CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118954

MEETING MINUTES

Ocular Technologies, SARL
c/o Point Guard Partners LLC
Attention: Jeremy Brace
Vice President of Regulatory Affairs
400 North Ashley Drive, Suite 2150
Tampa, FL 33602

Dear Mr. Brace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTX-101 (cyclosporine ophthalmic solution).

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2017. The purpose of the meeting was to discuss the clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) data proposed for inclusion in a New Drug Application (NDA) submission under the 505(b)(2) pathway.

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 Derek Alberding, Regulatory Health Project Manager at (240) 402-0963.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology
Office of Antimicrobial Products
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:	April 24, 2017, 1:00 PM – 2:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	118954
Product Name:	OTX-101 (cyclosporine ophthalmic solution)
Indication:	To increase tear production
Sponsor Name:	Ocular Technologies SARL
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Derek Alberding, PharmD

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, M.D.	Deputy Director, DTOP
William M. Boyd, M.D.	Clinical Team Leader, DTOP
Lucious Lim, M.D.	Clinical Reviewer, DTOP
Martin Nevitt, M.D.	Clinical Reviewer, DTOP
Lori Kotch, Ph.D.	Pharmacology/Toxicology Team Leader, DTOP
Aaron Ruhland, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Solomon Chefo, Ph.D.	Statistical Reviewer, OB/DBIV
Yongheng Zhang, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology/Division of Clinical Pharmacology IV
Benjamin Stevens, Ph.D.	Branch Chief, Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)
Chunchun Zhang, Ph.D.	Product Quality Team Leader, OPQ/ONDP
Su-Lin Lee, Ph.D.	Staff Fellow, OPQ/Scientific Staff
Katherine Schumann, M.S.	Associate Director for Regulatory Affairs, Office of Antimicrobial Products
Yasmeen Abou-Sayed, PharmD	Risk Management Reviewer, Office of Medication Error Prevention and Risk Management/Division of Risk Management

Roy Blay, Ph.D.	Reviewer, Office of Scientific Investigations
Derek Alberding, PharmD	Regulatory Health Project Manager, DTOP

OCULAR TECHNOLOGIES SARL

Sidney L. Weiss	Global Project Leader
Jeremy Brace	Vice President Regulatory Affairs, Point Guard Partners

(b) (4)

SUN PHARMA ATTENDEES

Hany Michail, M.D., Ph.D.	Vice President of Clinical Development, Ophthalmology,
Jeffrey Yuan, Ph.D.	Vice President, Regulatory Affairs

BACKGROUND

Ocular Technologies SARL is developing OTX-101 (cyclosporine ophthalmic solution) for improvement in tear production in patients with keratoconjunctivitis sicca.

A type B End-of-Phase 2 meeting to reach agreement on the data required to support the submission of a 505(b)(2) NDA application was granted for October 6, 2015. The Division issued Preliminary Comments on October 2, 2015, in response to questions included in the September 3, 2015 Meeting Package. Ocular Technologies SARL determined further discussion was not necessary and requested cancellation of the meeting.

On December 14, 2015, the Sponsor requested a type C meeting to seek clarification on the Division's Preliminary Comments, dated October 2, 2015. A meeting was granted for February 1, 2016. The Division issued Preliminary Comments on January 28, 2016, in response to questions included in the December 30, 2015 Meeting Package. Ocular Technologies SARL determined further discussion was not necessary and requested cancellation of the meeting.

Following completion of a Phase 3 study (OTX-101-2016-001) and a Phase I pharmacokinetic study (OTX-101-2016-003), Ocular Technologies SARL requested a type B Pre-NDA meeting to discuss the clinical, toxicology, and CMC data proposed for inclusion in a New Drug Application (NDA) to be submitted under the 505(b)(2) pathway, on January 5, 2017. A meeting was granted for April 24, 2017.

FDA sent Preliminary Comments to Ocular Technologies SARL on April 19, 2017, in response to questions included in the March 21, 2017 Meeting Package.

DISCUSSION

For the purposes of these minutes, the questions submitted in the March 21, 2017, Meeting Package are in **bold** font, FDA preliminary responses are in *italics* font, and the meeting discussions are in normal font.

