CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114720

MEETING MINUTES

Ocular Therapeutix, Inc.
Attention: Eric P. Ankerud
Executive Vice President, Clinical, Regulatory and Quality
36 Crosby Drive, Suite 101
Bedford, MA 01730

Dear Mr. Ankerud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTX-DP Dexamethasone punctum plug.

We also refer to the meeting between representatives of your firm and the FDA on April 14, 2015. The purpose of the meeting was to discuss the Phase 3 clinical results of OTX-DP for the treatment of post-surgical inflammation and pain associated with ocular surgery.

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 Ms. June Germain, Safety Regulatory Project Manager at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
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 14, 2015, 12:30 PM to 1:30 PM EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	IND 114720
Product Name:	OTX-DP Dexamethasone punctum plug.
Indication:	treatment of post-surgical inflammation and pain associated with ocular surgery
Sponsor/Applicant Name:	Ocular Therapeutix
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES

Renata Albrecht, MD	Division Director
Wiley Chambers, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Sonal Wadhwa, MD	Medical Reviewer
Martin Nevitt, MD	Medical Reviewer
Lucious Lim, MD	Medical Reviewer
Rhea Lloyd, MD	Medical Reviewer
Phillip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Abel Eshete, PhD	Statistical Reviewer
Yan Wang, PhD	Statistical Team Leader
June Germain, MS	Safety Regulatory Project Manager

SPONSOR ATTENDEES

Amar Sawhney, PhD	President and CEO
Deepa Mulani	Director Clinical Affairs
Eric Ankerud, JD	Executive Vice President, Clinical, Regulatory
Elizabeth McMeniman	Manager, Regulatory Affairs
Swati Sane	Director, Data Management and Biostatistics
(b) (4) (b) (4)	(b) (4) Consulting (b) (4) (b) (4)

1.0 BACKGROUND

OTX-DP is a corticosteroid indicated for the treatment of inflammation and pain following ocular surgery. An End-of-Phase 2 meeting was held on September 13, 2013. On January 8, 2015, Ocular Therapeutix submitted a request for a pre-NDA meeting to discuss the safety and efficacy data from the Phase 2 trial and the two Phase 3 trials. A meeting was granted for April 14, 2015. On March 12, 2015, Ocular Therapeutix submitted a briefing document that provided background information in support of the meeting. On April 3, 2015, Ocular Therapeutix On April 7, 2015, the Division issued preliminary comments in response to the clinical questions posted in the briefing document.

2.0 DISCUSSION

Question 1.

Does the Agency agree that the clinical studies and efficacy data are sufficient to support an NDA for the OTX-DP for the treatment of inflammation and pain following ocular surgery?

FDA Response: *The summary of the efficacy data submitted the meeting package appears acceptable for a NDA filing. The determination of whether the data is sufficient for NDA approval is a review issue and can only be made once a complete NDA is submitted.*
In the briefing package, the co-primary efficacy endpoints are listed as the proportion of eyes with absence of chamber cells at Day 14 and the proportion of eyes with absence of ocular pain at Day 8. Please confirm if the outcomes from the study eyes only are used in the primary efficacy analyses.

Meeting Discussion:

- The sponsor confirmed that the outcomes from the study eyes only are used in the primary efficacy analyses.

Question 2.

Does the Agency agree that the clinical studies and safety data are sufficient to support an NDA for the OTX-DP for the treatment of inflammation and pain following ocular surgery?

FDA Response: *On p. 12 of the meeting package, you provide what safety elements are collected but you do not specify at what time points. Additional detail is needed to better understand the safety data being collected.*
In addition, we recommend endothelial cell count studies with baseline and 3 month data collected on patients in both active and vehicle groups. Also, as stated in the EOP2 meeting on 9/13/13 we recommend that you follow subjects with retained punctal plugs until the plugs are no longer present.

Meeting Discussion:

- The sponsor noted that the PK study has been completed. However, endothelial cell count studies were not assessed. The Division recommended that a justification for not including the endothelial cell count be included at the time of NDA submission.
- The sponsor stated that throughout the study subjects were followed and exited the study only after the absence of the plug was confirmed.

Question 3.

Does the Agency agree with the pooling and analyses strategies for the ISE and ISS?

FDA Response: *We agree with the proposed pooling of data for the integrated summaries. However, we also need the results and data for each study separately.*

Does the Agency agree that the proposed subgroup analyses for the ISE and ISS are appropriate and sufficient?

FDA Response: *We agree with the proposed subgroup analysis for the ISE and ISS. Please perform the subgroup analysis for each study separately as well. Please also include subgroup analysis by region (US versus Others) if applicable.*

Meeting Discussion:

- The sponsor agreed to submit the results and data of each study separately in addition to ISE and ISS.
- The sponsor noted that studies were only conducted in the US and as such subgroup analysis by region were not applicable.

