] (b) (4) [REDACTED] to the following "Warning: Hazardous Drug" for consistency with the PI.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 7, 2022

-Prescribing Information (PI) and Patient Information (Image not shown) available from
\\CDSESUB1\evsprod\nda211875\0028\m1\us\1-14-1-3-nda-211875_012422.docx

(b) (4)



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/s/

SARAH E THOMAS
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ASHLEIGH V LOWERY
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 9, 2020
Requesting Office or Division: Division of Oncology 1 (DO1)
Application Type and Number: NDA 211875
Product Name and Strength: Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound), 100 mg/vial
Applicant/Sponsor Name: HBT Labs, Inc.
OSE RCM #: 2018-1967-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 2, 2020 for Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound). The Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

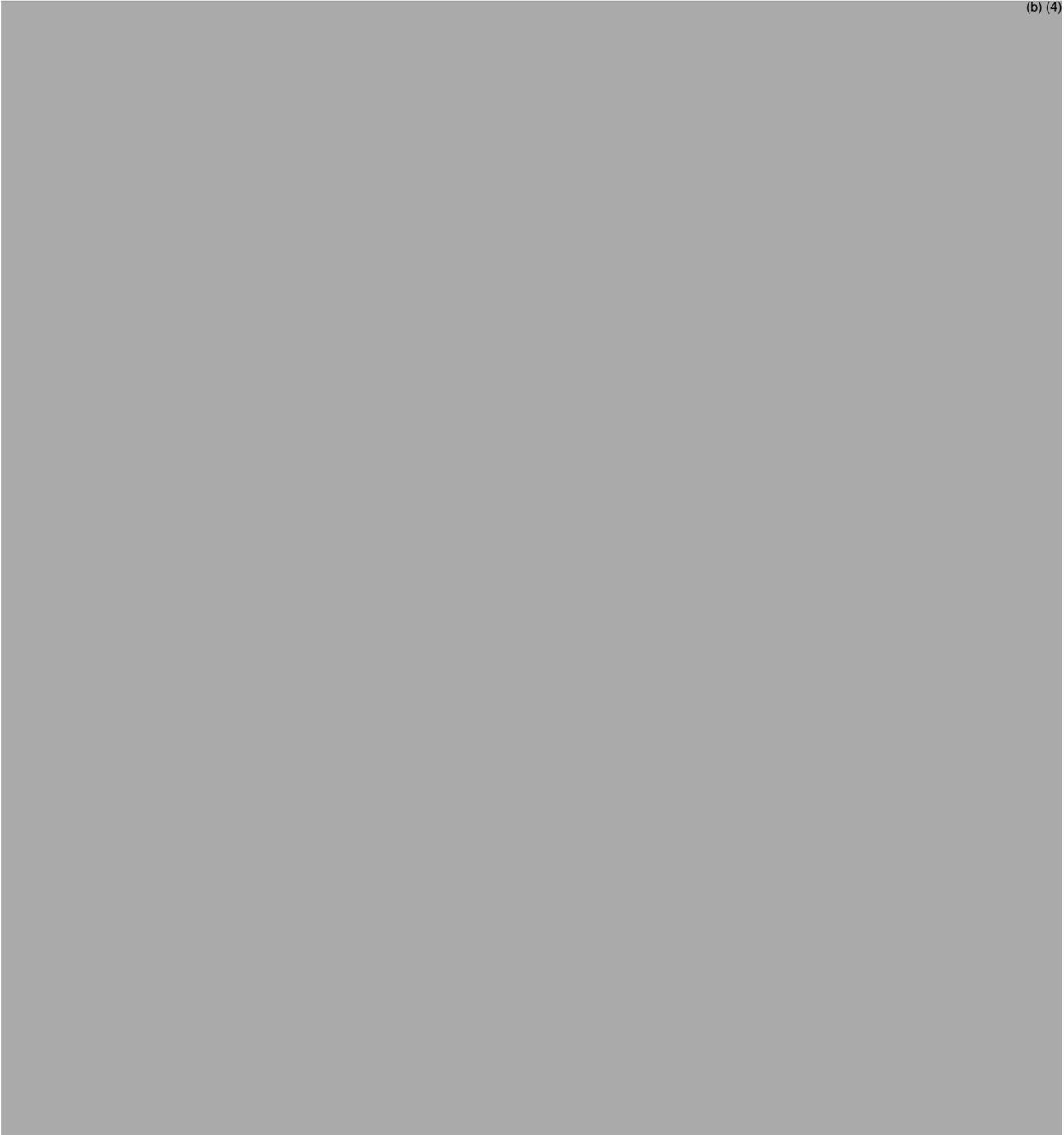
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Thomas S. Label and Labeling Review for Paclitaxel Protein-Bound Particles for Injectable Suspension (albumin-bound) (NDA 211875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JULY 24. RCM No.: 2018-1967.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 2, 2020

