HBT Labs, Inc.
536 Vanguard Way, Brea, CA 92821

August 30, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Dear Sir or Madam:

CITIZEN PETITION

HBT Labs, Inc. ("HBT") hereby submits this petition to the Food and Drug Administration ("FDA") pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act ("FD&C Act") and in accordance with 21 C.F.R. § 10.25(a) and 21 C.F.R. § 10.30.[1] For the reasons discussed below, HBT requests that FDA assign a Therapeutic Equivalence Evaluation Code ("TE Code") for Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial ("Paclitaxel Drug Product"), which FDA approved on July 27, 2022, under New Drug Application ("NDA") 211875, and that was submitted to the Agency pursuant to FDC Act § 505(b)(2).

A. Action Requested

HBT respectfully requests that FDA assign, in the Agency's Orange Book, a TE Code of "AP" to the drug product approved under NDA 211875. As demonstrated below, HBT's Paclitaxel Drug Product meets the requirements for a TE Code with respect to Abraxis BioScience, LLC's ("Abraxis'") ABRAXANE (paclitaxel protein bound particles for injectable suspension) (albumin – bound) for 100 mg/vial for injectable suspension, that FDA approved under NDA 021660. A TE Code is necessary for various reasons. First, the absence of a TE Code may stop a pharmacist or hospital from substituting HBT's competitively priced therapeutically equivalent

[1] In the Preface to FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Agency states that "[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 21 CFR 10.30)." Orange Book Preface (42nd ed., 2022), at xxiv.

drug product, forcing patients to pay for more the expensive brand product, ABRAXANE. Second, 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.

B. Statement of Grounds

1. Factual and Regulatory Background

The Orange Book Preface explains that there are "two basic categories into which multisource drugs have been placed": (1) "A-rated" drug products (i.e., "Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products"; and (2) "B-rated" drug products (i.e., "Drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products"). Orange Book Preface (42nd ed., 2022), at xiii (emphasis in original).

An FDA regulation defines the term "therapeutic equivalents" to mean "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." 21 C.F.R. § 314.3(b).[2] FDA further explains in the Orange Book Preface that:

> FDA classifies as therapeutically equivalent those drug products that meet the following general criteria:
>
> (1) they are approved as safe and effective;

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[2] Another FDA regulation defines the term "pharmaceutical equivalents" to mean:

> 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.

21 C.F.R. § 314.3(b).

(2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity;

(3) they are bioequivalent 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.

Orange Book Preface (42nd ed., 2022), at vii (reformatted).

Drug products designated with an "A" TE Code fall under one of two main policies:

(1) for those active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied by a showing that an acceptable in vitro dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated AA, AN, AO, AP, or AT, depending on the dosage form, as described below); or

(2) for those Drug Efficacy Study Implementation (DESI) drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo and/or in vitro studies the

bioequivalence of the product to a selected reference product (these products are designated as AB).

Orange Book Preface at xiii-xiv. The Orange Book Preface also defines and explains FDA's policies for various "A" sub-codes. In particular, the TE Code "AP" is defined as "Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions." Orange Book Preface at xvi.

FDA has approved two NDAs for pharmaceutically equivalent versions of Paclitaxel Protein-Bound Particles for Injectable Suspension (Albumin-Bound), 100 mg/vial: (1) HBT's Paclitaxel Drug Product, which was approved on July 27, 2022 under NDA 211875; and (2) Abraxis' ABRAXANE, which FDA approved under NDA 021660 on January 7, 2005. Both NDAs appear as follows in the electronic version of the Orange Book:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	PACLITAXEL	ABRAXANE	N021660	POWDER	INTRAVENOUS	100MG /VIAL	-	RLD	RS	ABRAXIS BIOSCIENCE LLC
RX	PACLITAXEL	PACLITAXEL	N211875	POWDER	INTRAVENOUS	100MG /VIAL		RLD	RS	HBT LABS INC

HBT's Paclitaxel Drug Product (NDA 211875), which was determined to be bioequivalent to, and is otherwise the same as Abraxis' ABRAXANE, 100 mg/vial (NDA 021660), was submitted to FDA pursuant FDC Act § 505(b)(2). HBT was required to submit a 505(b)(2) NDA instead of an Abbreviated New Drug Application ("ANDA") because of a so-called "non-exception excipient" formulation change in the company's drug product vis-à-vis the listed drug, Abraxis' ABRAXANE, 100 mg/vial (NDA 021660), that otherwise precluded the submission of an ANDA. *See* 21 C.F.R. § 314.94(a)(9)(iii). Specifically, HBT's Paclitaxel Drug Product (NDA 211875) formulation differs qualitatively from ABRAXANE in two excipients: hydrochloric acid and sodium hydroxide as pH adjusters; ABRAXANE does not contain these excipients.

The publication of the 2022 FDA draft guidance for industry "Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use," indicates that 21 C.F.R. § 314.94(a)(9)(iii) may be waived in the case of Q1 or Q2 differences in pH adjusters. This draft guidance was not published at the time of NDA 211875 submission. As such, HBT was required to submit a 505(b)(2) NDA instead of an ANDA.

Nevertheless, the draft guidance allowing for pH adjuster formulation waivers for ANDA submission purposes further support's HBT's request here for a TE Code, as such an application today would likely be submitted as an ANDA instead of a 505(b)(2) NDA and would automatically be assigned an "AP" TE Code upon ANDA approval.

2. Request for TE Code Assignment for HBT's Paclitaxel Drug Product

HBT's Paclitaxel Drug Product meets all applicable requirements for a TE Code with respect to ABRAXANE.

1. Both HBT's Paclitaxel Drug Product and Abraxis' ABRAXANE are pharmaceutical equivalents in that both drug products contain 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]).

2. Both HBT's Paclitaxel Drug Product and Abraxis' ABRAXANE are equivalent to one another and "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b).

In addition, HBT's approved Paclitaxel Drug Product is manufactured in compliance with Current Good Manufacturing Practices and is adequately labeled. As such, HBT's Paclitaxel Drug Product (NDA 211875) and Abraxis' ABRAXANE (NDA 021660) should be identified in the Orange Book with an "AP" TE Code.

C. Environmental Impact

The undersigned claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), the undersigned will submit an economic impact analysis upon request by the Commissioner.

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E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

Don Hodgson

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Date: 2022.08.30 15:39:25 -07'00'

Donald Hodgson, PhD
President, HBT Labs, Inc.
dhodgson@hbt-labs.com
714-989-5058

cc: Kurt R. Karst, Esq.
Hyman, Phelps & McNamara, P.C.