Clinical

1. **As recommended by the Division in its preliminary responses for the End-of-Phase 2 Meeting dated 02 Oct 2015, the Sponsor has conducted an additional adequate and well-controlled study to demonstrate a clinically meaningful improvement in tear production prior to submission of an NDA. The results of this study, OTX-101-2016-001, are summarized in the briefing document along with those previously reported from Study OTX-101-2014-001. (See Sections 5.2 and 5.3.) The Sponsor proposes that Studies OTX-101-2014-001 and OTX-101-2016-001 are adequate and well-controlled trials that, together, provide substantial evidence of efficacy for OTX-101 0.09% regarding clinically meaningful improvement in tear production.**

   Does the Division agree that these studies are adequate and sufficient to file a marketing application for OTX-101 in the proposed indication?

   FDA Response:

   There appears to be adequate data to support the filing of an NDA for OTX-101. The adequacy of the data to support approval is a review issue.

   Meeting Discussion: None.

2. **Study OTX-101-2014-001 and Study OTX-101-2016-001 exposed a total of 524 patients for up to approximately 12 weeks to OTX-101 0.09% cyclosporine A (CsA), and an additional 151 patients to OTX-101 0.05% CsA (see Table 4 for summary of exposure). All safety data from these two studies will be included in the NDA (see summary of safety data in Section 5.3).**

   Study OTX-101-2016-002 is being conducted to examine the long-term safety of OTX-101 0.09% when dosed BID in at least 100 patients for 1 year. This study is an ongoing open-label extension to Study OTX-101-2016-001. The Sponsor proposes to provide the long-term safety data from this extension study in the 120-Day Safety Update (see Section 5.4).

   Is this acceptable to the Division?

   FDA Response:

   No. At the time of the submission of the NDA, the application is expected to be complete. We recommend that safety data on at least 100 patients who would have completed 6 months of follow-up after initiation of treatment be submitted at the time of filing and that your safety update provide additional follow-up as available.

Meeting Discussion:

The Sponsor stated that final, cleaned data is available for more than 100 patients that have been treated for at least 6 months. The Sponsor proposed including these data as datasets, tables, and listings in the ISS in Module 5 and a text summary in the Summary of Clinical Safety (Module 2.7.4).

The Division found the proposal acceptable.

3. **As recommended by the Division, the Sponsor conducted Study OTX-101-2016-003 to measure cyclosporine blood levels following repeat BID dosing with OTX-101 0.09%. Using an assay with a lower limit of quantitation (LLOQ) of 0.1 ng/mL, the maximum blood level observed following 7 days of BID dosing with OTX-101 0.09% ophthalmic solution was 0.195 ng/mL; the mean maximum concentration (Cmax) was 0.093 ng/mL.**

   There were no detectable drug levels in any sample collected later than 4 hours post dosing. The Sponsor plans to include this text in the Pharmacokinetics section of the package insert. (See Section 5.5.)

   The Sponsor believes that this study, together with the other nonclinical and clinical data, present an adequate evaluation of the systemic safety with OTX-101. Does the Agency concur?

   FDA Response: *Concur.*

   Meeting Discussion: None.

4. **The Sponsor plans to provide clinical datasets in Study Data Tabulation Model (SDTM) format along with the reviewer guide, Define.xml, and annotated case report forms (CRFs) in lieu of providing the subject data listings (Section 16). ADaM format datasets will be provided for the analysis of the clinical data. For the Phase 1 pharmacokinetic study, raw SAS datasets in transport format will be provided. (See Section 5.6.)**

   Is this acceptable to the Division?

   FDA Response:

   Yes. Please also submit all programming codes used for generating the analysis datasets and the efficacy and safety analysis results (including tables, figures, and data listings) for the study reports for OTX-101-2014-001 and OTX-101-2016-001 studies.

   Meeting Discussion:

   The Sponsor agreed to submit all programming codes used for generating the analysis datasets and the efficacy and safety analysis results for the study reports for OTX-101-2014-001 and OTX-101-2016-001 studies as requested. The Sponsor stated that figures provided

in the study reports were generated using results from SAS that were entered into MS Excel and validated by an independent second party. The Sponsor asked if the Excel files should be submitted in addition to the SAS codes.

The Division stated that providing the figures and data in summary tables was sufficient if the data is included in the SAS datasets.