Question 4.

Does the Agency agree with the proposed format for submitting raw data for the individual clinical studies, as well as the format for analysis datasets for studies included in the ISE and ISS?

FDA Response: *Agree*

Meeting Discussion:

- The Division requested the sponsor submit the SAS codes used to generate the files; the sponsor agreed.

Question 5.

Does the Agency agree with the proposed approach for determining adverse events to be included in the package insert for OTX-DP?

FDA Response: *This appears acceptable; however final decisions regarding labeling are a review issue.*

Meeting Discussion:

- In order to support an inflammation indication, the Division recommended the sponsor conduct a 3rd Phase 3 trial to gather additional inflammation data and confirm the previous trial results. It would be the sponsor's choice concerning when to submit an NDA for a post-operative pain indication.

- The Division stated that the next trial could be shorter in duration, could be randomized 1:1, could exclude NSAIDS and could use some of the same trial sites used the previous study.

3.0 Post meeting clarification question from the sponsor regarding the hierarchical nature of the co-primary endpoints of inflammation and pain, with the inflammation endpoint being assessed first and then evaluation of the pain endpoint:

1. Does FDA agree that the pain endpoints from the OTX-DP Phase 2 and both Phase 3 clinical trials are appropriate to support an NDA approval for a pain only indication for use?

FDA Response:

The pain endpoints from the Phase 2 and two Phase 3 trials would support a NDA filing for a pain-only indication; approval is a review issue requiring submission and review of a NDA.

2. Does FDA agree (b) (4) **in the review of an NDA seeking approval for OTX-DP with a pain only indication?**

FDA Response:

No, we do not agree (b) (4)

4.0 Meeting Handouts

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/s/

WILEY A CHAMBERS
05/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114720

MEETING MINUTES

Ocular Therapeutix, Inc.
Attention: Eric Ankerud, J.D
Executive Vice President, Clinical, Regulatory and Quality
36 Crosby Drive, Suite 101
Bedford, MA 01730

Dear Mr. Ankerud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTX-DP Dexamethasone punctum plug.

We also refer to the meeting between representatives of your firm and the FDA on August 26, 2014. The purpose of the meeting was to discuss the proposal for a steroid class label for OTX-DP with cumulative study results from Phase 3 trials.

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 Ms. June Germain, Safety Regulatory Project Manager at (301) 796-4024.

Sincerely,

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Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
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: CMC Pre-NDA

Meeting Date and Time: August 26, 2014 3:00 PM to 4:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 114720
Product Name: OTX-DP Dexamethasone punctum plug
Indication: treatment of post-surgical inflammation and pain associated with ophthalmic surgery
Sponsor/Applicant Name: Ocular Therapeutix

Meeting Chair: Wiley A. Chambers
Meeting Recorder: June Germain, MS

FDA ATTENDEES

Wiley Chambers, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Sonal Wadhwa, MD	Medical Reviewer
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer
George Lunn, PhD	Product Quality Reviewer
Balajee Shanmugam, PhD	Product Quality Team Leader
Jessica Cole, PhD	Product Quality Microbiologist
Angelica Dorantes, PhD	Biopharmaceutics Team Leader
Solomon Chefo, PhD	Statistical Reviewer
June Germain, MS	Safety Regulatory Project Manager

SPONSOR ATTENDEES

Amar Sawhney, PhD	President and CEO
Eric Ankerud, J.D	Executive Vice President, Clinical, Regulatory & Quality
Arthur Driscoll	Vice President, Product Development
Michael Bassett	Associate Director, Development
Chuck Blizzard	Director, Formulations Science
(b) (4)	Consultant to Ocular Therapeutix

1.0 BACKGROUND

On June 5, 2014, Ocular Therapeutix requested a meeting to discuss the proposal for a steroid class label for OTX-DP with cumulative study results from Phase 3 trials in the treatment of ocular inflammation and pain associated with ocular surgery (b) (4) A meeting was granted for August 26, 2014. On July 2, 2014, Ocular Therapeutix submitted a briefing document that provided background information in support of the meeting. On August 20, 2014, the Division issued preliminary comments in response to the clinical comment posted in the briefing document and on August 25, 2014, Ocular stated that for the meeting discussion they were seeking clarification on questions 3, 7 and 9.

2. DISCUSSION

Regulatory

1. Does the Agency agree that the NDA for OTX-DP should be submitted as a 505(b)(2) application?

FDA Response: *It is acceptable to submit as a 505 (b)(2).*

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, in part, 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, in part, 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. trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X*

3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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.