(b) (4)



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/s/

SARAH E THOMAS
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ASHLEIGH V LOWERY
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: September 9, 2020

To: Jessica Kim, PharmD
Regulatory Project Manager
Division of Oncology 1 (DO1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted: Patient Package Insert
(PPI)

Drug Name (established name): Paclitaxel Protein-Bound Particles for Injectable Suspension
(Albumin-Bound)

Dosage Form and Route: for intravenous use

Application Type/Number: NDA 211875

Applicant: HBT Labs, Inc.

1 INTRODUCTION

On April 24, 2020, HBT Labs, Inc., submitted for the Agency's review a Class 2 Resubmission for their New Drug Application (NDA) 211875 for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), for intravenous use. The purpose of this resubmission is to address deficiencies identified in the Complete Response (CR) letter issued by the Agency dated June 14, 2019.

The proposed indication of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is for:

- the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
- the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

On May 20, 2020, the Division of Oncology 1 (DO1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), for intravenous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), for intravenous use.

2 MATERIAL REVIEWED

- Draft Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), for intravenous use PPI received on April 24, 2020, and received by DMPP on September 3, 2020.
- Draft Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), Prescribing Information (PI) received on April 24, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on September 3, 2020.
- ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) for intravenous use approved labeling dated August 25, 2020.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as received on September 3, 2020.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

- Upon approval of this NDA, the date at the end of the PPI should be revised to reflect Issued Month and Year.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
09/09/2020 09:54:39 AM

BARBARA A FULLER
09/09/2020 10:25:22 AM

LASHAWN M GRIFFITHS
09/09/2020 10:38:48 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 24, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 211875
Product Name and Strength:	Paclitaxel Protein-Bound Particles For Injectable Suspension (albumin-bound), 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	HBT Labs, Inc.
FDA Received Date:	March 6, 2020 and June 2, 2020
OSE RCM #:	2018-1967
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

HBT Labs, Inc. originally submitted a 505(b)(2) NDA 211875 for Paclitaxel on August 29, 2018, and the listed drug is Abraxane (Paclitaxel), NDA 021660. NDA 211875 received a Complete Response on June 14, 2019.

In response to the April 24, 2020 Class 2 resubmission for NDA 211875 and subsequent DO1 consult, this review evaluates the proposed Paclitaxel prescribing information (PI), container label, and carton labeling to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PI, container label, and carton labeling and provide recommendations in Section 4 to improve readability and ensure safe medication use.

4 CONCLUSION & RECOMMENDATIONS

The proposed PI, container label, and carton labeling for Paclitaxel could be improved to ensure safe medication use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information, Highlights Dosage and Administration Section

1. Revise the symbol ">" with its intended meaning to prevent misinterpretation and confusion.^a
2. Consider defining the ULN abbreviation the first time it is used for clarity and to prevent misinterpretation.
3. Consider adding a statement after the last bullet in the Highlights Dosage and Administration Section to alert the healthcare provider that additional important information is in the Full PI (e.g., "See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection.").

