CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129778

MEETING MINUTES

Corium International, Inc.
Attention: (b) (4)

Dear Dr. (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Corplex™ Donepezil Transdermal Delivery System (TDS).

We also refer to the meeting between representatives of your firm and the FDA on September 6, 2018. The purpose of the meeting was to discuss the contents and format of the planned New Drug Application (NDA) submission and obtain the Agency's feedback on questions related to the various sections of the planned NDA.

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

If you have any questions, call E. Andrew Papanastasiou, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 6, 2018, from 1:00 PM to 2:00 PM EDT
Meeting Location: FDA, White Oak

Application Number: 129778
Product Name: Corplex™ Donepezil Transdermal Delivery System (TDS)
Indication: Treatment of mild, moderate and severe dementia of the Alzheimer's type
Sponsor/Applicant Name: Corium International, Inc.

FDA ATTENDEES

Eric Bastings, M.D, Deputy Director, Division of Neurology Products (DNP)
Nick Kozauer, M.D, Associate Director, DNP
Ranjit Mani, M.D, Clinical Team Leader, DNP
David Hawver, Ph.D, Nonclinical Reviewer
Angela Men, Ph.D, Clinical Pharmacology Team Leader
Jagan Parepally, Ph.D, Clinical Pharmacology Reviewer
Martha Heimann, Ph.D, Pharmaceutical Quality Team Leader
Stephanie Emory, Ph.D, Pharmaceutical Quality Reviewer
Caroline Strasinger, Ph.D, Pharmaceutical Quality Reviewer
Kaushal Dave, Ph.D, Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Parminder "Bobby" Singh, Ph.D., Chief Technology Officer (CTO) and VP Research & Development
Michael Ray, B.S. Senior Director, CMC
Jarrod Bento, M.Eng. Associate Director, Process Development
(b) (4) Regulatory Affairs Consultant to Corium
(b) (4) Regulatory Affairs Consultant to Corium
(b) (4), Nonclinical Consultant to Corium
(b) (4) CMC Consultant to Corium
(b) (4) PK/PD Consultant to Corium
(b) (4) Statistics Consultant to Corium

1. BACKGROUND

This briefing document has been submitted in advance of a Type B Pre-New Drug Application (NDA) meeting that is being held to discuss a transdermal formulation of donepezil, the Corplex™ Donepezil Transdermal Delivery System (TDS). The Corplex™ Donepezil TDS is proposed to be indicated for the treatment of mild, moderate, and severe Alzheimer's Disease. In contrast to the currently-marketed tablet formulations of donepezil (ARICEPT® and others) which are administered once daily, the Corplex™ Donepezil TDS is to be applied once weekly. Two strengths of the Corplex™ Donepezil TDS appear to be proposed for marketing: 52.5 cm^2 (intended to deliver 5 mg/day); and 105 cm^2 (intended to deliver 10 mg/day).

The sponsor has proposed the proprietary name ADLARITY for the Corplex™ Donepezil TDS. The Agency has reviewed that proposed proprietary name and concluded that the same proprietary name is conditionally acceptable.

The NDA for the Corplex™ Donepezil TDS will be submitted under the Section 505(b)(2) pathway, referencing ARICEPT® as Listed Drug.

The proposed NDA for the Corplex™ Donepezil TDS is to be supported by the following completed clinical pharmacology studies:

- Study P-15086, which is intended to establish the bioequivalence of the Corplex™ Donepezil TDS with donepezil (ARICEPT®) tablets.

- The following additional studies of the Corplex™ Donepezil TDS:
  - Study P-16010, a second bioequivalence study.
  - Study P-16011, a skin irritation and sensitization study.
  - Study P-16012, a comparative bioavailability study.
  - Study P-16039, a study of the effect of heat on donepezil delivery profile.
  - Studies P-15007, P-15081, and P-16007, which were early clinical pharmacology studies intended to help design and identify a formulation of this product for further clinical development.

This information package covers information on the chemistry, nonclinical and clinical data for the Corplex™ Donepezil TDS, and extends to the integration of study data in the proposed NDA, aspects of the future product labeling for the proposed product, elements of ARICEPT labeling that the sponsor proposes to rely on in support of the planned NDA, and other miscellaneous items.

FDA sent Preliminary Comments to Corium on September 4, 2018.

2. DISCUSSION

(b) (4)

Question 2: In the NDA submission, Corium plans to submit the results of non-adhesive and non-API components extractable studies and leachable correlation studies, toxicological assessments as applicable, along with leachable profile information on the 10 mg/day strength product. The leachable profile information available at the time of NDA filing will consist of the following:

- 0, 6 and 12 months data from the registration batch 1 (10 mg/day),
- 0, 6 and 9 months data from the registration batch 2 (10 mg/day),
- 0 and 6 months data from registration batch 3 (10 mg/day), and
- 0, 18 and 24 months data from the bioequivalence batch (10 mg/day).

Section 11.2 outlines background information on the batches that Corium plans to submit. Is this set of leachable data adequate to support submission and review of the NDA for Corplex Donepezil TDS?

FDA Preliminary Response to Question 2:
This proposal is acceptable.

Meeting Discussion:
None.

(b) (4)

(b) (4)

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(b) (4)

Question 6: Corium has completed a 39-week repeated dose dermal toxicity study that applied one to four Corplex Donepezil TDS to minipigs (see Section 12.2.1). The unaudited draft results establish the absence of test article-related epidermal hyperplasia with repeated administration and obviate the need for a dermal carcinogenicity assessment. Does the FDA ,agree?

FDA Preliminary Response to Question 6:
Whether the results of the 39-week dermal toxicity study in minipig demonstrate that a dermal carcinogenicity study is not needed will be a matter of review of the final study report. A decision based on an audited draft report would be contingent upon the results of the final report not differing from those of the draft report in a way that would affect study validity or interpretation.

Meeting Discussion:
The Agency stated that if, upon review of the final report of the 39-week study, the study is found to be valid and to demonstrate little or no potential for dermal carcinogenicity, a dermal carcinogenicity study of the Corplex™ Donepezil TDS would not be required. The

Agency further explained that comments on the potential for dermal carcinogenicity cannot be provided on the basis of the information provided in this briefing document; however, an effort would be made to review the unaudited draft report of the 39-week minipig study in a timely manner upon its submission.

