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

Re: Docket No. FDA-2022-P-2075

Dear Dr. Hodgson:

This letter responds to the citizen petition that you submitted on behalf of HBT Labs, Inc. (HBT, Petitioner) on August 30, 2022 (Petition). In your Petition, you request that the U.S. Food and Drug Administration (FDA or the Agency) assign a therapeutic equivalence (TE) evaluation code (TE Code) of "AP" to Paclitaxel Protein Bound Particles for Injectable Suspension (albumin-bound), 100 milligrams (mg)/vial, approved under New Drug Application (NDA) 211875 (Paclitaxel (NDA 211875)) held by American Regent, Inc. (American Regent).[1] You state that Paclitaxel (NDA 211875) meets all the applicable requirements for an "AP" TE Code with respect to Abraxane (paclitaxel protein bound particles for injectable suspension) (albumin-bound) for 100 mg/vial for injectable suspension). Abraxane is the subject of NDA 021660, which is currently held by Bristol-Myers Squibb Company (BMS).[2] You further assert that a "TE code would allow HBT to be exempt from, or otherwise obtain a refund of, any Prescription Drug User Fee Act annual 'program fee' FDA may assess with respect to NDA 211875 for Fiscal Year 2023 and thereafter" (Petition at 2).

FDA has carefully considered the Petition and the comments to the docket.[3] For the reasons discussed below, your Petition is granted in part and denied in part.

[1] At the time the Petition was submitted, NDA 211875 was held by HBT, and the application was subsequently transferred to American Regent.
[2] NDA 021660 was originally held by Abraxis BioScience LLC, which was acquired by Celgene Corporation, and Celgene Corporation was subsequently acquired by BMS. NDA 021660 is currently held by BMS.
[3] Teva Pharmaceuticals (Teva) submitted a comment on September 19, 2022, that was a duplicate of a comment it submitted to FDA's draft guidance for industry *Evaluation of Therapeutic Equivalence* (July 2022) (TE Draft Guidance) (Docket No. FDA-2022-D-0528). Because the issues raised by Teva's comment relate to the TE Draft Guidance and not specifically to this Petition's requests, the comment will not be addressed in this petition response (see § 10.30(d) (21 CFR 10.30(d)) (providing that an interested person may support or oppose a petition; however, a request for an alternative or different administrative action must be submitted as a separate petition). FDA will continue to consider the comment Teva submitted to the public docket (Docket No. FDA-2022-D-0528) for the TE Draft Guidance as it evaluates whether any revisions to the TE Draft Guidance are warranted. BMS submitted a comment on January 18, 2023, contending that the Petition's request for an "AP" TE Code to Abraxane should not be granted. BMS's comment is further addressed in the Discussion section (section II) of this response.

I. BACKGROUND

A. Paclitaxel (NDA 211875)

On July 27, 2022, FDA approved NDA 211875 for Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial, currently held by American Regent. Paclitaxel (NDA 211875) 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.

- 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.

B. Drug Approval Pathways Under the FD&C Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Food, Drug, and Cosmetic Act (FD&C Act) to, among other things, add two abbreviated drug approval pathways. As amended, section 505 of the FD&C Act (21 U.S.C. 355) sets forth, in addition to the 505(b)(1) NDA stand-alone approval pathway, the 505(j) abbreviated new drug application (ANDA) approval pathway and the 505(b)(2) NDA abbreviated approval pathway.

1. 505(j) ANDA Approval Pathway

To obtain approval, an ANDA applicant is not required to provide evidence to independently establish the safety and effectiveness of the proposed drug product, as is required for a stand-alone 505(b)(1) NDA. Instead, an ANDA relies on FDA's previous finding that a reference listed drug (RLD) is safe and effective.[4] To rely on this finding, an ANDA applicant must provide sufficient information to show that its drug product is bioequivalent to the RLD.[5] An ANDA applicant generally must also demonstrate, among other things, that the proposed drug product has the same active ingredient(s), route of administration, dosage form, strength, and

[4] An *RLD* is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b) (21 CFR 314.3(b)). RLDs are identified in FDA's Orange Book, available at https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. See id.