B. Prescribing Information, Full PI Dosage and Administration Section

1. Add a comma to the 1,000 mg/m² Gemcitabine dose provided in Table 3 to improve readability.^a

4.2 RECOMMENDATIONS FOR HBT LABS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label & Carton Labeling)

1. We note the "LOT/EXP" designation used to label the lot number and expiration date on the container label, as well as the absence of a lot number and expiration date on the proposed carton labeling.
 - a. Add the lot number and expiration date to the carton labeling in accordance with 21 CFR 201.10(i) and 21 CFR 211.137, respectively.
 - b. Ensure the lot number and expiration date are clearly differentiated from one another on the container label and carton labeling.^b
 - c. Also ensure that the lot number and expiration date are not located in close proximity to other numbers on the container label and carton labeling where the numbers can be mistaken as the lot number or expiration date.^c
 - d. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format

^a ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 JUNE 22]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

^c Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.^d

B. Container label

1. Revise the usual dose statement on the container label (b) (4) () to read "Recommended Dosage: See prescribing information.", in order to ensure consistency with the Prescribing Information.
2. If space allows on the side panel, consider adding the following reconstitution instructions provided on the carton labeling: "Reconstitute with 20 mL of 0.9% Sodium Chloride Injection, USP resulting in a suspension containing 5 mg/mL of paclitaxel."

C. Carton Labeling

1. Add the usual dose statement ("Recommended Dosage: See prescribing information.") to a side panel of the carton labeling.
2. Consider revising the statement (b) (4) () to "Note: An albumin-bound form of paclitaxel. "

3. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.

The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier.

The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

NDC: [insert NDC]
SERIAL: [insert serial number]
LOT: [insert lot number]
EXP: [insert expiration date]

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>.

^d Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paclitaxel received on June 2, 2020 from HBT Labs, Inc., and Abraxane (listed drug).

Table 2. Relevant Product Information for Paclitaxel and the Listed Drug		
Product Name	Abraxane (NDA 021660) ^e	Paclitaxel
Initial Approval Date	January 7, 2005	N/A
Active Ingredient	Paclitaxel protein-bound particles for injectable suspension (albumin-bound)	Paclitaxel protein-bound particles for injectable suspension (albumin-bound)
Indication	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> 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.
Route of Administration	Intravenous	Intravenous
Dosage Form	For injectable suspension	For Injectable Suspension
Strength	100 mg/vial	100 mg/vial

^e Abraxane [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 June 22. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021660s046lbl.pdf.

Table 2. Relevant Product Information for Paclitaxel and the Listed Drug		
Product Name	Abraxane (NDA 021660) ^e	Paclitaxel
Dose and Frequency	<p>Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m² intravenously over 30 minutes every 3 weeks.</p> <p>Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m² intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE.</p> <p>Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m² intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after ABRAXANE.</p>	<p>Metastatic Breast Cancer: Recommended dosage of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is 260 mg/m² intravenously over 30 minutes every 3 weeks.</p> <p>Non-Small Cell Lung Cancer: Recommended dosage of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is 100 mg/m² intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).</p> <p>Adenocarcinoma of the Pancreas: Recommended dosage of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound) is 125 mg/m² intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound).</p>
How Supplied	100 mg of paclitaxel in a single-dose vial, individually packaged in a carton	100 mg of paclitaxel in a single-dose vial, individually packaged in a carton
Storage	Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.	Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.
Container Closure	(b) (4), 50mL, glass vial, closed with 20 mm (b) (4) (b) (4) rubber stopper and capped (b) (4)	(b) (4) glass vial closed with a (b) (4) rubber stopper and (b) (4) vial (b) (4).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 23 and 24, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, paclitaxel, Abraxane, and NDAs 211875 and 021660. Our search identified 8 previous reviews^{f,g,h,i,j,k,l,m}, and we considered our previous recommendations to see if they are applicable for this current review.

^f Duffy, F. Label and Labeling Review for Abraxane (NDA 021660). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2004 MARCH 4. ODS Consult #: 03-0303-1.

^g DeFronzo, K. Label and Labeling Review for Abraxane (NDA 021660/S-033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 MAY 23. RCM No.: 2012-780.