2. Does the Agency agree with the company's plans to request a second pre-NDA meeting to address clinical issues?

FDA Response: *Acceptable.*

CMC

3. Does the Agency agree that the proposed test parameters, test methods and specifications are acceptable to support commercial manufacturing of OTX-DP?

FDA Response: *No, we do not agree with the drug product specification. Please respond to the following comments:*

General Points

To enable us to better understand this product, please provide the following information concerning the manufacturing process.

- *Please provide narrative descriptions of the manufacture of the drug product. These descriptions should include quantities, times, temperatures, and descriptions of the equipment used. Please supply descriptions of the processes used to make Phase 2, Phase 3, and intended commercial product, if there are any differences.*

- *Please provide specifications for the* (b) (4) *used to manufacture the drug product as well as CMC information for any novel excipients.*

Drug Product Specification - Sterility

The drug product specification should include a sterility specification and test method. Sterility or container closure integrity testing should also be conducted on stability to

verify the final product sterility after storage. We refer to our previous comments sent on 05 November 2012 regarding the quality microbiology information to be included in the NDA. Those comments are reproduced here.

1. *The drug product specification should include sterility. While the conduct of a USP<71> sterility test would be acceptable, it is also acceptable to reference the radiation dose (≥25 kGy) as an indicator of sterility. At the time of NDA submission a sterility specification will be required.*
2. *At the time of NDA submission more detailed information should be provided on the sterilization validation studies and validated loading pattern(s). For more information we refer to the following Guidance document. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf*
3. *If parametric release of the drug product is proposed at the NDA stage please refer to the following Guidance document. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072180.pdf*

Meeting Discussion:

- The sponsor agreed to add a sterility specification and stated that they intend to [redacted] (b) (4) Additionally, the container closure integrity is included during stability using bubble point emission testing and a seal leak test.
- The Division stated that full sterilization validation studies as well as a description of the [redacted] (b) (4) should be submitted in the application for review.
- The Division stated that the [redacted] (b) (4) data should also be included in the NDA.

Drug Product Specification – In Vitro Release Test

Regarding the in vitro drug release test, we would like to remind you of our previous advice communications dated May 16 and Nov 5, 2013 and Sep 13, 2013 under the IND, which should be fully addressed in your NDA. Additionally, for setting the vitro drug release acceptance criteria, the following points should be considered:

a. *The specifications for the drug release test should encompass the timeframe over which at least 80% of the drug is released or where the plateau of drug release is reached if incomplete release is occurring.*
b. *Data (n=12) from lots used in the clinical trials and primary stability studies must be used.*
c. *At least three specification time-points should be included covering the initial, middle, and terminal phases of the complete drug release profile data. The acceptance criteria ranges must be based on the overall drug release data generated at these times.*
d. *The selection of the drug release acceptance criteria ranges is based on mean target value +10% and NLT 80% for the last specification time-point. Wider*

specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

Meeting Discussion:

- The sponsor noted that the current dissolution test is a quality control test and not an IVIVC model.
- The sponsor stated that the specifications for drug release capture the timeframe required for a minimum of (b) (4)% of drug release with initial, middle and terminal phases.
- The sponsor also agreed to include data from the clinical trials and registration stability studies to establish the final in vitro specification.
- The Division agreed that the tests appear acceptable and recommended that data to support the proposed acceptance criteria should be included in the NDA along with a justification.

Post Meeting Comment:

Regarding Slides 9 and 10, the following guidelines should be considered when defining the initial, middle, and final profile sampling time points: initial (10-30%), middle (40-60%), and terminal (>80%). Your proposed initial sampling time point occurs at > (b) (4)% dissolution and does not adequately capture the profile. We recommend that you provide complete, multi-point, dissolution profiles in your NDA to support setting appropriate acceptance criteria and note that the recommended range at any time point specification is ± 10%.

Drug product Specification – Other Points

Please also respond to the following questions concerning the drug product specification. Please note that all acceptance criteria are NDA review decisions.