Question 7: As per agreement with the FDA in its Pre-IND written response communication dated 28 April 2016 and based on EOP2 meeting minutes dated 22 September 2017, Corium will include results from three key nonclinical studies (described in Section 12.2) in support of a Section 505(b)(2) NDA submission: 1) a primary skin irritation study in rabbits, 2) a Buehler method skin sensitization study in guinea pigs, and 3) a 39-week repeated dose local dermal toxicity study in minipigs. Is the nonclinical program conducted for the Corplex Donepezil TDS adequate to support the submission and review of the NDA for Corplex Donepezil TDS?

FDA Preliminary Response to Question 7:
Unless it is concluded, upon review of the 39-week study in minipig, that a dermal carcinogenicity is needed, the nonclinical program appears sufficient to support the submission of the NDA.

Meeting Discussion:
None.

Question 8: Are the key studies of the clinical program (described in Section 13.1), including the bioequivalence study (P-15086), the skin irritation and sensitization study (P-16011), the evaluation of comparative bioavailability of the TDS when applied to different body regions (P-16012), and the impact of external heat on the TDS study (P-16039), adequate to support the submission and review of the NDA for Corplex Donepezil TDS?

FDA Preliminary Response to Question 8:
According to the description in this briefing document of the clinical development program for your proposed product, several key studies (P-16010, P-16012, and P-16039) utilized as their final formulation Corplex™ Donepezil TDS sizes of 53.5 cm^2 and 107 cm^2. However, on Page 60 of this briefing package, you state the following: "*Patch sizes with active delivery areas of 52.5 cm^2 and 105 cm^2 are intended to-be marketed for 5 mg/day and 10 mg/day strengths, respectively*." In your proposed pivotal bioequivalence study P-15086, Corplex™ Donepezil TDS sizes of 50 cm^2 and 105 cm^2 were compared to ARICEPT doses of 5 mg/day and 10 mg/day, respectively, at steady-state. Although the differences in size between corresponding TDS may be < 2%, you should clarify why TDS sizes of 52.5 cm^2 and 105 cm^2 were not also investigated in Studies P-16010, P-16012 and P-16039, instead of TDS sizes of 53.5 cm^2 and 107 cm^2.

If you intend to market Corplex™ Donepezil TDS sizes of 53.5 cm^2 and 107 cm^2 (instead of TDS sizes of 52.5 cm^2 and 105 cm^2), you should analyze the pharmacokinetic samples for, and submit the final study report of, Study P-16010 as the pivotal bioequivalence study in support of your NDA submission, instead of Study P-15086; we note that you currently do

not proposed to analyzed the pharmacokinetic samples that you obtained for Study P-16010. Our final determination of the acceptability of either Study P-15086 or Study P-16010 for demonstrating the bioequivalence of the Corplex™ Donepezil TDS and ARICEPT will be subject to the Agency's review of your NDA.

Meeting Discussion:
The sponsor stated an intention to commercialize only the 52.5 cm^2 and 105 cm^2 TDS formulations and to request [redacted] (b) (4). The sponsor also clarified that the 50 cm^2 TDS was only used (for one week) in the lead-in titration phase in the pivotal bioequivalence study P-15086. In addition, the sponsor reiterated that the current 52.5 cm^2 and 105 cm^2 TDS formulations are those to be marketed.

The Agency responded affirmatively in response to a question regarding whether the data provided for the 107 cm^2 TDS used in the comparative bioavailability study P-16012 were adequate.

Question 9: In Section 13.2, Corium has provided a justification to base the summary of he Clinical Safety and the Integrated Analysis of Safety on the individual safety summaries from all studies (P-15007, P-15081, P-16007, P-15086, P-16010, P-16011, P-16012, and P-16039) in its planned NDA submission. Corium does not plan to create integrated datasets (from all studies on a combined basis) containing safety data (specifically, adverse events, ECGs, vital signs, laboratory data, and suicidal ideation assessments), study drug administration, demographic and baseline characteristics, subject disposition, and PK. Does the FDA agree with respect to each of these data categories?

FDA Preliminary Response to Question 9:
Your proposal is acceptable.

Meeting Discussion:
None.

Question 10: In Section 13.3, Corium has provided a justification to integrate:

a) Skin tolerability data from studies P-15086 (including the sub study), P-16010, P-16011, P-16012, and P-16039 in the NDA submission. Skin tolerability results from other studies will be available in the individual study reports and will not be pooled. Does the FDA agree?

b) TDS adhesion data from studies P-15086, P-16010 and P-16012 in our planned NDA submission. Adhesion results from other studies will be available in the individual study reports and will not be pooled. Does the FDA agree?

FDA Preliminary Response to Question 10:
While you may provide summaries of pooled data from Studies P-15086, P-16010, and P-16012, the original data/score for adhesion (e.g., per subject, per treatment [size of TDS], and

per timepoint) should be provided in the NDA submission in Microsoft Excel format. We also encourage you to consider the following when providing your summary analysis or pooled data:

1. It may be inappropriate to pool subjects from individual studies if they were utilizing different sized products or study procedures/protocols with respect to adhesion. For example, based on the information in this Pre-NDA package, it is unclear if a sufficient number of subjects from each study followed the criterion of "*not reinforced with tape or the adhesion properties altered by pressing or smoothing*...," and how this was tracked or enforced, if daily adhesion scores were self-reported or observer-reported (e.g., in subject diaries or in clinic observations), or how many products were exposed to water (e.g., during routine showering or bathing).

2. You should provide adhesion data for Study P-16012 for each of the application sites (back, thigh, and buttock).

Meeting Discussion:

(b) (4)

The subset of questions submitted prior to the meeting, and after the above preliminary response was received by the sponsor, were discussed as follows:

Does the Division agree with the proposed approach summarized as follows:

1. **Pooled data across the three studies described above will provide supportive data for assessing adhesion.**

   FDA Response: The approach appears appropriate; the adequacy of the data and adhesion of the product will be a matter of review.

2. **The mapping of the adhesion scales from studies P-16010 and P-16012 to the scales used in P-15086 is appropriate to allow pooling of data.**

   FDA Response: The mapping approach appears appropriate for pooling across the three studies however we request you to retain and provide the original scores for Studies P-16010 and P-16012 and ensure that the data sets are provided independently (as per study) in addition to the pooled summaries.

3. **Corium proposes to provide two datasets as described above**

   FDA Response: Please provide the raw data/original scores per subject (in Excel format) and the pooled data as you have proposed. In the NDA submission, we also request you to provide 3-5 photographs of each score you collected (i.e., across the

range of adhesion scores and different subjects, as representative examples). For Studies P-16010 and P-16012, you do not need to provide photographs of scores of 6-11 at this time. Additional photographs may be requested during the review cycle.