^h Abdus-Samad, J. Label and Labeling Review for Abraxane (NDA 021660/S-031). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 SEPT 19. RCM No.: 2012-59.

ⁱ Abdus-Samad, J. Label and Labeling Review for Abraxane (NDA 021660/S-033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 NOV 27. RCM No.: 2012-1985.

^j Abdus-Samad, J. Postmarketing Review for Abraxane (NDA 021660). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAY 19. RCM No.: 2013-2586.

^k Mathew, D. Label and Labeling Review for Abraxane (NDA 021660/S-040). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JUNE 27. RCM No.: 2014-754.

^l Mathew, D. Memorandum Review of Revised Label and Labeling for Taxel (NDA 020262). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 21. RCM No.: 2014-1335.

^m Mathew, D. Label and Labeling Review for Abraxane (NDA 021660/S-041). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 28. RCM No.: 2015-190.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,ⁿ along with postmarket medication error data, we reviewed the following Paclitaxel label and labeling submitted by HBT Labs, Inc.

- Container label received on March 6, 2020
- Carton labeling received on March 6, 2020
- Prescribing Information (Image not shown) received on June 2, 2020

G.2 Label and Labeling Images



ⁿ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH E THOMAS
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ASHLEIGH V LOWERY
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MEMORANDUM

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

DATE: August 7, 2019

TO: Julia Beaver, M.D.
Division Director
Division of Oncology Products 1(DOP 1)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE, OSIS

SUBJECT: Routine inspections of Arensia Exploratory Medicine SRL,
Chisinau, Republic of Moldova and Arensia Exploratory
Medicine, LLC., Tbilisi, Georgia.

Inspection Summary

Per the request of OND/OHOP/DOP 1, the Office of Study Integrity and Surveillance (OSIS) arranged inspections of the clinical portion of **Study HBT001-BE-01 (NDA 211875)** conducted at Arensia Exploratory Medicine SRL, Chisinau, Republic of Moldova and Arensia Exploratory Medicine, LLC., Tbilisi, Georgia.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out of both sites. The final inspection classification is No Action Indicated (NAI) for both sites.

Recommendation

After reviewing the inspectional findings, I conclude the clinical data from the audited study are reliable to support a regulatory decision.

Inspected Study

NDA 211875

Study Number: HBT001-BE-01

Study Title: "A Phase 1, Randomized, Open-Label, Two-Way Crossover,
Two-Stage Group Sequential Design Bioequivalence Study
of Paclitaxel Protein-Bound Particles for Injectable
Suspension (Albumin-Bound) in Patients with Breast
Cancer"

Dates of conduct: February - November 2017

Clinical Site #1: Arensia Exploratory Medicine SRL (Study Site #010)
IMSP Institutul Oncologic, Phase 1 Unit
30 Nicolae Testemiteanu Street
Chisinau, 2025
Republic of Moldova

ORA Investigator Craig Garmendia (OBIMO) inspected Arensia
Exploratory Medicine SRL, Chisinau, Republic of Moldova from June 17
- 20, 2019.

This was the first inspection of the clinical site. The inspection
included a thorough examination of study records, subject records,
informed consent process, protocol compliance, institutional review
board approvals, sponsor and monitor correspondence, test article
accountability and storage, randomization, adverse events (AE), and
case report forms (CRF).

During the inspection, Investigator Garmendia verified that the
clinical site randomly selected and properly stored the BE reserve
samples during the study. The BE reserve samples were later
transferred to a third-party storage facility, (b) (4)
(b) (4). Investigator Garmendia instructed the
clinical site to have the storage facility directly ship three vials
each of test and reference products to CDER/DPA.

Inspectional Findings

At the conclusion of the inspection, Investigator Garmendia did not
observe any objectionable conditions and did not issue Form FDA 483
to the site. However, Investigator Garmendia discussed the following
item with the study Principal Investigator at the inspection close-
out.