- *Please provide a justification for the test name "* (b) (4) *We suggest something more meaningful and specific such as "Dry dimensions".*

- *For the expansion test the acceptance criterion is "Length of OTX-DP must not increase…" Please clarify if this means that the hydrated plug should be no longer than that dry plug dimension or if it means that the hydrated plug length should not be outside the range* (b) (4) *mm.*

- *Please propose a test for* (b) (4) *particles.*

- *Please propose acceptance criteria for specified impurities, unspecified impurities, and total impurities following the recommendations of ICH Q3B. In this respect please note that we regard USP specifications as minimal specifications and we frequently recommend tighter specifications. In this regard you may find the European Pharmacopeia to be helpful.*

- *Excessive hydrolysis during storage could indicate a changed performance. Please propose tests and acceptance criteria for degradants arising from the hydrolysis of the excipients.*

Meeting Discussion:

- The sponsor agreed that the test name for the product specification with be changed to "dry dimensions".
- The sponsor noted that for the expansion test, the length must not increase compared to dry dimension baseline for each individual plug.
- The sponsor noted that the appearance specification for foreign particulate matter includes (b) (4)
- The sponsor also noted the OTX-DP is neither an ophthalmic solution nor an injectable; therefore tests for the particulate are not applicable. The Division agreed.
- The sponsor agreed to add additional acceptance criteria detailing specified and unspecified impurities
- The sponsor noted that for hydrolysis testing, the hydrogel is susceptible to hydrolysis and they propose to measure water content (b) (4)
- The sponsor noted that the effects of hydrolysis will be captured through performance criteria and measurement of dimensional parameters.
- The Division requested the sponsor provide a report to show how the hydrogel is absorbed in the body and describe the fate of the fluorescein.

4. **Does the Agency agree that since the dexamethasone drug substance is (b) (4) OTX-DP as provided by the manufacturer which tests it to meet USP specifications by USP analytical methods and Ocular Therapeutix tests the incoming drug substance for several test parameters to meet USP specifications and confirms other specifications as listed on the incoming Certificate of Analysis, no additional testing is necessary to support the drug substance?**

FDA Response: *Please note that all specifications are NDA review issues. Generally the USP specification is a minimum quality standard and we expect drug substance specifications to be more detailed.*

In the context of an NDA submission FDA would be prepared to accept testing of incoming dexamethasone using the proposed specification in Table 7 (Page 25) in connection with a manufacturer's Certificate of Analysis such as that provided by (b) (4) *(Appendix D) which contains the results of testing for particle size, microbial limits,* (b) (4) *, residual solvents, specified impurities, and unspecified impurities. Such material should be used before the retest date given in the Certificate of Analysis. In this context the Certificate of Analysis provided by* (b) (4) *would not be adequate.*

You should show that the proposed drug substance particle size range is appropriate for the correct functioning of the product.

Additionally, your proposed controls during manufacture should ensure the consistency of the API distribution within the plug, as aggregates could impact drug release. It is unclear whether the previously submitted in vitro drug release testing on particle size effects was completed using a test method that was appropriately discriminating to detect meaningful differences and we request that you provide a full assessment in your future NDA. In addition, a clear discussion on the postulated API solid state changes noted upon storage should be included in the NDA.
Please provide the results of a one-time test investigating the in vitro hydrolysis of the drug substance.

Please note that all dexamethasone drug substance CMC information will need to be reference to a DMF and a letter of authorization included in the NDA.

5. Does the Agency agree with the approach for qualification of an alternate API manufacturer?

FDA Response: *In general your proposal seems appropriate. However, detailed information about the dexamethasone manufacturing process used by the new supplier should either be submitted directly by you or by means of a Drug Master File and a Letter of Authorization. In addition, each batch of incoming material should be accompanied by a manufacturer's Certificate of Analysis similar to that provided by* (b) (4) *(Appendix D) which contains the results of testing for particle size, microbial limits,* (b) (4) *, residual solvents, specified impurities, and unspecified impurities. The tests and acceptance criteria may be different given that the alternate manufacturer may use a different manufacturing process. However they should be comparable to those in the* (b) (4) *example. The Certificate of Analysis should contain a retest or expiration date.*

Before commercial distribution you should obtain 3 months of stability data for product made with drug substance from the new supplier.

6. Does the Agency agree with the company's plan to scale up the current pilot manufacturing process within one year following NDA approval by executing a one lot comparability study?

FDA Response: *Your proposal appears generally appropriate. The comparability protocol should be provided in the NDA. Final acceptability and the number of batches necessary is an NDA review decision. The manufacturing process should be validated prior to commercialization.*

7. Does the Agency agree that if the company provides twelve months of refrigerated storage stability data from a single commercial scale lot and two additional commercial scale lots with 6 months of refrigerated data at the time of NDA

submission, it is acceptable for the company to request a minimum of (b) (4) months refrigerated storage shelf life at time of approval?

FDA Response: *The amount of stability data that you propose to provide at the time of NDA submission (Table 9, page 30) is not appropriate. You should provide 12 months of data for 2 batches of at least (b) (4) units. We note that the intended commercial size is (b) (4) units. ICH Q1A recommends that two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified.*

Please note that the acceptability of the data and the proposed expiration dating period of (b) (4) months are NDA review decisions. The acceptability of the stability testing protocol will depend upon reaching agreement concerning the drug product specification.