[5] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); § 314.3(b) (defining reference listed drug); § 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); and § 314.127(a)(6)(i) (stating that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

(with certain permissible differences) labeling as the RLD.[6] The general scientific premise underlying the ANDA abbreviated approval pathway is that bioequivalent drug products that have the same active ingredient(s), route of administration, dosage form, and strength, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling, are therapeutically equivalent.[7]

2. 505(b)(2) NDA Abbreviated Approval Pathway

A 505(b)(2) application shares characteristics of both an ANDA and a stand-alone NDA. Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness as a stand-alone NDA. For a 505(b)(2) NDA, however, some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[8] A 505(b)(2) NDA is similar to an ANDA in that it may rely, in part, on FDA's previous finding that a listed drug is safe and effective as evidence in support of the proposed product's safety and effectiveness. A 505(b)(2) NDA may also rely, in part, on published literature.[9]

A 505(b)(2) NDA can describe a drug with substantial differences from the listed drug it references. These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, formulation, and/or route of administration.[10] To the extent that the listed drug and the drug proposed in the 505(b)(2) NDA differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.

3. 505(b)(2) NDAs and Bioequivalence and Bioavailability Studies

Although bioequivalence and bioavailability studies are not statutorily required for every NDA, such studies can be integral to showing a 505(b)(2) NDA meets the statutory approval standard.[11] For example, if an applicant of a 505(b)(2) NDA relies upon the Agency's previous finding of safety and/or effectiveness for a listed drug, then a scientific bridge to that listed drug is needed. This scientific bridge often includes a bioavailability or bioequivalence study comparing the exposures of the proposed product with those of the listed drug. An acceptable

[6] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also § 314.94(a).
[7] See § 314.3(b) (definition of "therapeutic equivalents").
[8] Specifically, section 505(b)(2) of the FD&C Act contemplates: "An application [may be] submitted under [section 505(b)(1)] for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . .."
[9] See FDA's draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999) (505(b)(2) Draft Guidance) at 2. When final, this guidance will represent FDA's current thinking on this topic. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[10] See 505(b)(2) Draft Guidance at 4-5.
[11] See, e.g., FDA's guidance for industry *Bioavailability Studies Submitted in NDAs or INDs–General Considerations* (April 2022).

scientific bridge enables the applicant to rely on the Agency's previous finding of safety and/or effectiveness for the listed drug.[12]

C. TE Code Criteria

Therapeutically equivalent products are defined in the regulations as:

> approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[13]

In the publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), FDA further explains that therapeutically equivalent products must meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents[14] in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent[15] in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.[16]

The information needed to evaluate the therapeutic equivalence for products approved pursuant to 505(b)(2) NDAs is drawn from the approval process for such products. In many cases, the differences between a product approved in a 505(b)(2) NDA and a listed drug foreclose a finding that the products are therapeutically equivalent, for example, if they are not pharmaceutically equivalent. In other cases, however, a drug product approved pursuant to a 505(b)(2) NDA and a listed drug may satisfy the therapeutic equivalence criteria. FDA publishes TE Codes reflecting the Agency's conclusions regarding therapeutic equivalence in the Orange Book.

Drug products are assigned an "A" as the first letter of their TE Code if they are products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. Drug products are assigned a "B" as the first letter of their TE Code if they are products that

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[12] See 505(b)(2) Draft Guidance at 8-9.

[13] § 314.3(b) (defining *therapeutic equivalents*).

[14] Pharmaceutical equivalents are "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates" (§ 314.3(b)).

[15] Bioequivalence is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (§ 314.3(b)).

[16] See the Orange Book, 44th edition (2024), Preface at vii.