Discussion Item #1

The informed consent document in Romanian or Russian does not specify
which regulatory authorities will have access to subject records.

Site's Response: During the inspection, the corporate quality assurance manager acknowledged the finding and indicated that procedures will be updated to ensure that consents clearly indicate the regulatory authorities that will have access to subject records.

OSIS Evaluation

Although the discussion item focused on the Romanian and Russian versions of the informed consent form (ICF) used in Study HBT001-BE-01, the below evaluation is based on the English version of the ICF, which states that "the Regulatory Authorities that approved this study will have direct access to [study subject] medical records" (**Attachment 1**), without specifying which regulatory authorities would access the records.

Bioequivalence Study HBT001-BE-01 is linked to IND 129370 and regulated under CFR 312 (Investigational New Drug Application). Specifically, CFR 312.40(a)(2) specifies that "Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56." Additionally, CFR 50.25 Elements of informed consent (a) (5) also require "a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and the possibility that the Food and Drug Administration may inspect the records." However, since the clinical site is located outside of the US, there are limitations in enforcing applicable IND regulations.

Additionally, the Institutional Review Board (IRB) is responsible for ensuring that each consent document contains the required elements as specified in 21 CFR 50.20 and 50.25. In this case, the ICF was approved by an Institutional Ethics Committee (IEC) instead of an IRB. According to Investigator Garmendia, the IEC approval letters for the clinical trial had no additional stipulations required for the consenting of subjects.

Because a foreign IEC approved the study's ICF and the site is located outside of the US, there are limitations on enforcing IND and BA/BE regulations. Ultimately, study subjects were aware that regulatory agencies could access their records. Therefore, I conclude that the finding did not affect the reliability of study data. In addition, the finding had little or no impact on the rights, welfare, or safety of the study subjects.

Clinical Site #2: Arensia Exploratory Medicine, LLC (Study Site #011)
13a Tevdore Mgvdeli Street
Tbilisi, 0112
Georgia

ORA Investigator Craig Garmendia(OBIMO) inspected Arensia Exploratory
Medicine, LLC., Tbilisi, Georgia from June 10 - 13, 2019.

This was the first inspection of the clinical site. The inspection
included a thorough examination of study records, subject records,
informed consent process, protocol compliance, institutional review
board approvals, sponsor and monitor correspondence, test article
accountability and storage, randomization, AE, and CRFs.

During the inspection, Investigator Garmendia verified that the
clinical site randomly selected and properly stored the BE reserve
samples during the study. The BE reserve samples were later
transferred to a third-party storage facility, (b) (4)
(b) (4). Investigator Garmendia instructed the
clinical site to have the storage facility directly shipped three
vials each of test and reference products to CDER/DPA.

Inspectional Findings

At the conclusion of the inspection, Investigator Garmendia did not
observe any objectionable conditions and did not issue Form FDA 483
to the site. However, Investigator Garmendia discussed the following
item with the study Principal Investigator at the inspection close-
out.

Discussion Item #1

The informed consent document in Romanian or Russian does not specify
which regulatory authorities will have access to subject records.

Site's Response: During the inspection, the corporate quality
assurance manager acknowledged the verbal observation and indicated
that procedures will be updated to ensure that consents clearly
indicate the regulatory authorities that will have access to subject
records.

OSIS Evaluation

Although the discussion item focused on the Romanian and Russian
versions of the informed consent form (ICF) used in Study HBT001-BE-
01, the below evaluation is based on the English version of the ICF,
which states that "the Regulatory Authorities that approved this
study will have direct access to [study subject] medical records"
(**Attachment 1**), without specifying which regulatory authorities would
access the records.

Bioequivalence Study HBT001-BE-01 is linked to IND 129370 and
regulated under CFR 312 (Investigational New Drug Application).

Specifically, CFR 312.40(a)(2) specifies that "Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56." Additionally, CFR 50.25 Elements of informed consent (a) (5) also require "a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and the possibility that the Food and Drug Administration may inspect the records." However, since the clinical site is located outside of the US, there are limitations in enforcing applicable IND regulations.