Question 11: In Section 14.1 and Appendix 7, Corium has prepared a draft version of the US Prescribing Information for Corplex Donepezil TDS/ADLARITY. This version was created by drafting labeling based on the Corplex Donepezil TDS development program and combining it with approved labeling from the Aricept USPI. This draft ADLARITY USPI is intended to illustrate the general approach taken to create the USPI for the Corplex Donepezil TDS for the transdermal route of administration. Does the FDA agree with the general approach and changes to the USPI for Corplex Donepezil TDS? Are there any other comments on the proposed general approach and changes to the USPI?

FDA Preliminary Response to Question 11:
Although your general approach to creating the Prescribing Information for the Corplex™ Donepezil TDS may be acceptable, we will be able to comment about the specifics of the labeling text that you have proposed only after your planned NDA is submitted and reviewed.

Meeting Discussion:
None.

Question 12: (b) (4)

FDA Preliminary Response to Question 12: (b) (4)

(b) (4)

Meeting Discussion:
None.

Question 13: (b) (4)

(b) (4)

Meeting Discussion:
None.

Question 14: In the NDA, Corium plans to provide CDISC compliant format datasets for nonclinical chronic (39 week) repeated dose dermal toxicity study and clinical studies P-15086, P-15086 Sub-study, P-16010, P-16011, P-16012 and P-16039 conducted under the US IND in the Corplex Donepezil TDS development program. Clinical study reports for the three early TDS formulation identification Phase 1 studies (P-15007, P-15081, and P-16007) conducted in Australia during 2015 and 2016 will be provided; however, Corium does not plan to provide datasets for these three Australian studies due to the early stage formulation selection nature of these studies.

Pooled adhesion data from clinical studies P-15086, P-16010, and P-16012 and pooled skin irritation data from clinical studies P-15086, P-15086 Sub-study, P-16010, P-16011, P-16012 and P-16039 conducted under the US IND will be submitted using the ADaM analysis data standard.

The plan for including these datasets in the NDA is described in Section 15.1. Is this data submission plan acceptable to FDA?

FDA Preliminary Response to Question 14:
Please refer to our response to Question 10 regarding the pooling of skin adhesion data for Studies P-15086, P-16010, and P-16012. Your proposal is otherwise acceptable.

Meeting Discussion:
None.

Question 15: Corium plans to extensively rely on the Agency's previous findings of safety and effectiveness for the listed drug Aricept in support of the 505(b)(2) NDA for the Corplex Donepezil TDS. A detailed table that lists the labeling that Corium will rely upon is located in Appendix 8. Does the FDA agree with our plan to rely on the ARICEPT labeling presented in Appendix 8?

FDA Preliminary Response to Question 15:
Your proposal as presented in Appendix 8 of your briefing document is acceptable.

Meeting Discussion:
None.

Question 16: Corium acknowledges that transdermal patch systems are combination products. However, since these products involve well-precedented transdermal technology, Corium assumes the review of the CMC information will be performed under the Office of Pharmaceutical Quality, New Drug Products within CDER. As such, Corium intends to submit complete Chemistry, Manufacturing and Controls information in Module 3. Further, Corium plans to implement and satisfy applicable cGMPs and quality requirements by complying fully with 21 CFR 210 and 211 in order to ensure manufacture of a safe and effective product. Corium does not intend to submit information specific only to the device component. Does the FDA agree?

FDA Preliminary Response to Question 16:
Your proposed approach appears adequate in regard to your proposed NDA, but you should note the following regarding transdermal system combination products.

As reflected in the final rule on Current Good Manufacturing Practices (cGMPs) for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in Part 4 from the other of these two sets of requirements. Information to

demonstrate your compliance with 21 CFR Part 4 must be available upon inspection. Please ensure that the information available describes how your firm has applied each applicable regulation to your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and references to the types of protocols used by your firm for each activity. For further information on 21 CFR Part 4, you should refer to the Guidance for Industry and FDA Staff entitled "*Current Good Manufacturing Practice Requirements for Combination Products*" (January 2017), which is available at:

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

Meeting Discussion:
None.

Question 17: Corium intends to submit a categorical exclusion for an environmental assessment in accordance with 21 CFR (b) (4) .

Donepezil is currently approved for the treatment of dementia of the Alzheimer's type. Approval of Corplex Donepezil TDS for the treatment of mild, moderate and severe dementia of the Alzheimer's type will not increase the use of the active moiety. Section 15.2 outlines the draft environmental impact statement for this product.

Does the FDA agree with categorical exclusion of an environmental assessment for our NDA submission for Corplex Donepezil TDS?

FDA Preliminary Response to Question 17:
(b) (4), the approval of a new dosage form may increase usage of the active moiety. Therefore, a claim for categorical exclusion under 21 CFR 25.31(b) [which is entitled: "*Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion*"] may be more appropriate. To assist in the determination of whether or not the Corplex Donepezil TDS qualifies for a claim of categorical 21 CFR-based exclusion, please provide the expected introduction concentration (EIC) of donepezil that would result from use of your product and, per the Agency's Guidance for Industry entitled "*Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*" (published March 2016 and available at https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf), briefly evaluate existing information such as nonclinical studies, ecological toxicity studies of donepezil or similar substances, endocrine disruptor studies, existing literature, modeling, structural elements, or other scientific data to support the position that donepezil does not have

potential estrogenic, androgenic, or thyroid hormone pathway activity that represents an extraordinary circumstance.

Meeting Discussion:
None.

Question 18:
In addition to the bioequivalence study, P-15086, the development program for the Corplex Donepezil TDS includes new clinical investigations of skin irritation and skin sensitization, a clinical study evaluating bioavailability after application of the patch to various locations on the body, and a heat effect study, all of which are essential to support a marketing application. As a 505(b)(2) application, Corium believes that if approved, the Corplex Donepezil Transdermal Delivery System would be entitled to 3-years of new drug product Hatch-Waxman exclusivity.

See Section 15.3 for additional information. Does the FDA agree?

FDA Preliminary Response to Question 18:
Please be advised that the Agency does not make exclusivity determinations until after approval of a NDA. As described at 21 CFR 314.50(j), an applicant should include in an NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. For additional information on the determination of exclusivity, please see the information available at the following:

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm323412.htm.

Meeting Discussion:
None.

3. ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 4, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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. Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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* and *Pregnancy and Lactation Labeling Final Rule* 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 the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.				

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), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. 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 http://www.regulations.gov).

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.

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.

4. ATTACHMENTS AND HANDOUTS

Sponsor provided handout from the September 6, 2018, meeting.

