CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214253Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 141631

MEETING MINUTES

Custopharm, Inc.
Attention: Rebecca Lynch
Director, Regulatory Affairs
2325 Camino Vida Roble, Suite B
Carlsbad, CA 92011

Dear Ms. Lynch:

Please refer to your Pre-Investigational New Drug Application (PIND) file for levothyroxine sodium injection.

We also refer to the telecon between representatives of your firm and the FDA on January 30, 2020. The purpose of the meeting was your proposed submission of a New Drug Application (NDA) in mid-2020.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda Galgay, Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 30, 2020, 12:00 PM ET to 1:00 PM ET

Application Number: PIND 141631

Product Name: levothyroxine sodium injection
Indication: Treatment of myxedema coma
Owner: Custopharm, Inc. (Custopharm)

Meeting Chair: Lisa Yanoff, MD
Meeting Recorder: Linda Galgay, RN, MSN

FDA ATTENDEES

Lisa B. Yanoff, MD	Director (Acting)
Shannon Sullivan, MD, PhD	Clinical Team Leader
Lee Elmore, PhD	Pharmacology/Toxicology Supervisor
Jaya Vaidyanathan, PhD	Clinical Pharmacology Team Leader
Min Li, PhD	Biopharmaceutics Team Leader
Rajesh Savkur, PhD	Biopharmaceutics Reviewer
Linda Galgay, RN, MSN	Senior Regulatory Project Manager

CUSTOPHARM ATTENDEES

William Larkins, PhD	CEO
Leena Selvaraj, PhD	Director, Product Development
Namjin Baek, PhD	Director, Formulation Development
David Quiggle, PhD	Vice President, Regulatory Affairs Custopharm, Inc.
Rebecca Lynch	Director, Regulatory Affairs Custopharm, Inc.
[redacted]	(b) (4)

1.0 BACKGROUND

Custopharm developed a new ready-to-use injectable solution of levothyroxine sodium injection. A 505(b)(2) NDA will be submitted in mid-2020 for the 100 mcg/mL product. The listed drug (LD) is Levothyroxine Sodium for Injection, NDA 202231, held by Fresenius Kabi USA.

According to the firm, the proposed product differs from the LD in the following:

- Presentation: The LD is a sterile lyophilized powder in vials, whereas the proposed formulation is a sterile ready-to-use solution in vials
.
- Formulation: The qualitative and quantitative compositions of the 100 mcg strengths of the LD and proposed product are different, as described in Section 15 of the meeting package.

The active ingredient, route of administration, labeling claim and indications of the two products are identical.

The purpose of this meeting was to obtain feedback on whether the comparative physicochemical data (including pH and osmolality) and the protein binding study conducted on the proposed product and the LD are sufficient to support a biowaiver.

FDA sent Preliminary Comments to Custopharm on January 25, 2020. Custopharm responded with 3 clarifying questions via email on January 29, 2020.

2.0 DISCUSSION

2.1. BIOPHARMACEUTICS

Original Question 1: Custopharm has performed full specification testing on the proposed drug product and comparative testing for the RLD as described in Section 15.0 of this document, along with a human plasma protein binding study. Does FDA agree that these studies are adequate to demonstrate sameness in support of a biowaiver and that no additional studies are required?

FDA Preliminary Response to Original Question 1:
Since the formulation of your proposed drug product differs in component and composition from that of the listed drug product, a biowaiver under 21 CFR 320.22(b)(1) is not feasible for your proposed drug product. However, the "bridge" between the proposed and the listed drug product may be supported by required information, based on 21 CFR 320.24(b)(6). To support the "bridge", we recommend that you provide additional Information/evidence (including, but not limited to your own study results and/or literature data) to demonstrate that the differences in the inactive ingredients will not affect the PK performance or efficacy/safety of the drug product.

Please be advised that the adequacy of the bridging information will be a review issue for the formal NDA submission. If you would like feedback from the Agency on your proposed "bridge" prior to NDA submission, you may request a Type C guidance meeting.