FDA, currently, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.[17]

TE Codes also include a second letter that provides additional information based on FDA's therapeutic equivalence evaluations. The TE Code "AP", which your Petition requests be assigned to Paclitaxel (NDA 211875), is used for injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions.

Drug products in 505(b)(2) applications generally do not have a TE Code assigned at the time they are approved. Specifically, because a 505(b)(2) NDA is not required to demonstrate bioequivalence to a listed drug, FDA does not routinely make a determination regarding the therapeutic equivalence of a 505(b)(2) NDA drug product at the time of approval.[18] The Orange Book Preface acknowledges this possibility:

> The coding system for therapeutic equivalence evaluations is designed to allow users to determine quickly whether the Agency has evaluated a particular approved prescription drug product . . . as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With some exceptions (e.g., therapeutic equivalence evaluations for certain 505(b)(2) applications), the therapeutic equivalence evaluation date is the same as the approval date.[19]

Furthermore, the Orange Book Preface states that:

> We recognize that certain drug products approved in 505(b)(2) applications may not have therapeutic equivalence codes, and that FDA may undertake therapeutic equivalence evaluations with respect to such drug products. A person seeking to have a therapeutic equivalence rating for a drug product approved in a 505(b)(2) application may petition the Agency through the citizen petition procedure (see 21 CFR 10.25(a) and CFR 10.30). [Additionally,] Section 3222 of the Food and Drug Omnibus Reform Act of 2022 (enacted December 29, 2022) amended the FD&C Act by adding a new provision to Section 505(j)(7)(A). Section 505(j)(7)(A)(v)(I) sets forth certain conditions under which FDA considers therapeutic equivalence evaluation requests in an application for an eligible drug submitted or approved pursuant to Section 505(b)(2) of the FD&C Act.[20]

D. User Fee Requirement and Pharmaceutically Equivalent Exception

On September 30, 2022, the FDA User Fee Reauthorization Act of 2022 was signed into law. This law reauthorized user fees relating to drugs, including the Prescription Drug User Fee Amendments of 2022 (PDUFA VII), codified at sections 735 and 736 of the FD&C Act.[21] The PDUFA VII provisions are applicable to prescription drug user fees for FY 2023, which began October 1, 2022, and authorizes collection of two types of fees: (1) human drug application fees

[17] See id. at xii-xx.
[18] See FDA's draft guidance for industry *Evaluation of Therapeutic Equivalence* (July 2022), at 5, 10-11. When final, this guidance will represent FDA's current thinking on this topic.
[19] See the Orange Book, 44th edition (2024), Preface at xii-xiii.
[20] Id. at xxiv and xxiv n.22.
[21] 21 U.S.C. 379g and 379h.

and (2) prescription drug program fees, which are collected annually for certain prescription drug products.

In general, under PDUFA VII, each person who is named as the applicant in a human drug application must pay a program fee for each eligible prescription drug product. The FD&C Act defines a "prescription drug product" as a specific strength or potency of a drug in final dosage form for which a human drug application has been approved, which may be dispensed only by prescription pursuant to section 503(b) of the FD&C Act, and which is on the list of products described in section 505(j)(7)(A) of the FD&C Act (i.e., the Prescription Drug Product List in the Orange Book), not including the Discontinued Drug Product List (the discontinued section) of such list.[22] The program fee is due on the later of the first business day on or after October 1 of each fiscal year or the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such fiscal year, whichever occurs later.[23]

Prior to PDUFA VII, under section 736(a)(2)(B)(ii) of the FD&C Act, a prescription drug product was not assessed a program fee if the product was the same product as another product that – (I) was approved under an application filed under section 505(b) or 505(j) of the FD&C Act; and (II) was not in the list of discontinued products compiled under section 505(j)(7) of the FD&C Act (FDA's Orange Book) (i.e., the "same product" exception). The revised section 736(a)(2)(B)(ii) of the FD&C Act states that "a prescription drug program fee shall not be assessed for a prescription drug product… if such product is… pharmaceutically equivalent (as defined in section 314.3 of title 21, Code of Federal Regulations (or any successor regulation))[24] to another product on the list of products compiled under section 505(j)(7) of this title (not including the discontinued section of such list)" (i.e., the "pharmaceutically equivalent" exception). Thus, with passage of PDUFA VII, this "same product" exception provision was revised to a "pharmaceutically equivalent" exception.