Meeting Discussion:

- The sponsor stated that the planned commercial scale is (b) (4) units.
- (b) (4)
- The sponsor noted that at the planned time of NDA submission the Phase 2 clinical stability batch will have 20 months of stability data and for the Phase 3 batches lot 1 will have 12 months of stability data, lot 2 will have 6 months of stability data, and lot 3 will have 6 months of stability data
- The Division stated that a report of how each batch was made should be provided in the application.
- The Division noted that it usually requires 3 batches with 12 months of stability data at the time of NDA submission.

8. **Does the Agency agree that photostability requirements for OTX-DP have been adequately addressed?**

FDA Response*: Generally we agree. The final labeling should contain warnings that the package should not be opened until required and that excess exposure to light should be avoided. The results of a one-time in-use study that includes illumination with a blue-light source would be helpful to us.*

9. **Ocular Therapeutix will request a minimum of (b) (4) months refrigerated storage shelf life at time of submission. An additional 6 months of refrigerated data will be accumulated during the NDA review process, totaling (b) (4) months of refrigerated storage shelf life for Stability Lot 1. Ocular Therapeutix intends to use this (b) (4) months of data to extend the shelf life labeling from (b) (4) months to (b) (4) months at time of NDA approval. What is the process for submitting additional stability into the review cycle that would allow for (b) (4) months expiry dating at NDA approval without interruption of the NDA review process?**

FDA Response: *Generally the NDA should be complete at the time of submission. If the NDA is granted priority review status it may not be possible to review additional data submitted during the review cycle. Please also refer to the response to Question 7.*

Meeting Discussion:

- The sponsor inquired into the process for submitting additional stability data during the NDA review cycle. The Division recommended the NDA application be complete at the time of submission.

- The Division noted that an amendment that contains a significant amount of new information that is submitted within three months of the action date is considered a major amendment and can extend the review clock by an additional three months if the Agency decides to review it. The Agency may decide not to review the amendment during that review cycle.

10. Does the Agency agree that if the company evaluates and confirms product performance following exposure to freeze-thaw and simulated shipping and handling conditions, additional excursion studies will not be needed?

FDA Response: *Generally your proposal appears appropriate and the proposed testing may be conducted on a one-time basis. We should prefer freeze thaw cycling to take place with 24 hours at each condition.*

11. Does the Agency agree that since the manufacturers of the OTX-DP container-closure system have performed extraction testing on the packaging materials and Ocular Therapeutix has evaluated OTX-DP in combination with the container closure materials for extractables, no additional extractables and leachables testing is needed?

FDA Response: *Generally your approach seems appropriate but the adequacy of the testing will be an NDA review decision. In the NDA please provide information to show that the packaging materials comply with the relevant 21 CFR sections.*

Please provide the results of a one-time study for extractables from the equipment used to prepare the plugs.

12. Does the Agency agree the Ocular Therapeutix proposal to use a single analytical method to satisfy requirements for both Assay and Content Uniformity?

FDA Response: *Generally your proposal seems appropriate. Please indicate how you will be determining impurities: from the content uniformity runs or from other determinations.*

Additional Agency Comment:

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- *The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products*
- *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 42 important format items from labeling regulations and guidances.*

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

3.0
In addition, we note that a multidiscipline pre-submission meeting is planned for the future. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 ATTACHMENTS AND HANDOUTS

(b) (4)

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/s/

WILEY A CHAMBERS
09/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114720

MEETING MINUTES

Ocular Therapeutix, Inc.
Attention: Eric Ankerud, J.D
Executive Vice President, Clinical, Regulatory and Quality
36 Crosby Drive, Suite 101
Bedford, MA 01730

Dear Mr. Ankerud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTX-DP Dexamethasone punctum plug.

We also refer to the end of Phase 2 teleconference between representatives of your firm and the FDA on September 13, 2013. The purpose of the meeting was to discuss the results of the Phase 2 study and the proposed Phase 3 development plan.

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

If you have any questions, call Ms. June Germain, Safety Regulatory Project Manager at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
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:	End of Phase 2
Meeting Date and Time:	September 13, 2013, 9:00 AM-10:00 AM, EDT
Meeting Location:	Teleconference
Application Number:	IND 114720
Product Name:	OTX-DP Dexamethasone punctum plug
Indication:	treatment of ocular inflammation and pain associated with ophthalmic surgery
Sponsor/Applicant Name:	Ocular Therapeutix
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	June Germain, M.S.