10 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

ERIC P BASTINGS
10/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129778

MEETING MINUTES

Corium International, Inc.
(b) (4)

Dear Dr. (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Corplex™ Donepezil Transdermal Delivery System.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on August 23, 2017.

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

If you have any questions, call Teresa Wheelous, Regulatory Project Manager at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: August 23, 2017 11 AM
Meeting Location: White Oak Bldg. 22, Conference Room 1309

Application Number: IND 129778
Product Name: Corplex Donepezil Transdermal Delivery System
Indication: Alzheimer's disease
Sponsor/Applicant Name: Corium International

FDA ATTENDEES
Billy Dunn, MD – Director, Division of Neurology Products (DNP)
Eric Bastings, MD – Deputy Director, DNP
Ranjit Mani, MD – Clinical Reviewer, DNP
J. Edward Fisher, PhD – Nonclinical Reviewer
David Hawver, PhD – Nonclinical Reviewer
Angela Men, PhD – Clinical Pharmacology Team Lead
Jagan Parepally, PhD – Clinical Pharmacology Reviewer
Martha Heimann, PhD – CMC Lead
Stephanie Emory, PhD – CMC Reviewer
Kaushalkumar Dave, PhD, Biopharmaceutics Reviewer (OPQ)
Ta-Chen Wu, PhD, Biopharmaceutics Team Lead (OPQ)
Caroline Strasinger, PhD – CMC
Teresa Wheelous, RPh – Sr. Regulatory Project Manager

Corium International ATTENDEES
Parminder "Bobby" Singh, PhD. - Chief Technology Officer & VP Research & Development
Michael Ray, BS. - Senior Director, CMC
Dan Arsulowicz - VP Operations for Corium
(b) (4) - Regulatory Affairs Consultant to Corium
(b) (4). - Nonclinical Consultant
(b) (4) - CMC Consultant
(b) (4). - Clinical/Medical Affairs Consultant
(b) (4). - PK/PD Consultant
(b) (4). - Statistics Consultant

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 23, 2017, 11 AM - Noon, White Oak Bldg. 22 conference room 1309 between Corium International and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND
This briefing package has been submitted in advance of a Type B End-of-Phase 2 meeting whose objective is to discuss the further development of the Corplex™ Donepezil Transdermal Delivery System, a product which is intended for weekly administration. The proposed indication for this product is the treatment of mild, moderate, and severe dementia of the Alzheimer's type. All formulations of donepezil that are currently approved in the United States are administered once daily and by the oral route only.

The sponsor has completed a pilot bioequivalence study (P-15086) of the Corplex™ Donepezil Transdermal Delivery System prototype that is intended for marketing, and concluded that the same study has established the bioequivalence of that product to an approved oral formulation of donepezil (Aricept® tablets), and that an earlier-proposed pivotal bioequivalence study of a design similar to Study P-15086 is no longer needed. The results of Study P-15086 and those of two additional planned studies, a skin irritation and sensitization study and a study to evaluate the comparative bioavailability of the Corplex™ Donepezil Transdermal Delivery System when that product is applied to different body regions, are to support a planned Section 505(b)(2) New Drug Application (NDA) submission.

The End-of-Phase 2 meeting is intended to discuss the further development of the Corplex™ Donepezil Transdermal Delivery System as it pertains to the following disciplines: chemistry, manufacturing, and controls (CMC); biopharmaceutics; clinical pharmacology; nonclinical; and clinical.

DISCUSSION

CHEMISTRY, MANUFACTURING, AND CONTROLS QUESTIONS

This briefing document contains appropriate data and information to enable the Agency to address the following questions:

(b) (4)

(b) (4)

NONCLINICAL QUESTIONS

Question 10.

As explained in Section 12.6 of this briefing document, Corium does not intend to conduct photosafety evaluations for the following reasons:

- The design of the patch, which incorporates an opaque fabric overlay, will minimize the ability of light to penetrate the area where the donepezil formulation is applied to the skin.
- The potential sites of application for the patch will be the back, buttocks, and/or upper thigh, all of which are expected to be covered with clothing considering the intended patient population.
- In addition, there have been no occurrences of photosafety issues with orally administered donepezil despite distribution of donepezil to the skin with oral administration.

Based on this information, does the Agency agree that a nonclinical photosafety test is not required?

FDA Response to Question 10:
Based on the information provided in the briefing document, it appears that the amount of drug remaining on the skin surface is minimal; therefore, a nonclinical photosafety study would not be needed.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 11.
As described also in Section 12.6, Corium does not intend to conduct an *in vitro* ocular irritation study for the Corplex Donepezil TDS based upon the following background:

- Ocular irritation data for donepezil hydrochloride were not found in the Aricept labelling or the Pharmacology/Toxicology section of the Aricept NDA. However, safety data

sheets prepared by Pfizer for the Aricept film-coated tablet and the orally disintegrating tablet indicate that donepezil hydrochloride is an eye irritant.

- [redacted] (b) (4) should minimize the amount of donepezil that could potentially be transferred to the hands during the brief period of patch application and removal. Nevertheless, language will be added to the product label (refer to Appendix 6) to instruct the user to wash hands with soap and water immediately after handling the patch and to rinse their eyes with water if there is contact.

Based on this information, does the Agency agree that a nonclinical ocular irritation study is not required and that ocular safety concerns can be mitigated by appropriate language in the product label?

FDA Response to Question 11:
We agree that a nonclinical ocular irritation study is not needed.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 12.

Corium previously communicated in the nonclinical section of the pre-IND #129778 that, whenever possible, the Corplex Donepezil TDS would contain inactive ingredients that are listed in the FDA Inactive Ingredient Database (IID) and are well characterized. However, since the final TDS formulation was not provided at the time, the Agency was unable to comment on the need for further characterization of the proposed inactive ingredients. The formulation composition has now been finalized and is provided in this briefing document (Table 3) along with an assessment of the TDS excipient levels in comparison to the FDA IID (Section 12.3.1) and other safety information gathered from literature (Section 12.3.2).

Based on this information, and the results of the nonclinical studies, including minimal skin irritation, no skin sensitization, and the planned evaluation of clinical multiples of the TDS in the 39-week non-rodent repeated dose dermal toxicity study, does the Agency agree that no further toxicity assessments of the TDS, pertaining to the inactive ingredients, are needed?

FDA Response to Question 12:
The need for further nonclinical studies to assess the toxicity of the inactive ingredients in the Corplex™ Donepezil Transdermal Delivery System will depend on the results of the 39-week study in minipig.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 13.