II. DISCUSSION

In your Petition, you request that FDA assign a TE Code of "AP" to Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial (NDA 211875) (Petition at 1). You contend that Paclitaxel (NDA 211875) meets all the applicable requirements for a TE Code with respect to Abraxane for the reasons discussed below. You also state that a TE Code:

> would allow HBT to be exempt from, or otherwise obtain a refund of, any Prescription Drug User Fee Act annual "program fee" FDA may assess with respect to NDA 211875 for Fiscal Year 2023 and thereafter.

[22] 21 U.S.C. 379g(3).
[23] 21 U.S.C. 379h(a)(2)(A)(i).
[24] As stated in § 314.3(b), "*Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates."

(Petition at 1-2).[25]

A. Abraxane and Paclitaxel (NDA 211875) Are Pharmaceutical Equivalents

The Petition asserts that Paclitaxel (NDA 211875) is pharmaceutically equivalent to Abraxane (NDA 021660), because the products have "identical amounts (100 mg/vial) of the identical active drug ingredient (i.e., paclitaxel), and are in identical dosage forms (i.e., lyophilized powder for reconstitution) for the same route of administration (i.e., IV [infusion])" (Petition at 5).

As discussed above in section I, pharmaceutical equivalents are "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient[;] . . . do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates."[26]

Both Paclitaxel (NDA 211875) and Abraxane have identical dosage forms and routes of administration—lyophilized powder for suspension administered intravenously by infusion. Specifically, both finished drug products are a lyophilized powder in a 50 milliliters (mL) single-dose glass vial intended for reconstitution with 20 mL 0.9% sodium chloride injection into a suspension, without further dilution. According to the approved labeling of both Paclitaxel (NDA 211875)[27] and Abraxane,[28] based on the patient's body surface area, the appropriate amount of the 5 mg/mL paclitaxel suspension is transferred into an empty IV bag, then administered as an intravenous infusion over the course of 30 to 40 minutes.

In addition, the two products contain identical amounts of the identical active drug ingredient. According to the approved labeling for Paclitaxel (NDA 211875)[29] and Abraxane,[30] both drug products contain 100 mg paclitaxel bound to human albumin in an amorphous nanoparticle with a mean diameter of approximately 130 nanometers (nm). The approved labeling also states that both products contain 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate), and that each milliliter (mL) of the reconstituted suspensions contains 5 mg

[25] As noted in FN 3, BMS submitted a comment (BMS comment) requesting that FDA deny the Petition on several grounds, including that the Petition has failed to provide necessary information to support its request. In particular, the comment, in part, contends that changes in formulation between Paclitaxel (NDA 211875) and Abraxane suggest potential differences between the two products that can only be resolved through clinical comparison of the products; adjusting the pH of Paclitaxel (NDA 211875) calls into question whether HBT's manufacturing process materially alters the human albumin so as to require a final pH adjustment to bring it into an acceptable range; and that it is not clear from the Petition whether a showing of sameness has been demonstrated with regard to the Paclitaxel Draft Guidance for establishing bioequivalence to Abraxane (NDA 021660) (BMS Comment at 3-5). The comment's assertions are addressed in subsections II.A, B, and C of this response.
[26] See § 314.3(b).
[27] See NDA 211875 Paclitaxel's labeling (2022), Section 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211875s000lbl.pdf.
[28] See Abraxane's labeling (2020), Section 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021660s047lbl.pdf.
[29] See NDA 211875 Paclitaxel's labeling (2022). Section 11.
[30] See Abraxane's labeling (2020), Section 11.

paclitaxel formulated as albumin-bound particles.