Division of Transplant and Ophthalmology Products/FDA ATTENDEES

Renata Albrecht, MD	Director
Wiley A. Chambers, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Martin Nevitt, MD	Medical Reviewer
Jennifer Harris, MD	Medical Reviewer
Lori Kotch, PhD	Pharmacology/Toxicology Team Leader
Andrew McDougal, PhD	Pharmacology/Toxicology Reviewer
Balajee Shanmugam, PhD	Product Quality Lead
Milton Sloan, PhD	Product Quality Reviewer
Minerva Hughes, PhD	Biopharmaceutics Reviewer
Abel Eshete, PhD	Statistical Reviewer
Dongliang Zhuang, PhD	Statistical Reviewer
June Germain, M.S.	Acting Safety Project Manager

OCULAR THERAPEUTIX ATTENDEES

Amar Sawhney, Ph.D.	President/CEO
Eric Ankerud, J.D.	Executive Vice President, Clinical, Regulatory & Quality
Peter Jarrett, Ph.D	Chief Technology Officer
Suzanne LaScalza, M.S.	Director, Clinical & Regulatory Affairs
Virginia Pappalardo	Senior Regulatory Affairs Specialist
Art Driscoll	Vice President, Product Development

Chuck Blizzard	Director, Formulations Research
Mike Bassett	Associate Director, Development
Deepa Mulani	Manager, Clinical Affairs
Stephen Curwen	Clinical Project Manager
(b) (4)	(consultant to Ocular Therapeutix)

1. BACKGROUND

OTX-DP is indicated for treatment of post-surgical inflammation and pain associated with ophthalmic surgery. On June 24, 2013 Ocular Therapeutix requested an end-of-Phase 2 meeting to discuss the Phase 2 study results and the proposed plans for the Phase 3 development.

2. DISCUSSION

Question 1- Raw materials

Ocular Therapeutix is qualifying a new vendor for manufacture of the (b) (4) raw material component of OTX-DP. Due to differences in the manufacturing processes, the levels and type of (b) (4) in the (b) (4) raw material differ from the (b) (4) for the vendor used in the OTX-DP Phase 2 trial (#114720). The (b) (4) represents approximately (b) (4) % of the final OTX-DP batch formula composition (b) (4)), and the carry-through (b) (4) for both vendors are within USP specifications for the final OTX-DP drug product. Ocular Therapeutix intends to qualify the new vendor of (b) (4) by testing final OTX-DP drug product from three lots to demonstrate the (b) (4) are within specifications in the manufacturing process. Does the Agency agree with this approach for OTX-DP to be used in the Phase 3 studies?

FDA Response:

You intend to obtain the raw material (b) (4) from a new supplier for use in the Phase 3 study drug product. The (b) (4) is formulated at (b) (4) % in a modified release drug product. No change is proposed in the formulation.

FDA agrees with your approach to qualify a new vendor. Based on good scientific principles of stability testing comparative studies should be carried out to assure no change and that the drug product meets the applicable specifications throughout the study. Comparative data, such as COAs, impurity characterizations, and specifications should be submitted.

Meeting Discussion:

- The Division stated that because a new vendor is being qualified for the raw material (b) (4) stability testing comparative data is needed to compare the old drug product to the new drug product.
- The Division also noted that impurity characterization is an example of comparative data. The Division agreed that COAs (certificate of analysis) to compare and the old and new product would be acceptable.

Question 2 – Drug Product Manufacturing
The manufacturing process for OTX-DP employs (b) (4)

(b) (4)

(b) (4) **Does the Agency agree with this approach for OTX-DP to be used in the Phase 3 studies?**

FDA Response:

The uniformity of dosage can be demonstrated either by content uniformity or weight variation in accorded with the USP <905>.

(b) (4)

Meeting Discussion:

No further discussion

Question 3 – Drug Product Specifications
Ocular Therapeutix intends to use the (b) (4) dexamethasone drug substance referenced in the Phase 2 IND (ref DMF# (b) (4)) to support the Phase 3 IND and registration stability studies. Ocular Therapeutix does not intend changes, other than scale of manufacture, to the Phase 2 drug product during Phase 3 and registration stability evaluation. Therefore, since the manufacturing processes are comparable, Ocular Therapeutix intends to (b) (4)

FDA Response:

FDA does not agree (b) (4) *Generally, there are inherent changes in going to full scale manufacture. Prior to making registration batches, a demonstration /process evaluation /validation batch should be minimally manufactured to simulate full production scale and to confirm the pre-determined specifications.* (b) (4) *. Include in your NDA the summary statistics for the datasets analyzed independently and pooled as part of your drug product specification justification.*

Meeting Discussion:

No further discussion

Question 4 – Drug Product Analytical Methods
The proposed in vitro release method was developed to demonstrate the critical quality attributes of the OTX-DP product. The in vitro assay is used to ensure product quality (reproducibility) and safety (i.e. no dose dumping), and is not a test indicative of clinical performance. Additionally, Ocular Therapeutix intends to use non-standard USP dissolution equipment to test release rate of the OTX-DP product, as the USP apparatus are more suited for oral dosage forms. Justification for the use of non-standard USP equipment will be provided in the method development report. Does the Agency agree with this approach?