In this briefing document, Corium has provided a detailed study outline for the 39-week repeated dose dermal toxicity study in minipigs (Section 12.5.2). Briefly, the study will evaluate the local and systemic toxicity of the once-weekly Corplex Donepezil TDS applied consecutively for 39 weeks, followed by a (b)(4) week recovery period. Male and female Gottingen minipigs will be allocated to five treatment groups: untreated controls, placebo TDS controls, and three Corplex Donepezil TDS dose levels. Toxicokinetic sampling will be performed at various intervals during the 9 months and the appropriate tissues/organs, including treated and untreated skin, will undergo histopathology evaluations after the main study and recovery period.

Does the Agency agree with the proposed design, including the treatment groups, dose levels, toxicokinetic sampling, and histopathology assessments, of the 39-week repeated dose dermal toxicity study in minipigs?

FDA Response to Question 13:
We cannot concur on the design of the 39-week dermal toxicity study in minipig without data from a dose-ranging study to assess the tolerability of the proposed doses.

However, we have the following general comments:

- Doses should be selected based on the results of a dose-ranging study in minipig.
- The frequency of application at the same site should be similar to or greater than that proposed for humans.
- If a dose-ranging study is conducted, there may be no need for the 12-week interim necropsy.
- At least 4/sex/group should be assessed in the main study, with additional animals (at a minimum, 2/sex/group for control and high dose) if recovery is to be assessed.
- Systemic toxicity of donepezil and excipients appears to have been adequately assessed; therefore, evaluation of local toxicity may be sufficient.
- We recommend that you submit a protocol for the pivotal study, with supportive data, for feedback prior to study initiation.

The adequacy of the planned study will be a matter of review.

If issues (e.g., leachables/extractables) arise that would require a safety assessment, additional nonclinical studies may be needed.

Sponsor Response Prior To Meeting:
See “ATTACHMENTS AND HANDOUTS” below.

Meeting Discussion:
The sponsor asked for feedback on the revised study outline for the 39-week minipig dermal toxicology study (see "ATTACHMENTS AND HANDOUTS" below). The Agency noted that under the revised protocol outline the number of animals to be included had been increased to 4/sex/group for the 9-month assessment (except for the untreated group). However, the Agency also stated that concurrence on the proposed dose selection could not be given in the absence of data from a dose range-finding study in minipig. The pharmacokinetic study in minipig described by the sponsor is considered inadequate to provide support for the doses proposed for the 39-week minipig study because no tolerability data were provided at the proposed high dose of 4 patches per animal or with repeated application to the same site. The Agency expressed concern that initiation of the pivotal 9-month study without having data on the tolerability of the Corplex Donepezil TDS at the doses proposed could compromise that study. The Agency again recommended that the sponsor conduct a repeated-dose range-finding study in minipig, of at least one month's duration prior to conducting the pivotal 9-month study.

Question 14.

Does the Agency agree that a lack of preneoplastic effects found with repeated transdermal donepezil patch administration in minipigs, together with Aricept data, adequately evaluates carcinogenicity potential without conducting an additional transdermal carcinogenicity study?

FDA Response to Question 14:
The need for a dermal carcinogenicity study in one species will be determined based on the results of the 39-week study in minipig.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

PILOT BE QUESTIONS

Question 15.

Does the FDA agree that the Pilot BE study can be used as the sole basis to document bioequivalence based on the following considerations and information provided in the briefing package?

FDA Response to Question 15:
In form, the justification you have provided in this submission for using the study data that you have described for the completed pilot bioequivalence study (Study P-15086) as the sole basis of establishing bioequivalence for your product appears reasonable. However, our final determination of the acceptability of those data for that study for that purpose will be subject to

the Agency's review of your NDA. Please provide sample size calculations for that study based on intra-subject variability.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
The sponsor provided sample size calculations based on intra-subject and inter-subject variability. The numbers of subjects used in the pilot study were less than the initial estimates based on variability. The observed pharmacokinetic data for the pilot bioequivalence study (Study P-15086) were then further discussed.

The Agency could not provide a definitive answer at the meeting regarding whether the aforementioned pilot bioequivalence study would suffice, in form, as the sole basis for establishing the bioequivalence of the Corplex Donepezil TDS or whether a further bioequivalence study would be required; that subject required further internal discussion. However the Agency agreed to address that question further in a post-discussion addendum to be included in the meeting minutes.

Post-Meeting Addendum to Meeting Discussion:
Following the meeting, the Agency had a further internal discussion regarding whether the pilot bioequivalence study could, in form, suffice as the sole basis for determining the bioequivalence of the Corplex Donepezil TDS. However, in the absence of a full report for Study P-15086, the Agency was unable to provide further guidance to the sponsor regarding that matter; the sponsor should therefore submit the full report for that study together with a detailed description of the subjects eliminated from the pharmacokinetic analysis.

Question 16.

Corium has presented an assessment of steady state achievement in Section 13.3.4.4 of this briefing document**.** Does the FDA concur that BE assessment during the 4th week of 10 mg treatment is sufficient to support assessment of bioequivalence at steady state?

FDA Response to Question 16:
In your briefing package, the results of the bioequivalence assessment during the 5^{th} week were presented, not those for the 4^{th} week as stated in your question. Please clarify whether the reference to the 4^{th} week in your question is an error.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
The sponsor's pre-meeting response provided the clarification requested by the Agency: each treatment period in the pilot bioequivalence study was 5 weeks in duration, with a first-week lead-in period (during which either the Corplex Donepezil TDS in a dose of 5 mg/day or Aricept 5 mg once daily was administered) followed by 4 consecutive weeks during which either once-

weekly Corplex Donepezil TDS 10mg/day or Aricept 10 mg once daily was administered; and the bioequivalence assessment referred to by the Agency was performed during Week 5 of the treatment period (i.e., the fourth week of treatment at the 10 mg/day dose of each formulation). Based on that clarification, the Agency responded affirmatively to the sponsor's original question, indicating that the bioequivalence assessment during Week 5 of the treatment period was acceptable.

Question 17.

In the Pilot BE study, C_{maxss} observed during the steady state week for Corplex Donepezil TDS was compared to C_{maxss} during the 24-hour dosage interval at steady state for Aricept, as described in the Corium's PIND submission. $AUC_{0\text{-}tau}$ over the 7-day dosage interval at steady state for Corplex Donepezil TDS was compared to $AUC_{0\text{-}tau}$ during the 24-hour dosage interval at steady state for Aricept (multiplied by 7 to allow comparison to Corplex Donepezil TDS). Both C_{maxss} and $AUC_{0\text{-}tau}$ meet the statistical criteria of bioequivalence (see Table 1 above and Section 13.3.4.2). Does the FDA concur that bioequivalence has been established using primary PK parameters based on C_{max} and $AUC_{0\text{-}tau}$?