Furthermore, based on comparative in vitro characterization data submitted in support of the approval of Paclitaxel (NDA 211875) (see also section II.B.), the two products meet the same standard of identity, strength, quality, and purity, including potency.

Accordingly, we agree that Abraxane and Paclitaxel (NDA 211875) are pharmaceutical equivalents.

B. Abraxane and Paclitaxel (NDA 211875) Are Bioequivalent

Second, you state that Paclitaxel (NDA 211875) and Abraxane were "determined to be bioequivalent" (Petition at 4). You explain that Paclitaxel (NDA 211875) "was required to submit a 505(b)(2) NDA instead of an [ANDA] because of a so-called 'non-exception excipient' formulation change" (Petition at 4). Specifically, Paclitaxel's (NDA 211875) formulation differs qualitatively from Abraxane in two excipients, hydrochloric acid, and sodium hydroxide as pH adjusters (Petition at 4). Nonetheless, you state, the two products are determined to be bioequivalent.

The recommendations from FDA's draft guidance on Paclitaxel (August 2021) for establishing bioequivalence to Paclitaxel Injectable Suspension for IV administration (NDA 021660) (Paclitaxel Draft Guidance) are informative in determining whether Paclitaxel (NDA 211875) and Abraxane are bioequivalent. The Paclitaxel Draft Guidance describes, among other things, the design of bioequivalence studies and the type of information recommended to support ANDAs referencing NDA 021660. Specifically, the Paclitaxel Draft Guidance recommends an in vivo bioequivalence study with pharmacokinetic (PK) endpoints, an in vitro bioequivalence study characterizing particle size distribution, and additional comparative in vitro characterization tests to support similarity in formulation characteristics/performance.[31]

The in vivo bioavailability study that was submitted in support of Paclitaxel's (NDA 211875) approval was an in vivo bioequivalence study with PK endpoints that is consistent with the recommendation in the Paclitaxel Draft Guidance and demonstrates bioequivalence between Paclitaxel (NDA 211875) and Abraxane. In addition, the in vitro particle size distribution study submitted in support of the approval also meets the BE acceptance criteria specified in the Paclitaxel Draft Guidance.

Furthermore, the Petitioner, in support of its application, conducted additional in vitro characterization, as recommended in the Paclitaxel Draft Guidance, for three production lots of Paclitaxel (NDA 211875) and three lots of Abraxane, including, but not limited to: particle morphology, particle size, surface potential, paclitaxel crystallinity, fraction of free (in solution) and particle-bound paclitaxel and albumin in reconstituted suspension, nature of bond between paclitaxel and albumin, and the oligomeric status of albumin in both the albumin excipient and

[31] See Paclitaxel Draft Guidance for additional details.

the final drug product.[32] The in vitro characterization tests demonstrated acceptable sameness between Paclitaxel (NDA 211875) and Abraxane.

The BMS comment contends that Paclitaxel (NDA 211875) cannot meet the bioequivalence recommendations of the Paclitaxel Draft Guidance because Q1/Q2 sameness is "[t]he prerequisite for demonstrating bioequivalence under the guidance[,]" and Paclitaxel (NDA 211875) is not Q1/Q2 to Abraxane due to the additional pH adjusters (i.e., sodium hydroxide and hydrochloric acid) in Paclitaxel (NDA 211875) (BMS comment at 5). Although the Paclitaxel Draft Guidance recommends Q1/Q2 sameness for demonstrating bioequivalence for ANDAs,[33] another draft guidance explains FDA's current scientific thinking that, in certain circumstances, differences in pH adjusters between an ANDA intended for parenteral, ophthalmic, or otic use, and its RLD may be appropriate and use of a particular bioequivalence approach can be scientifically justified.[34] This is the case for Paclitaxel (NDA 211875) because the bioequivalence data described above demonstrates that the additional pH adjusters in Paclitaxel (NDA 211875) do not affect Paclitaxel's (NDA 211875) relative bioavailability as compared to Abraxane and demonstrates bioequivalence. Specifically, the physicochemical properties data for Paclitaxel (NDA 211875) demonstrate acceptable sameness to those of Abraxane and the particle size distribution study and the in vivo bioequivalence study with PK endpoints both met BE acceptance criteria.[35]