Additionally, the Institutional Review Board (IRB) is responsible for ensuring that each consent document contains the required elements as specified in 21 CFR 50.20 and 50.25. In this case, the ICF was approved by an Institutional Ethics Committee (IEC) instead of an IRB. According to Investigator Garmendia, the IEC approval letters for the clinical trial had no additional stipulations required for the consenting of subjects.

Because a foreign IEC approved the study's ICF and the site is located outside of the US, there are limitations on enforcing IND and BA/BE regulations. Ultimately, study subjects were aware that regulatory agencies could access their records. Therefore, I conclude that the finding did not affect the reliability of study data. In addition, the finding had little or no impact on the rights, welfare, or safety of the study subjects.

Conclusion

After reviewing the inspectional findings, I conclude that the clinical data from **Study HBT001-BE-01 (NDA 211875)** conducted at Arensia Exploratory Medicine SRL, Chisinau, Republic of Moldova and Arensia Exploratory Medicine, LLC., Tbilisi, Georgia are reliable to support a regulatory decision.

Based on the inspectional findings, clinical data from studies of similar design conducted at Arensia Exploratory Medicine SRL, Chisinau, Republic of Moldova and Arensia Exploratory Medicine, LLC., Tbilisi, Georgia between the beginning of audited **Study HBT001-BE-01** (February 2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Yiyue Zhang, Ph.D.
Staff Fellow

Final Classification

Clinical Sites

NAI - Arensia Exploratory Medicine SRL, Chisinau, Republic of Moldova
(FEI#: 3011683142)

NAI - Arensia Exploratory Medicine, LLC., Tbilisi, Georgia
(FEI#: 3012077373)

Attachment:

Attachment 1. Informed Consent Form (ICF), English version

cc:

OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/[CDER-OSIS-
BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

ORA/OMPTO/OBIMO/Garmendia

Draft: YZ 07/31/2019, 08/02/2019, 08/06/2019

Edit: RCA 7/31/2019, 8/2/2019, 8/06/2019; AD 07/31/2019, 8/2/2019; CB
8/7/2019

ECMS:

Cabinets/CDER OTS/Study Integrity and Surveillance/INSPECTIONS/BE
Program/CLINICAL/Arensia Exploratory Medicine SRL, Chisinau, Republic
of Moldova

Cabinets/CDER OTS/Study Integrity and Surveillance/INSPECTIONS/BE
Program/CLINICAL/Arensia Exploratory Medicine, LLC., Tbilisi, Georgia

OSIS File#: BE 8345

FACTS: 11912291

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/s/

YIYUE ZHANG
08/07/2019 01:53:28 PM

RUBEN C AYALA
08/07/2019 02:16:23 PM

CHARLES R BONAPACE
08/07/2019 04:22:09 PM

Memorandum of Review

STN:	NDA 211875
Subject:	Immunogenicity Consult Review
Submission Date:	08/29/2018
Review/Revision Date:	03/08/2019
Primary Reviewer:	Tao Wang, MD, PhD Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Fred Mills, PhD Staff Scientist, OPQ/OBP/DBRR IV
Tertiary Reviewer:	N/A
Consults:	Immunogenicity
Applicant:	HBT LABS INC
Product:	Paclitaxel protein-bound particles for injectable suspension
Indications:	Metastatic Breast Cancer
Action Due Date:	05/14/2019

I. Summary Basis of Recommendation:

a. Recommendation: We conclude that human serum albumin (HAS) used in this application is unlikely to increase the risk of immunogenicity.

b. Justification:

- This NDA submission cross-references the CBER approved human serum albumin (BLA 125154) for which there are no immunogenicity issues raised during the review process, as well as after approval.
- Albumin is the most abundant protein in human serum. Albumin should be immunologically inert. Although there is evidence that albumin infusion can cause side effects in patients, none of them are reported due to immunogenicity. 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 ABRAXANE™ 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 issue of albumin-related immunogenicity risk has been discussed in our internal Immunogenicity Working Group. The conclusion is that Albumin is unlikely to increase immunogenicity related risk.