5. **The Sponsor intends to provide an integrated analysis and summary of safety data (ISS). The ISS will be split with the narrative portion located in Section 2.7.4 and the datasets located in Section 5.3.5.3. A clear explanation of where the specific information is located will be placed in Module 2 (2.7.4) and in Module 5 (5.3.5.3). Descriptions of the proposed content of the ISS and for summaries of efficacy are provided in Sections 5.7 and 5.8.)**

   Does the Agency agree with the Sponsor's plan as described?

   FDA Response:

   Agree. Please also submit all programing codes used for generating the ISS reports.

   Meeting Discussion: None.

6. **The Sponsor does not intend to pool efficacy data from Studies OTX-101-2014-001 and OTX-101-2016-001 and instead will present the results of each, side-by-side in Module 2 (2.7.3), using the statistical methods of Study OTX-101-2016-001 to demonstrate consistency across the studies. The efficacy analysis will be split with the narrative portion located in Section 2.7.3 and datasets in Section 5.3.5.3. A clear explanation of where the specific information is located will be placed in Module 2 (2.7.3) and in Module 5 (5.3.5.3). (See Section 5.8.)**

   Does the Agency agree with the Sponsor's plan for the efficacy analysis?

   FDA Response:

   Agree. In addition, we have the following comments for your consideration:

   a. *Regarding Tables 5, 6 and 11 presented in your briefing document, please provide a 95% confidence interval for the response rate for each treatment group and a 95% confidence interval for the difference in the response rates between the treatment groups. Please provide details on the methods for calculating these 95% confidence intervals.*

   b. *For the proportion of eyes with ≥ 10 mm increase in STT score and for the uncategorized mean change in STT score from baseline at Day 84; please provide the analyses results based on the average of eyes and using the study eye, fellow eye, and worse eye (Ref. Table 2 and Table 3 of Type C Meeting Clinical Briefing Document).*

c. *Also, for the proportion of eyes with ≥ 10 mm increase in STT score provide the results by the baseline STT score categories (≤ 5 mm, 5 mm - 10 mm, and ≥10 mm) and for the uncategorized change in STT score from baseline at Day 84 provide the cumulative distribution function graph by treatment group.*

d. *In Table 7 and Table 9, there is a mismatch in the table titles and footnotes. The table titles stated that analysis was based on average of eyes whereas the footnote stated that data from both eyes were used. Please clarify.*

e. *In Table 11 (Analysis of complete clearance [CC] of Central Corneal Staining), about 38% of eyes in each treatment arm had CC at baseline and these eyes were included in the evaluation of CC at Day 84. Since evaluation of CC at Day 84 would be more meaningful in the subgroup of eyes with no CC at baseline, we recommend that evaluation of CC at Day 84 also be performed in this subgroup of eyes.*

Meeting Discussion:

a. The Sponsor agreed to provide a 95% confidence interval for the response rate for each treatment group and a 95% confidence interval for the difference in the response rates between the treatment groups as requested in the Clinical Summary of Efficacy (Module 2.7.3).

   The Division stated the Sponsor should submit this information in the study report or as an appendix to the study report in Module 5.

b. The Sponsor stated that a study eye was not determined in the Phase 3 Study. The Sponsor proposed providing the analyses results based on the average of both eyes and worse eye based on the STT.

   The Division stated that these were analyses for robustness and recommended that in addition to average of eyes and worse eye that the sponsor also provide analyses by left eye and right eye. The Division stated that this information should be presented in the study report or as an appendix to the study report.

   The Sponsor agreed with this recommendation.

c. The Sponsor stated that the efficacy data from the two efficacy studies was not pooled in their analysis. The Sponsor proposed submitting the analyses requested for each study separately, and presenting the results side by side in the Summary of Clinical Efficacy (Module 2.7.3).

   The Division agreed that presenting the data by study is acceptable, but that results should be submitted in the clinical study report or as an appendix to the clinical study report.

d. The Sponsor stated there was a mismatch between the table titles and footnote in Table 7 and Table 9. The Sponsor stated that the analysis was based on average of eyes and that the footnote would be clarified.

e. The Sponsor stated that the complete clearance was not evaluated at baseline, and noted the treatment effect at Day 84 was statistically and clinically valid. The Sponsor stated the recommended data could be provided but asked whether this was a meaningful analysis to conduct.