In addition, the results of the comparative in vitro studies of albumin-bound paclitaxel submitted in support of NDA 211875, the nature of the bond between paclitaxel and human albumin, and characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product support that the addition of sodium hydroxide and hydrochloric acid does not materially alter the paclitaxel-human albumin nanoparticle in Paclitaxel, i.e., the difference in the formulations of Paclitaxel (NDA 211875) and Abraxane would not result in differences in their

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[32] During the approval of Paclitaxel (NDA 211875), FDA determined based on the total review package that an additional in vitro characterization also recommended by the Paclitaxel Draft Guidance, in vitro release kinetics, was not necessary for Paclitaxel's (NDA 211875) quality control purposes. (b) (4)

[redacted]

[33] We note that recommendations in FDA guidance documents are not binding and applicants may use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

[34] See FDA draft guidance for industry *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (April 2022). When final, this guidance will represent FDA's current thinking on this topic.

[35] Because the bioequivalence data demonstrate that Paclitaxel (NDA 211875) is bioequivalent to Abraxane despite the formulation differences between the two products, we do not agree with BMS's comment that FDA should require an in vivo assessment of tissue distribution to support a finding of bioequivalence for Paclitaxel (NDA 211875) (BMS comment at 5). In addition, the BMS comment also questions whether HBT's manufacturing process for Paclitaxel (NDA 211875) materially alters the human albumin to require a final pH adjustment to bring it into an acceptable range (BMS comment at 3). The results of the comparative in vitro studies of albumin-bound paclitaxel submitted in support of Paclitaxel (NDA 211875), the nature of the bond between paclitaxel and human albumin, and characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product support that HBT's manufacturing process for Paclitaxel (NDA 211875) does not materially alter the paclitaxel-human albumin nanoparticle in Paclitaxel (NDA 211875).

PK parameters that would potentially require an in vivo assessment of tissue distribution to support a finding of bioequivalence.

Accordingly, despite the additional pH adjusters in Paclitaxel (NDA 211875), FDA finds that Paclitaxel (NDA 211875) and Abraxane are bioequivalent based on the in vivo bioequivalence study with PK endpoints, in vitro particle size distribution study, in vitro characterization tests, and characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product that were all submitted in support of Paclitaxel's (NDA 211875) approval pursuant to the 505(b)(2) pathway.[36]

C. Abraxane and Paclitaxel (NDA 211875) Can Be Expected to Have the Same Clinical Effect and Safety Profile

The Petition asserts, quoting the "therapeutic equivalents" definition, that both Paclitaxel (NDA 211875) and Abraxane "'can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling'"[37] (Petition at 5).

Based on the conclusions that Paclitaxel (NDA 211875) and Abraxane are pharmaceutically equivalent, and bioequivalent, a review of both products' labeling, and FDA identifying no new safety signals for Paclitaxel (NDA 211875), both products can be expected to have the same clinical effect and safety profile when administrated under the conditions specified in their respective labeling.

Moreover, the two excipients used as pH adjusters in Paclitaxel (NDA 211875) that are not used in Abraxane, hydrochloric acid and sodium hydroxide, are not expected to alter the clinical effect and safety profile based on the results of the comparative in vitro studies of albumin-bound paclitaxel, the nature of the bond between paclitaxel and human albumin, and characterization of the oligomeric status of albumin in both the albumin excipient and the final drug product, all of which were provided in support of Paclitaxel's (NDA 211875) approval (see also section II.B., above).