FDA Response:

Although not a requirement, the FDA highly encourages the development of an in vitro-in vivo relationship (IVIVR) or in vitro-in vivo correlation (IVIVC) model especially for modified release products. The existence of an IVIVR or IVIVC can help in the establishment of a dissolution method that is clinically relevant and in setting wider (e.g. > ± 10% variation) dissolution acceptance criteria, among other advantages. Owing to the unique attributes of your ocular plug product, we agree that a noncompendial apparatus may be better suited for developing a robust method, provided that its discriminating ability is justified (e.g. by showing that the dissolution method is able to reject batches that are not bioequivalent).

In your future IND amendment containing the complete method development report, clearly indicate in the cover letter that the submission includes the dissolution test method development and validation data for Agency review and comment.

Meeting Discussion:

- The sponsor agreed to explore developing an IVIVC; however they note that the process is not straightforward and if a model could be constructed, it will likely be submitted post approval.
- The Division acknowledged the challenges of developing an IVIVC model and noted that sponsors are encouraged but not required to develop an IVIVC model. The Division stated that there are many publications on IVIVC that may provide guidance, including resources on the FDA website. The Sponsor was encouraged to review the published literature then follow-up with the Division with specific IVIVC questions. The Division also stated that it may be appropriate to use a suitable animal model to develop the IVIVC given the design and intended use for the proposed product.

Question 5 – Drug Product Container Closure
Ocular Therapeutix intends to change the (b) (4) of the Phase 2 foam carrier and foil pouch container closure system for Phase 3 to a commercially representative design. The foam carrier will be a (b) (4) (b) (4) Because of the number of units required for the Phase 3 product, (b) (4) version of the same foam material specified for the commercial product

(b) (4) commercial foam piece for the Phase 3 IND and registration stability studies. The foil pouch used for the OTX-DP drug product container closure in stability studies supporting the Phase 3 IND and registration studies will be the commercial foil pouch. Does the Agency agree that use of the representative (b) (4) foam carrier of equivalent composition can be used to support Phase 3 and registration stability configurations?

FDA Response:

Formal stability studies should be performed in the container closure system proposed for marketing.

Stability study data obtained in simulated container closures can be supportive. A determination can be made with full details of the final container closure system and simulated container closure.

Meeting Discussion:

No further discussion

Question 6 – Registration Stability

The OTX-DP drug product is intended for refrigerated storage conditions. Per ICH Q1AR2 guidelines, Ocular will test shelf life of a single pilot batch lot at real time refrigerated conditions (2-8C) and accelerated room temp (25C w/ 60% RH) conditions to support Phase 3 IND submissions. Two additional pilot batch lots will be used to support registration stability shelf life claims. Additional stress and stability testing, such as freeze thaw, oxidation and photo-stability testing per ICH QIB, will be completed prior to NDA submission. Does the Agency agree that the current stability plan is sufficient to support registration?

FDA Response:

The approach appears consistent with the ICH Q1A (R2) guidance. Additionally, you should include a proposed stability protocol for the formal stability studies. The proposed tests should be stability indicating. The test for identification can be performed at release and is not required as part of the stability program.

Meeting Discussion:

No further discussion

Question 7 – Pharmacology and Toxicology

The hydrogel carrier in the OTX-DP product has been used extensively in investigational and commercially approved medical devices including ReSure Sealant (PMA P130004) and DuraSeal Dural Sealant (PMA PO40034) and has a well understood safety profile. As cited in the pharmacology package of the OTX-DP Phase 2 IND (#114720), the safety, efficacy, and distribution of dexamethasone to the ocular surface is well understood. The toxicology study to support Phase 2 evaluated 35 days with a 2-week recovery period. Supporting pharmacokinetic preclinical studies and samples explanted in this toxicology evaluation demonstrate complete drug release by 30

days. The Phase 2 trial results indicate the hydrogel carrier may last longer than this period of time. Because safety of the hydrogel carrier is well understood, complete dexamethasone release was demonstrated in the toxicology evaluation, and no additional safety issues were observed in the Phase 2 clinical evaluation, Ocular Therapeutix proposes using the current Phase 2 IND toxicology study to support Phase 3 IND and NDA submissions. Ocular Therapeutix does not intend to perform additional preclinical safety studies, including carcinogenicity or reproductive toxicology, to support the NDA submission. The OTX-DP product is intended for one time use; therefore, Ocular Therapeutix does not intend to evaluate chronic toxicity. Does the Agency agree that no further preclinical safety testing is required to support an NDA submission?

