

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218711Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 146359

**MEETING REQUEST-
WRITTEN RESPONSES**

Zhuhai Beihai Biotech Co, Ltd.
c/o: Yuanchao (Derek) Zhang, PhD
8115 Maple Lawn Blvd
Suite 350
Fulton, MD 20759

Dear Dr. Zhang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BH009.

We also refer to your submission dated September 28, 2022, containing a meeting request. The purpose of the requested meeting was to discuss whether Zhuhai Beihai has adequate data to support an NDA application, based on the results of the bioequivalence study of BH009 and Taxotere in cancer patients, and to discuss the content of the NDA submission.

Further reference is made to our Meeting Granted letter dated October 5, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 21, 2022, background package.

If you have any questions, contact Rashida Redd, Regulatory Project Manager, at 301-796-5489 or Rashida.Redd@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rashida Redd, BA
Senior Regulatory Health Project Manager
Oncology 1 Group
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Enclosure:

- Written Responses



WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: IND 146359

Product Name: BH009
Indication: Breast cancer, non-small cell lung cancer, castration resistant prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck.

Sponsor Name: Zhuhai Beihai Biotech Co, Ltd
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Zhuhai Beihai Biotech Co. (Zhuhai), Ltd requests a Type B meeting to discuss the development of BH009, under the 505(b)(2) regulatory pathway. BH009 is a polysorbate 80-free formulation of docetaxel injection with the same dosing regimens, that is being developed for the same indications as Taxotere (docetaxel, DTX) Injection, the Listed Drug (LD). Docetaxel is currently indicated for:

- Breast cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC,
- Non-small cell lung cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC,
- Castration-resistant prostate cancer (CRPC): with prednisone in metastatic castration-resistant prostate cancer, and
- Gastric adenocarcinoma (GC): with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction,
- Squamous cell carcinoma of the head and neck (SCCHN): with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN.

The specific objectives of the meeting are to:

- To confirm with the Division whether the Sponsor has adequate data to support an NDA application, based on the results of the bioequivalence study of BH009 and Taxotere in cancer patients, and
- To discuss and confirm with the Division regarding the content of the NDA submission.

Zhuhai states that they will also request a separate Type B Pre-NDA Quality/CMC meeting.

DTX contains a high concentration of (b) (4) polysorbate 80 (b) (4) which has been associated with hypersensitivity, nephrotoxicity, neurotoxicity and incompatibility with common polyvinyl chloride intravenous administration sets. The rationale for development of BH009 is to achieve the equivalent systemic exposure of DTX but eliminate the toxicities associated with polysorbate 80 (b) (4). The proposed dosage regimen of BH009 is intravenous infusion (IV) over 1 hour every 3 weeks, and the dosage strength of BH009 is 20 mg/mL in a single-dose with the final infusion solution of BH009 made by adding (b) (4) % Human Albumin solution for infusion followed by adding BH009 drug product solution.

Zhuhai conducted a single dose, open label, crossover bioequivalence study of BH009 [Docetaxel Injection 80 mg/4 mL (20 mg/mL) and Winthrop (Docetaxel) Injection (20 mg/mL, the authorized generic drug of Taxotere; manufactured by Sanofi-Aventis Deutschland GmbH) in 41 patients with solid tumors. According to Zhuhai, the study results demonstrated bioequivalence; however, they noted differing effects on alcohol content. Each administration of DTX at 100 mg/m² delivers 2.0 g/m² of ethanol. Each administration of BH009 at 100 mg/m² delivers 4.0 g/m² of ethanol. For a patient with a BSA of 2.0 m², this would deliver 8.0 grams of ethanol. There was a change to the informed consent for this study in August 2020 to reflect the risks of alcohol content of the drug. Additionally, the predicted end-of-infusion blood ethanol concentration following a maximum 200 mg dose of BH009 is about 19 mg/dL, much less than 100 mg/dL, which is known to result in impairment.

2.0 QUESTIONS AND RESPONSES

Question 1: Although there was no nonclinical toxicity study with BH009, extensive nonclinical toxicity and clinical safety data of docetaxel injection are available from Taxotere and other docetaxel injection drug products containing polysorbate 80 and/or alcohol (ethanol). All impurities and residual solvent(s) in the drug substance (docetaxel) of BH009 and all impurities in the drug product of BH009 are below the qualification levels as required by the respective principles of ICH Q3A, Q3B and Q3C guidelines. All excipients used in BH009 are known and the quantity does not exceed the respective amount used in the FDA approved intravenous drug products, except

ethanol, based on FDA's Inactive Ingredient Database. Additional ethanol safety assessment will be provided to support the clinical use of BH009. Pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, BH009 is a novel polysorbate 80-free formulation of docetaxel injection with the same route of administration and same dosing regimen for the same indications. Thus, Zhuhai Beihai Biotech Co., Ltd. plans to rely on the prior nonclinical toxicity findings of the Listed Drug, Taxotere® to waive nonclinical toxicity studies to be included in the NDA of BH009.

Does the Division concur that the proposal is adequate to support the 505(b)(2) NDA of BH009?

FDA Response to Question 1: We agree with your proposal to rely on the FDA's finding of safety, as described in the label of the US-approved listed drug, Taxotere, for nonclinical safety assessment of BH009.

Question 2: Zhuhai Beihai Biotech Co., Ltd. conducted a single dose, open label, crossover bioequivalence study of BH009 [Docetaxel Injection 80 mg/4 mL (20 mg/mL) and Winthrop (Docetaxel) Injection (20 mg/mL, the authorized generic drug of Taxotere; manufactured by Sanofi-Aventis Deutschland GmbH) in 41 evaluable patients with solid tumors requiring treatment with docetaxel monotherapy (Dose: 75 mg/m²). The study results demonstrated the bioequivalence between BH009 and Taxotere following the intravenously administration and both products were well tolerated with comparable safety observations.

Does the Division agree that the bioequivalence study is adequate to support the 505(b)(2) NDA of BH009?

FDA Response to Question 2: Yes. A final determination regarding the adequacy of the bioequivalence study to support the NDA will be determined during review of the NDA.

Question 3: Does the Division agree that the iPSP submission plan?

FDA Response to Question 3: We agree with your plan to submit an iPSP waiver request within 60 days of this meeting; however, a decision about whether a waiver will be granted will be made at the time of iPSP submission.

Question 4: Zhuhai Beihai Biotech Co., Ltd. intends to rely on the information and presentation of the currently approved labeling/package insert for Taxotere but to change/modify information that is specific to BH009. Particularly, the labeling will not need to include verbiage regarding toxicity and hypersensitivity of polysorbate 80. Does the Division agree with the proposed approach for the labeling/package insert of BH009?

FDA Response to Question 4: Product labeling will be reviewed at the time of NDA submission. In general, to support changes in labeling clinical data is required.

3.0 OTHER IMPORTANT INFORMATION

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).¹ In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.²

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <http://www.regulations.gov>

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a “bridge” to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>

(3) <i>Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other

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time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.³

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁴

³ <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁷: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid⁸

⁷ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

⁸ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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