FDA Response to Question 17:
Please see our response to Question 15. Our preliminary review of the summary data that you have included in this submission suggests that bioequivalence may have been established for your product using the pharmacokinetic parameters that you have specified. However, as has already been stated in our response to Question 15, the Agency's final determination of the acceptability of those data will be subject to the Agency's review of your NDA.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 18.

In the pre-IND written response to Question 13 (Appendix 7), FDA mentioned "There are no restricted criteria for supportive PK parameters only if these are not significantly different from the reference product. Other PK parameters for each treatment should also include individual and mean values for trough levels (Cmin ss), mean peak levels (Cmax ss), steady state AUCinterdose, percent fluctuation and time to peak concentration."

Based on FDA response, Corium proposes to assess supportive PK parameters as follows.

- $AUC_{(0\text{-}24h)}$ during each of the seven 24-hours periods during the steady state week for Corplex Donepezil TDS assessed for significant difference compared to $AUC_{(0\text{-}24h)}$ during the 24-hour dosage interval at steady state for Aricept (7 comparisons)

- C_{minss} observed during the steady state week for Corplex Donepezil TDS assessed for

significant difference compared to C_{minss} during the 24-hour dosage interval at steady state for Aricept.

- t_{max}: Provide descriptive statistics without formal statistical difference testing (since t_{max} is a categorical parameter with expected differences due to the dosage interval differences between treatments, 0-168 hr for Corplex Donepezil TDS, 0-24 hr for Aricept)

- % Fluctuation: Provide descriptive statistics without formal statistical difference testing (since % Fluctuation is an exposure-normalized parameter independent of bioequivalence)

The supportive PK parameters from the Pilot BE study were assessed based on the above proposal, and the results are presented in Section 13.3.4.2 and Table 2 above. Does the FDA confirm the adequacy and sufficiency of assessments performed on the supportive PK parameters in the Pilot BE study?

FDA Response to Question 18:
The comparisons that you performed of additional pharmacokinetic parameters appear reasonable on preliminary review of the summary data that you have provided, and subject to our review of those data in full when they are submitted with your planned NDA.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
The sponsor's pre-meeting response contained an additional question to which the Agency responded in the affirmative.

Question 19.

An assessment of dose proportionality for the Corplex Donepezil TDS is presented in Section 13.3.4.3. The dose proportionality has been demonstrated in the Pilot BE study, and as a result, Corium does not plan to conduct a separate dose proportionality study. Does the FDA agree with the outcome of this assessment?

FDA Response to Question 19:
You should provide more details of your dose proportionality calculations to enable us to provide further comments.

Sponsor Response Prior To Meeting
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
In the pre-meeting response, the sponsor had provided additional details of the dose proportionality calculations that the Agency had requested. The sponsor then asked if the Agency concurred that the methodology used to determine dose proportionality in the pilot

bioequivalence study was acceptable for demonstrating dose proportionality and that a separate dose proportionality study would not be required. The Agency responded in the affirmative.

Question 20.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 21.

Does the FDA concur that the study design and results adequately support the skin adhesion of the patch?

FDA Response to Question 21:
The design of the pilot bioequivalence study (Study P-15086) supports the assessment of adhesion of the product (size and formulation) used in that investigation. Should the formulation or size (of the active or inactive area) change from what was investigated in that study, additional *in vivo* adhesion studies may be necessary. The adequacy of the adhesion data for all studies previously conducted and planned for the future will be a matter of review when the NDA is submitted.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

ADDITIONAL CLINICAL STUDIES QUESTIONS

Question 22.

Does FDA agree that demonstration of bioequivalence, and presence of sustained concentrations from the long elimination half-life for donepezil, obviates the need to conduct an Aricept to TDS switching study?

FDA Response to Question 22:
There is a significant difference in the pharmacokinetic profile of donepezil following the administration of the Corplex™ Donepezil Transdermal Delivery System due to a lag time in absorption, as compared with the oral formulation used in Study P-15086. You should justify the proposal stated in your question adequately by using pharmacokinetic simulations to demonstrate that the exposure differences will have no impact on clinical effectiveness.

Sponsor Response Prior To Meeting
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
In the pre-meeting response, the sponsor had provided the results of the pharmacokinetic simulations requested by the Agency. The Agency indicated that although preliminary review indicated that those results may obviate the need for the sponsor to conduct an Aricept to Corplex Donepezil TDS switching study, full justification for why a switching study does not need to be conducted should be submitted with the planned NDA; whether that justification is sufficient would then be a matter of review.

Question 23.

Does the FDA concur that the proposed study design is an adequate assessment of skin irritation?

a. Does the FDA concur that the mean cumulative irritation score and other assessments described are sufficient to evaluate skin irritation potential of the Corplex Donepezil TDS?
b. Given that there are no currently marketed donepezil transdermal patches to use as a reference in the study, only a vehicle-control patch has been included. Does the FDA concur with the use of a vehicle-control comparator?

FDA Response to Questions 23a and 23b:
Your proposals are acceptable, pending our review of the full protocol for that study when it is formally submitted to this IND.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 24.

Does the FDA concur that the proposed study design and analysis are adequate to assess skin sensitization?

FDA Response to Question 24:
Your proposal is acceptable, pending review of the full protocol for that study when it is formally submitted to this IND.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 25.

Does the FDA concur that the study design is sufficient to evaluate the comparative bioavailability of different skin regions?

FDA Response to Question 25:
The design of the proposed relative bioavailability study (P-16012) appears reasonable.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

REGULATORY QUESTIONS
Question 26.

In accordance with the Guidance for Pediatric Study Plans, it is our understanding that an iPSP should be submitted "not later than 60 calendar days after the date of the end-of-phase 2 meeting"… or "if a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the iPSP no later than 210 calendar days before it submits a marketing application or supplement". Given that the Corplex Donepezil TDS is intended to treat patients with Alzheimer's disease, and this patient population does not include pediatrics, it is assumed that we would be granted a "Waiver" from performing pediatric studies under PREA. Does the Agency agree?

FDA Response to Question 26:
Please see the section below headed "PREA REQUIREMENTS" and follow the procedures described in that section. While we cannot make at this time a final determination as to whether a waiver from performing pediatric clinical studies with the Corplex™ Donepezil Transdermal Delivery System will be granted, such an outcome appears very likely.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 27.