New Question 1 Custopharm response to preliminary comments (email January 29, 2020): In FDA's comments you recommended to provide additional information/evidence to support the "bridge" and you reference 21 CFR 320.24(b)(6) on in-vivo and in-vitro approaches, which says, "Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence." We interpret your (b)(6) recommendation to mean that alternate approaches to a human in-vivo BE test are potentially acceptable. Is our interpretation correct?

a. Could the agency elaborate on the [concerns or] type of studies envisioned to support a more complete bridge?
b. Were there any specific issues/concerns the Agency had regarding the Protein Binding study?

Meeting Discussion: *The Agency confirmed that Custopharm's interpretation of 21 CFR 320.24(b)(6) was correct. To demonstrate the "bridge" via 21CFR 320.24(b)(6), any alternate approach might be acceptable. These approaches might include an in vitro approach and/or any scientific rationale and evidence from historical/literature data or other supportive information.*

Specifically, for the provided in vitro protein binding study, the Agency specified their concern on its clinical relevance and whether the study reflected the in vivo PK performance (distribution and elimination) of the drug product. Therefore, additional justification is needed to convince the Agency that the in vitro binding study can appropriately indicate the in vivo PK performance. For the difference in the inactive ingredients between the proposed and reference drug products, justifications should be provided to show that there is no impact on the PK performance.

The sponsor asked if the Agency could elaborate on the type of studies envisioned to support a more complete bridge. The Agency stated there were no specific recommendations on which approach should be used. The sponsor should choose any approach they consider appropriate with a scientific rationale. The Agency indicated that additional comments will be provided as post-meeting comments.

The Agency agreed that the study reports/information submitted previously to justify the safety of the excipients, including the permeability data, could be submitted for the bridging. Also, in response to Custopharm's comment regarding submission of stability data of the proposed product and the LD, the Agency recommended that it should be submitted as part of the NDA submission.

Post-meeting Comments*: *The justification can include information that the presence of excipients unique to the proposed product (e.g., SBECD and Disodium edetate dihydrate) does not affect levothyroxine PK in the proposed product. The justification could be historical or literature data or any other data deemed supportive.

New Question 2 Custopharm response to preliminary comments (email January 29, 2020): Understand a biowaiver under 21 CFR 320.22(b)(1) is not feasible for your proposed drug product.

a. Do you envision 21 CFR 320.22(d)(3) to be feasible for an in-vitro approach?

The Drug Product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

Meeting Discussion: *The Agency clarified that a biowaiver request is not necessary for bridging referred to in 21 CFR 320.24(b)(6). If there is an in vitro test that has been correlated with in vivo data, the Agency stated that 21 CFR 320.22(d)(3) can be used for the basis for this bridging and no biowaiver request is necessary for this scenario.*

2.2. NONCLINICAL

Additional Preliminary Comments:
Your NDA submission should address the safety of intravenously administered sulfobutylether-β-cyclodextrin (SBECD), (b) (4) which is present in the proposed ready-to-use product at 80 mg/mL. You should base the assessment on the maximum daily doses of SBECD anticipated clinically (e.g., 400 mg/day). The safety assessment could rely on publicly available literature information as well as prior use in other approved products for intravenous administration (e.g., NDA 208611, Baxdela). The assessment should address the need for product-specific labeling to address potential risks associated with intravenous administration of SBECD.

New Question 3 Custopharm response to preliminary comments (email January 29, 2020): For the FDA's second question (cyclodextrin safety), in the current meeting package desk copies we provided a full annex to the Oct 2018 information on cyclodextrin safety. This information included a survey of cyclodextrin in approved products, animal PK and NoAEL (no adverse effect level) data, and oral and infusion studies in humans (pIND 141631, SN0000, pages 43-51). Can the agency confirm whether this information was considered when the current recommendations were prepared? Can the agency provide any additional feedback on what items would be needed to demonstrate a complete safety assessment?

Meeting Discussion regarding NONCLINICAL Additional Preliminary Comments:
The Agency stated that the information submitted previously (i.e., October, 2018) on cyclodextrin safety appeared adequate in scope to support short-term use of SBECD, but the Agency reiterated its request for additional scientific justification regarding the need for product-specific labeling to address potential risks of SBECD administered by the intravenous route.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.
Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 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 Information[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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 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.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

6.0 505(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).[3] 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.[4]

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.

[3] 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.
[4] http://www.regulations.gov

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.

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)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(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.

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/

LISA B YANOFF
02/05/2020 04:12:29 PM