II. Deficiencies to be conveyed to the sponsor:

N/A.

III. Review

Background and Consult Request

Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial, is an albumin nanoparticle form of paclitaxel with a mean particle size of approximately 130 nm. The reference listed drug (RLD) is Abraxane®. The active ingredient, dose form, route of administration, and strength for HBT proposed drug product are same as those of Abraxane®.

The CMC reviewers from OPQ/ONDP/DNDP1 for this NDA raised concerns about potential immunogenicity due to changes of DP manufacturing process for HSA, which might change the (b) (4) HSA.

Reviewer's Comment:

There is no section in this NDA submission dedicated to immunogenicity assessment. With the help of CMC reviewers, we focused on reviewing the data on the impurity profile and aggregates. The results

from analyses of the impurity profile and aggregates demonstrated there are no significant differences between the HBT proposed drug product and Abraxane®. No novel impurity is found in the HBT proposed drug product. Taking this lack of novel impurities together with a long history of Abraxane without immunogenicity-related safety events, as well as lack of document HSA immunogenicity, we predict that there will be no immunogenicity safety risk for the HBT drug product relative to Abraxane.

Notes from DPV memos

From

Pharmacovigilance Review

Date: May 9, 2018

Reviewer: Pritpal Singh, PharmD, BCPS, BCOP, Safety Evaluator
Division of Pharmacovigilance II (DPV II)

Subject: Taxane cross-hypersensitivity reactions

This review evaluates 23 cases of cross-HSR between paclitaxel and docetaxel or vice versa. We retrieved 20 cases of cross-HSR to docetaxel from FAERS (n=9) and literature (n=11) searches following initial exposure to paclitaxel, and three cases from the literature of cross-HSR following initial exposure to docetaxel. We identified 29 additional cross-HSR cases from the sponsor PBRER (NDA 020449, Taxotere®) that were not retrieved in our FAERS search; however, we could not include and characterize these cases in our case series because case level information was not provided. Notably, we did not retrieve any cases of cross-HSR to cabazitaxel or Abraxane from our FAERS search for reports of cross-HSR following initial HSR to another taxane.

From

Pharmacovigilance Memo

Date: June 20, 2018

Reviewer: Pritpal Singh, PharmD, BCPS, BCOP
Division of Pharmacovigilance II (DPV II)

Subject: Taxane cross-hypersensitivity reactions

Celgene Corporation. Celgene Response to FDA Information Request: NDA 021660 – Abraxane® (Submitted May 15, 2018).

Celgene Corporation searched the global safety database through April 20, 2018, and identified 21 total reports of hypersensitivity to Abraxane® in patients with a prior hypersensitivity to another taxane. We classified 18 reports as cross-HSR cases and three reports as a reaction not likely to be hypersensitivity/anaphylaxis (Figure 1).

Figure 1. Evaluation of Sponsor Identified Cross-HSR Reports

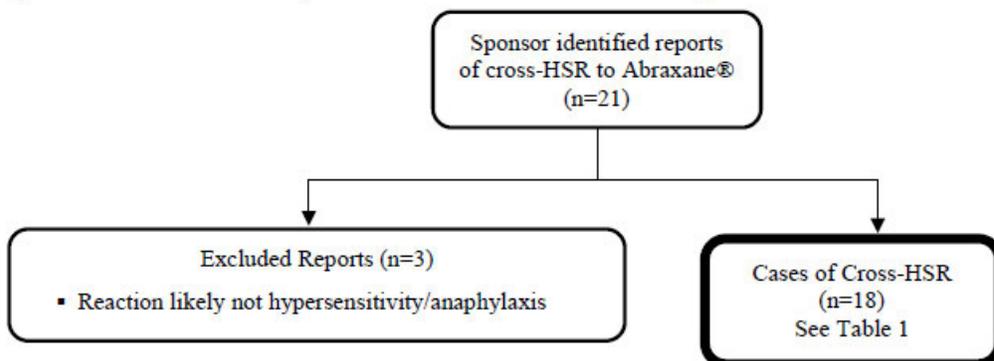


Table 1 summarizes the 18 sponsor cases of cross-HSR between a prior taxane and Abraxane® including our classification of the type of reaction using the aforementioned case definition criteria.