Corium has drafted a mock version of a few key sections the US Package Insert (USPI) for Corplex Donepezil TDS (refer to Appendix 6). This version was created from the Aricept USPI and the "track changes" illustrate the general approach proposed to revise the USPI for the transdermal administration route. We recognize that it is premature to solicit comments on specific labeling language. But, we would appreciate any initial comments the Agency can provide on the general approach described.

FDA Response to Question 27:
We have no comments at this time.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

Question 28.

As described throughout this briefing book, the entire clinical development program for the transdermal product will be performed in healthy volunteers. As a result, the Adverse Event profile of the transdermal product will be from healthy volunteers. Nonetheless, we believe that there is meaningful data on the safety profile of the transdermal product to include in the USPI (refer to Appendix 6). Does the Agency agree with the approach proposed?

FDA Response to Question 28:
Please see our response to Question 27. However, your proposal may, in form, be acceptable.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
The sponsor asked if it was appropriate for systemic adverse event data for the Corplex™ Donepezil TDS to be presented in the Prescribing Information since those data were derived from studies conducted in healthy volunteers. The Agency indicated that since those data, including those derived from the pilot bioequivalence study (P-15086), (b) (4) Since those data are to be submitted with the planned NDA for the Corplex Donepezil TDS, it can then be determined as to which data are to later be included in in the labeling for that product.

Question 29.

To support approval of Corplex Donepezil TDS, Corium will be required to perform several clinical studies. In addition to the Pilot BE study, we will need to evaluate skin irritation and sensitization in a clinical study (refer to Section 14.1). Does the Agency agree that these are "new clinical investigations" that are essential to support a marketing application and therefore, Corplex Donepezil TDS should be eligible to be granted 3 years of exclusivity under the provision of Hatch-Waxman?

FDA Response to Question 29:
FDA does not award, comment on, or grant exclusivity prior to approval of a drug product; therefore, concurrence at this time would be premature.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:
The sponsor asked if the pilot bioequivalence study together with the proposed skin irritation and sensitization studies were "essential" to support the planned NDA for the Corplex Donepezil TDS. The Agency indicated that these studies were a standard requirement for transdermal formulations for which marketing approval was being sought.

Question 30.

In the PIND Written Response (Appendix 7), FDA encouraged Corium to *"identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature"*. A table is provided in Section 14.2 (Table 63). Does the Division agree with our approach to referencing existing data to establish the safety and effectiveness of donepezil?

FDA Response to Question 30:
As noted in the response to Question 32, non-US labeling or non-US regulatory assessments may not be relied upon to support approval of a 505(b)(2) application as these are neither FDA's findings related to a listed drug, nor are they published literature. However, if the studies on which the non-US conclusions are based have been published, you may be able to rely on that literature.

Please note that 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 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.

For additional information for sponsors considering the submission of an application through the 505(b)(2) pathway, please see the information in the 505(b)(2) REGULATORY PATHWAY section in this document.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None

Question 31.

Corium is pursuing approval of Corplex Donepezil TDS based primarily upon establishment of bioequivalence (BE) to Aricept oral tablets. To the best of our understanding, the core battery of safety pharmacology studies (in accordance with ICH S7a) has not been performed for donepezil. Based upon the assumption that BE will be established between our patch and Aricept tablets, and the fact that the safety of donepezil is well-characterized, Corium believes that there is no incremental risk associated with the Corplex Donepezil TDS patch that would warrant conduct of Safety Pharmacology studies to support our 505(b)(2) application. Furthermore, numerous ANDAs for donepezil have been approved, including one as recent as 2016, and there has been no requirement imposed to perform Safety Pharmacology studies. As a result, Corium proposes not to perform Safety Pharmacology studies for Corplex Donepezil TDS. Does the Agency agree?

FDA Response to Question 31:
It is well known that heat from external sources such a heating blanket or a sauna, and potentially from strenuous exercise, may affect the rate of drug release and absorption of drug substances from many transdermal systems. You should investigate the impact of an elevated transdermal system/skin surface temperature (e.g., 42 ± 1°C) on the delivery profile of the drug product relative to its delivery profile at a normal transdermal system/skin surface temperature (e.g., 32 ± 1°C). These studies should be conducted with the proposed commercial product and as part of a clinical protocol. The identification of critical factors in the design of transdermal system heat effect studies such as appropriate elevated test temperatures, heat exposure durations and cycles, and mechanisms of heat exposure should be carefully considered in designing a clinically meaningful heat study.

Sponsor Response Prior To Meeting:
See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:

(b) (4)

the investigation of the impact of heat for new transdermal formulations of drugs should be performed *in vivo* in the absence of IVIVC.

Question 32.

General toxicology studies including single-dose and repeat-dose (up to 12 months in rats and dogs) have been completed for donepezil as part of the development program for Aricept. This is broadly described in the FDA Pharm/Tox review documents for Aricept as well as in some documents in the public domain (i.e. Product Monograph for Donepezil in Canada). However, these general toxicology studies are not described in the US Package Insert, nor in the scientific literature. The 505(b)(2) guidance states that "This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug." and further states "Section 314.54 permits a 505(b)(2) applicant to rely on the Agency's finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j). This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug." Can the Agency confirm that Corium can rely upon the Agency's prior finding of Safety (from Aricept NDA #020690), as it relates general toxicology, to support its planned 505(b)(2) marketing application?

FDA Response to Question 32:

"Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. FDA reviewers' public summaries, the Summary Basis of Approval (SBA), and advisory committee materials do not constitute full reports of investigations. See 21 CFR 314.430(e)(2). A 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding as reflected in the FDA-approved labeling for the listed drug.

Additionally, non-US labeling or non-US regulatory assessments may not be relied upon to support approval of a 505(b)(2) application as these are neither FDA's findings related to a listed drug, nor are they published literature. However, if the studies on which the non-US conclusions are based have been published, you may be able to rely on that literature.

Sponsor Response Prior To Meeting:

See "ATTACHMENTS AND HANDOUTS" below.

Meeting Discussion:

The Division stated, in response to a pre-meeting question from the sponsor (see "ATTACHMENTS AND HANDOUTS" below), that additional nonclinical studies (including general toxicity studies) may be needed if the results of the 39-week study in minipig raise safety

issues. The sponsor was referred to the preliminary responses to Questions 12 and 13, regarding inactive ingredient and leachables/extractable issues.