D. FDA Will Assign an "AB" TE Code to Paclitaxel (NDA 211875) and Abraxane

Because FDA finds Paclitaxel (NDA 211875) and Abraxane to be pharmaceutical equivalents, bioequivalent, and expected to have the same clinical effect and safety profile when administered under the conditions specified in their labeling, they are therapeutically equivalent.

While the Petition requests that FDA assign an "AP" TE Code (Petition at 1), an "AB" and not an "AP" TE code would be appropriate here. Per the Orange Book Preface, an "AP" TE Code

[36] FDA, Center for Drug Evaluation and Research, Summary Review, Application Number: 211875Orig1s000, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/211875Orig1s000SumR.pdf.
[37] See § 314.3(b).

applies to products where "there are no known or suspected bioequivalence problems,"[38] whereas an "AB" TE code applies where "actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence."[39] In this case, the Petitioner in support of its application submitted in vivo and in vitro studies to resolve potential bioequivalence problems and support bioequivalence between Paclitaxel (NDA 211875) and Abraxane. This follows the approach for an "AB" TE Code. Additionally, we note that FDA has already assigned Abraxane (and ANDA 216338 referencing Abraxane) an "AB" TE Code. Therefore, the more appropriate TE Code is an "AB" TE Code,[40] and, as a result, we will assign an "AB" rating to Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial, approved under NDA 211875.[41]

E. Paclitaxel (NDA 211875) Is Exempted From Certain User Fees

Finally, you argue in the Petition that "a TE code would allow HBT to be exempt from, or otherwise obtain a refund of, any Prescription Drug User Fee Act [PDUFA] annual 'program fee' FDA may assess with respect to NDA 211875 for Fiscal Year 2023 and thereafter" (Petition at 1).

To determine whether Paclitaxel (NDA 211875) should be excepted from fees under section 736(a)(2)(B)(ii) of the FD&C Act, the product must be pharmaceutically equivalent to another product on the Prescription Drug Product List in the Orange Book. Because Abraxane is on the Prescription Drug Product List of the Orange Book, the key inquiry here is whether Paclitaxel (NDA 211875) is pharmaceutically equivalent to Abraxane. As discussed above, Paclitaxel (NDA 211875) is pharmaceutically equivalent to Abraxane, and accordingly, Paclitaxel (NDA 211875) qualifies for the pharmaceutically equivalent exception to annual PDUFA program fees.

To qualify for consideration for the return of any program fees, an applicant must submit to FDA a written request for a return not later than 180 calendar days from the date the fee is due.[42] This is the case even if the applicant has submitted a citizen petition that may relate to a potential claim for a refund.[43] Details regarding the address for and content and format of requests can be found in the guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* (October 2019).[44]

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[38] See the Orange Book, 44th edition (2024), Preface at xiii. As the Orange Book Preface explains, the "AP" TE Code applies where "no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is either presumed and considered self-evident (based on other information in the application for some dosage forms (e.g., solutions)), or satisfied by a showing that an acceptable in vitro approach is met." Orange Book Preface at xiii.

[39] See the Orange Book, 44th edition (2024), Preface at xiii.

[40] Id. at xiii.

[41] In granting a TE Code, we do not need to reach the question of whether Paclitaxel (NDA 211875) would be eligible for approval under section 505(j) if it were submitted today, which the Petition and BMS Comment both address (Petition at 4-5 and BMS Comment at 3-4).

[42] Section 736(i) of the FD&C Act.

[43] See FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* (October 2019) at 18.

[44] Available at https://www.fda.gov/media/131797/download.

III. CONCLUSION

For the foregoing reasons, your Petition is granted in part and denied in part.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2024.05.06 14:54:40 -04'00'

Patrizia Cavazzoni
Director
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