Table 1. Analysis of Sponsor Identified Cases of Cross-HSR Between a Prior Taxane and Abraxane (n=18)*		
<u>Prior Taxane Hypersensitivity</u>		
Paclitaxel (non-protein bound formulation)	12	
Docetaxel	4	
<u>Hypersensitivity to Multiple taxanes</u>		
Docetaxel+paclitaxel	1	
Docetaxel+cabazitaxel	1	
<u>Type of Reaction</u>†		
Hypersensitivity	<u>Initial Taxane</u> 5	<u>Abraxane®</u> 16
Anaphylaxis	0	2
Details of reaction not specified	13	0
* We used sponsor manufacturer case numbers to search in FAERS and retrieved three reports that were not captured by our initial FAERS search. These three reports were submitted via a MedWatch form 3500 and the image was scanned into the FAERS database. Our initial FAERS search did not retrieve these cases because our search employed a narrative text search which does not search scanned images.		
† DPV II classification of the type of reaction to the initial taxane and subsequent Abraxane®		

Abraxane® and cabazitaxel are both labeled for hypersensitivity/anaphylaxis in multiple sections of the product label (Appendix C). The Abraxane® label states that its use in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin.

has not been studied. The data provided by the sponsor of Abraxane® indicates that there is evidence for the potential cross-HSR in patients with history of hypersensitivity or anaphylaxis to another taxane, including docetaxel and paclitaxel. Of note, one report described hypersensitivity to both docetaxel and cabazitaxel prior to hypersensitivity to

Abraxane®, indicating that the similar taxane ring among these products may play a role in conferring cross-HSR.

Reviewer comments

This research indicates that hypersensitivity to Abraxane is likely to result from reactivity to the taxane moiety. The Abraxane label contains wording describing hypersensitivity, and since the HBT drug product will have a similar label, physicians will receive adequate caution about hypersensitivity for the HBT product.

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/s/

TAO WANG
05/21/2019 02:51:49 PM

FREDERICK C MILLS
05/21/2019 04:34:11 PM

GERALD M FELDMAN
06/06/2019 09:18:55 AM

MEMORANDUM

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

DATE: 4/1/2019

TO: Division of Oncology Products (DOP1)
Office of New Drugs

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211875/S-001

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: BLAs (b) (4) and (b) (4). The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

NICOLA M FENTY-STEWART
04/01/2019 10:33:38 AM

MEMORANDUM

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

DATE: 2/21/2019

TO: Division of Oncology Products (DOP1)
 Office of New Drugs

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
 Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211875

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Arensia Exploratory Medicine SRL: Although OSIS has no inspection history for this site, the requested review goal date of May 2, 2019 outlined in the consult, does not provide sufficient time for the inspection to be completed and for OSIS to submit an Establishment Inspection Report review to the review division.

Arensia Exploratory Medicine, LLC: Although OSIS has no inspection history for this site, the requested review goal date of May 2, 2019 outlined in the consult, does not provide sufficient time for the inspection to be completed and for OSIS to submit an Establishment Inspection Report review to the review division.

(b) (4)

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: BLAs (b) (4) and (b) (4). The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Arensia Exploratory Medicine SRL	IMSP Institutul Oncologic, Phase 1 Unit, MD-2025, 30 Nicolae Testemiteanu Street, Chisinau, Republic of Moldova
Clinical	Arensia Exploratory Medicine,	13a Tevdore Mgvdeli Street, Tbilisi,

Facility Type	Facility Name	Facility Address
	LLC.	Georgia
Analytical	[REDACTED]	[REDACTED] (b) (4)

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/s/

ANGEL S JOHNSON
02/21/2019 02:09:09 PM