ADDITIONAL BIOPHARMACEUTICS COMMENTS

We have the following advice and other comments about the information that should be provided in your NDA regarding the development of an *in vitro* drug release method and establishing *in vitro* drug release acceptance criteria for your product:

1. *In Vitro* Drug Release Testing:
   a. Provide a detailed description of the drug release test method being proposed for the evaluation of your product and the developmental parameters (e.g., solubility data for the drug substance as a function of pH range, selection of the equipment/apparatus, release media, agitation/rotation speed, pH, assay, sink conditions, and other items). The testing conditions used for each test should be clearly specified. The drug release profile should cover the complete drug release of the label amount or extend to whenever a plateau is reached (i.e., no increase over three consecutive time points). Please note that you have the option of establishing an *in- vitro-in vivo* correlation (IVIVC)/*in-vitro-in vivo* relation (IVIVR) using the *in vitro* skin permeation and *in vivo* pharmacokinetic data for your product.
   b. Provide the complete drug release profile data (n=12; individual, mean, standard deviation, and profiles) for your product. The drug release data should be reported as the cumulative percentage of drug released with time (the percentage is to be based on what is stated in the product label).
   c. Provide data to support the discriminating ability of the selected drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the drug release profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables [i.e., ± 10-20% change to the specification ranges of these critical material attributes (CMA) and critical process parameters (CPP)].
   d. Provide supportive validation data for the *in vitro* drug release methodology (e.g., method robustness) and analytical method (e.g., precision, accuracy, linearity, and stability).

2. Critical Method Attributes (CMA) and Critical Process Parameters (CPP):
   Provide a list of CMA and CPP that may affect the drug release from your TDS product.

3. *In Vitro* Drug Release Acceptance Criteria:
   For the setting of the drug release acceptance criteria, the following should be considered:

   a. The setting of the *in vitro* drug release acceptance criteria should be based on multi-point drug release profile encompassing the timeframe over which at least (b)(4)% of the drug is released or until when the plateau of drug release is reached if incomplete drug release occurs (i.e., no increase over three consecutive time points).

b. Data from the lots used in the clinical trials and primary stability studies should be used for the setting of the acceptance criteria. The generated data supporting the proposed acceptance criteria must be provided.
c. At least three specification sampling time points covering the initial, middle, and terminal phases of the complete drug release profile data must be selected. The acceptance criteria ranges must be based on the overall average drug release data generated at those times.
d. In general, the selection of the drug release acceptance criteria ranges is based on a mean target value ± 10%.
e. The drug release acceptance criteria should be set in a manner so as to ensure consistent performance from lot to lot and those criteria should not allow the release of any lots with drug release profiles outside those that were tested clinically.

4. Data Presentation:
In the *in vitro* drug release method development report, please present detailed experimental data as follows.

a. Include individual vessel data as much as possible in the narrative portion of the report, particularly data regarding the selection of equipment, media, agitation speed, and other items.
b. In addition to the mean drug release data presented in graphical and tabular formats in the drug release method development report, submit all individual vessel drug release data for the clinical and registration/stability batches in .xpt format.
c. Batch release and stability drug release data should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.

Sponsor Response Prior To Meeting:
None.

Meeting Discussion:
None.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER

strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site,* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

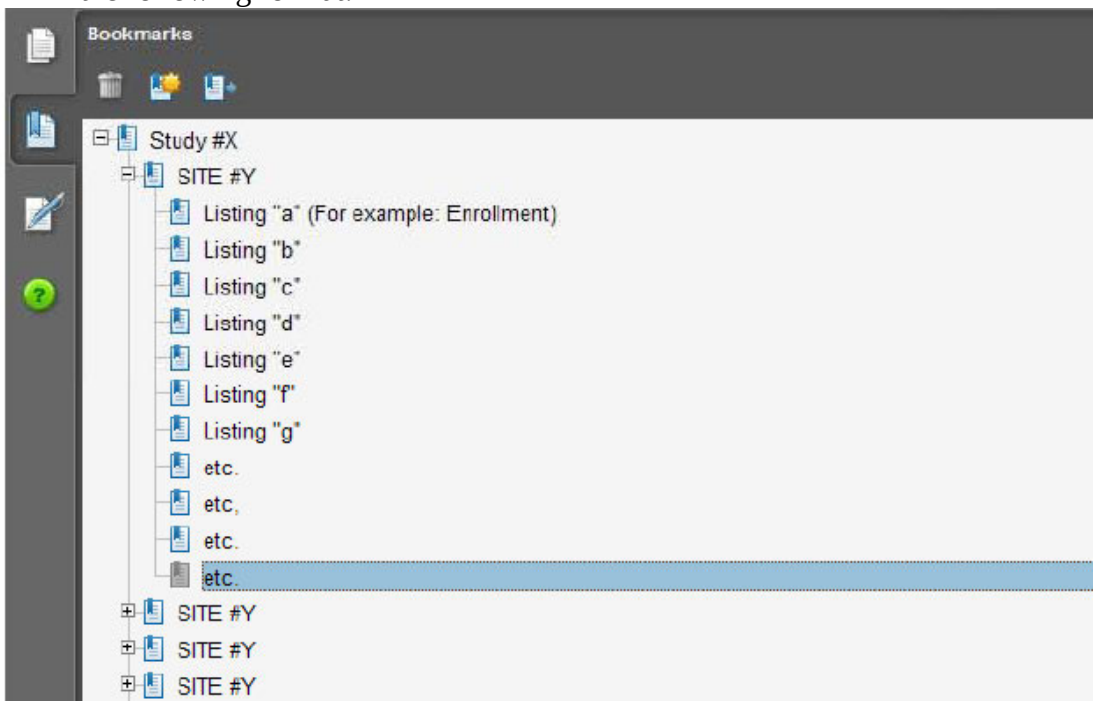
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates

g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

ISSUES REQUIRING FURTHER DISCUSSION

None – See Action items below

ACTION ITEMS

Action Item/Description	Owner	Due Date
At the end of our discussion, Dr. Angela Men (Clinical Pharmacology Team Lead) identified a potential discrepancy in the number of patients presented in one of our documents.	Sponsor	The sponsor provided the information by email on 8/28/17 followed by the official submission on 8/29/17
At the end of our discussion of Question #15, the Division agreed to look further at the information provided, including datasets, to comment further on the acceptability of the sample size for study P-15086	FDA – Clinical Pharmacology	If not at the time that the official meeting minutes issue, then upon completion of the review.

ATTACHMENTS AND HANDOUTS

The following is a copy of the sponsor's handout provided prior to the meeting:

10 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
09/22/2017