   The Division stated the subgroup analyses potentially help inform labeling decisions. The results of the subgroup analysis should be submitted in the clinical study report or as an appendix to the clinical study report. The Division stated that SAS code for all additional analyses should be provided.

   The Sponsor agreed.

Chemistry

7. **The Sponsor plans to submit the executed batch record for the largest of the NDA drug product registration batches (b) (4) The intended commercial scale is (b) (4) and the Sponsor commits to the validation of three full-scale commercial batches (b) (4) prior to distribution of the drug product. Does the Agency have any comment? (See Section 6.1.)**

   FDA Response:

   Please submit executed batch records for all registration batches (stability batches) per 21 CFR 314.50(d)(1). We are not commenting on the plan for process validation, but refer you to the Guidance for Industry, Process Validation: General Principles and Practices (2011).

   Meeting Discussion: None.

8. **Does the Division agree that the proposed drug substance and drug product release testing and acceptance criteria, which are based on development (b) (4) and three registration batches (b) (4) are adequate to support an NDA? (See Sections 6.1 and 6.2.)**

   FDA Response:

   The proposed drug substance specifications appear adequate; however, please add the following details:

   a. *Include elemental impurity testing as per USP <232>/<233> or ICH Q3D guidelines for parenteral solutions.*
   b. *Add an optical rotation test and acceptance criteria.*
   c. *Monitor the genotoxic impurities in drug substance as per ICH M7 guidance.*

The proposed acceptance limits for osmolality and viscosity will be assessed in the NDA review.

Please provide data to justify not including % water loss in the drug product release or stability specification upon future NDA submission.

(b) (4)

In addition to USP <1111> (Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use), the drug substance specification should include the corresponding methods for microbial enumeration (e.g. USP <61>) and tests for specified microorganisms (e.g. USP <62>) for the Microbial Quality test. Drug Product specifications are appropriate from the Product Quality Microbiology review perspective.

Meeting Discussion: None.

Pharmacology/Toxicology

9. A summary of the nonclinical information planned for inclusion in the NDA is provided (see Section 7.2) and is consistent with previous discussions with the Division.

Does the Division agree that the completed program of nonclinical studies satisfies all requirements to support the filing of an NDA for OTX-101? Also, is the proposed use of publicly available information, including that from the US Prescribing Information for Sandimmune and Neoral, appropriate and sufficient; and is the administration of OTX-101 in the clinical formulation at the proposed clinical concentration of 0.09% in the 26-week Ocular toxicity/toxicokinetic (TK) study in rabbits (Study No. CTD1529) sufficient to qualify the 1% HCO-40 concentration in the formulation? (See Section 7.)

FDA Response:

We agree that the completed program of nonclinical studies satisfies all requirements to support the filing of an NDA for OTX-101. The 26-week ocular toxicity study conducted in rabbits should be sufficient to qualify (b) (4) *to a concentration of 1% for topical ocular administration, assuming safety was established at that dose.*

Meeting Discussion: None.

Regulatory

10. Does the Agency agree that the proposed marketing application dossier organization and structure is acceptable for the Agency's review of an NDA? (See Section 8.1.)

FDA Response: Agree.

Meeting Discussion: None.

11. The Sponsor intends to request a full waiver for pediatric assessments, supported by the Pediatric Study Plan agreed to with the Agency (Sequence 0026). Is this acceptable to the Agency?

FDA Response: Acceptable.

Meeting Discussion: None.

12. The Sponsor does not plan to provide a Risk Evaluation and Mitigation Strategy (REMS) or a Risk Management Plan (RMP) as part of the proposed NDA. Is this acceptable to the Division? (See Section 8.3.)

FDA Response:

At this time, we agree that neither a REMS, nor a RMP need to be included in the original NDA submission.

Meeting Discussion: None.

13. Does the Agency agree with the proposed presentation of the draft drug labeling? (The draft drug labeling is provided in Appendix C.)

FDA Response:

The Agency cannot make a determination at this time. Labeling is a review issue.

Meeting Discussion: None.

14. Does the Division consider the proposed indication to be acceptable based on the clinical data as presented? (See Section 8.2.)

FDA Response:

The Agency cannot make a determination at this time. Labeling is a review issue. The specific language of the indication section will be determined after review of the data submitted in the NDA. We note that the data in the meeting package does not appear to support the indication, (b) (4)

Meeting Discussion:

The Division stated that the meeting package does not appear to support the indication (b) (4) The Division stated that the endpoint of increased tear (b) (4) .

The Sponsor inquired whether the data submitted may support alternate wording of (b) (4)

(b) (4)

The Division stated the replication of complete clearing of the total conjunctival staining and an increase of ≥ 10 mm from baseline in Schirmer's Test Score needs to be demonstrated in two adequate and well-controlled studies to be considered as an endpoint for approval. The complete clearing of fluorescein staining in specific quadrants (e.g., inferior or central cornea) is not relevant due to the continued risk of infection.

Additional Meeting Discussion

The Sponsor inquired about the Office of Scientific Investigations (OSI) "Request for Site Level Dataset" in the Preliminary Comments letter.

OSI stated that three items are requested in the Preliminary Comments letter:

a. General study related information and comprehensive clinical investigator information, including updated addresses and contact information for sites.

b. Subject Level Data Listings by Site

c. Site Level Datasets

OSI stated that electronic submission of site level datasets is voluntary, and is intended to facilitate a risk-based approach for the identification of clinical investigator sites for FDA inspection. If the Sponsor chooses to voluntarily provide a dataset, 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) describes FDA's recommendation for the structure and format of summary level clinical site datasets.

Additional FDA Comments

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 pdit@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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.				

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.

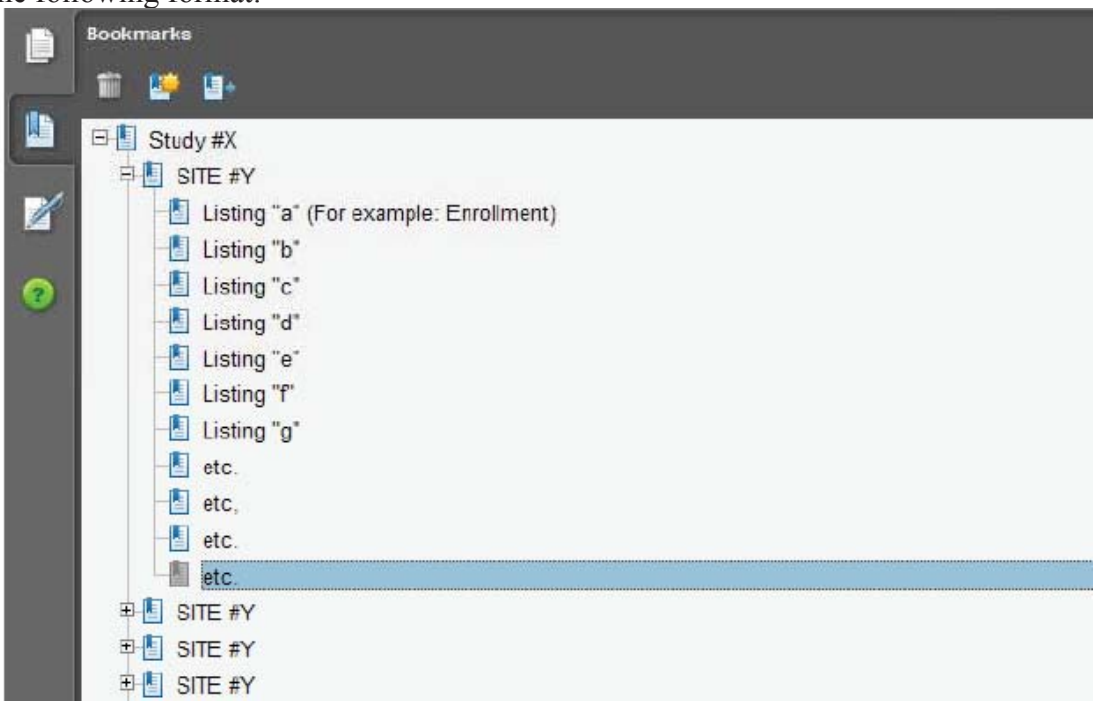
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

WILEY A CHAMBERS
05/16/2017