FDA Response:

Yes, FDA concurs that no additional nonclinical studies are needed to support an NDA for the proposed indication. Please be aware that if changes to the formulation or product sterilization result in new impurities, the safety of those impurities should be addressed.

Meeting Discussion:

No further discussion

Question 8: – Phase 3 Study Design

Does FDA agree that this clinical study plan is sufficient to support NDA approval of OTX-DP for sustained topical ophthalmic delivery of dexamethasone to the ocular surface for the treatment of ocular inflammation and pain associated with ophthalmic surgery?
FDA Response:

The study plan is acceptable to support NDA filing; approval is review issue.

You are proposing two well controlled, prospective, multicenter, randomized, parallel-arm, double masked, vehicle controlled Phase 3 clinical trials to evaluate OTX-DP for the treatment of post-surgical inflammation and pain. The primary study endpoints to be evaluated are: 1) Absence of cells (i.e. score of '0') in the anterior chamber of the study eye at Day 14 and 2) Absence of pain (i.e. score of '0') in the study eye at Day (b) (4). *We recommend that you evaluate absence of pain* (b) (4) *; we would have no objection to evaluation of pain at Day 1.*

Meeting Discussion:

- The sponsor stated they do plan to evaluate pain in the study eye at Day 1; however Day 8 would be the proposed primary study endpoint based on results of the Phase 2 study.
- The Division stated that Day 1 is likely to show a treatment difference; however whichever day is chosen should be a day likely to show a significant treatment difference.

Question 9 – Phase 3 Study Design
Subjects in the Phase 2 clinical trial underwent follow-up visits at post-operative Days 1, 4, 8, 11, 14 and 30. If the punctum plug vehicle was still visible in the canaliculus at Day 30,

subjects returned every 15 days until the punctum plug vehicle was absent. Evaluation of preliminary safety results indicates that there are no safety issues or concerns associated with the punctum plug vehicle being present beyond the thirty day drug delivery period. In addition, the safety of the hydrogel carrier in OTX-DP has been established as a medical device. Subjects in the proposed Phase 3 clinical study will undergo follow-up visits at post-operative Days 1, 8, 14 and 30 (not on Day 4 or Day 11). If the punctum plug vehicle is still visible in the canaliculus at Day 30, subjects will undergo a follow-up visit on Day 45 and if the punctum plug vehicle is still visible in the canaliculus at Day 45, subjects will undergo a final follow-up visit on Day 60. (b) (4) **Does the Agency agree with this proposed follow-up schedule for Phase 3?**

FDA Response:

No. We would recommend that you follow subjects with retained punctal plugs until the plugs are no longer present. For safety reasons, we have an interest in knowing the percentage of subjects who retain plugs past Day 60.

Meeting Discussion:

- The sponsor agreed to follow subjects with retained punctum plug and to appropriately revise the Phase 3 protocol.

Question 10 – Phase 3 Study Design

The Phase II clinical trial included the following co-primary endpoints evaluated at Day 8: 1) absence of anterior chamber cells (i.e., score of "0") and 2) absence of pain (i.e., score of "0"). The proposed Phase III co-primary endpoints include the absence of anterior chamber cells (i.e., score of "0") and absence of pain (i.e., score of "0") in the OTX-DP group compared to the control group at Day (b) (4) **Does FDA agree that** (b) (4) **is an acceptable primary time point to assess absence of inflammation and pain?**

FDA Response:

We recommend that you evaluate absence of pain (b) (4) *; we would have no objection to evaluation of pain at Day 1.*

We understand that subjects who are exited from the study because of a removed or lost punctum will be included in the primary efficacy analysis using the LOCF. We recommend that you perform sensitivity analyses with these subjects set as treatment failures and also using different imputation methods such as multiple imputations for all missing subjects and discuss any noticeable differences in the results of the primary efficacy analysis and the sensitivity analyses.

Meeting Discussion:

No further discussion

Additional FDA comments:

1. *Previous requested information regarding acceptance criteria for level of impurities has not been submitted.*
   Meeting Discussion:
   - The Division referred the sponsor to the May 16, 2012 meeting minutes where it was requested that information on the level of impurities be submitted to the IND.
   - The sponsor noted that the information and characterization at testing with solvent and metals was submitted to the IND. The sponsor also agreed to provide an update concerning this information in an upcoming submission.

2. *Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting.*

   The PSP 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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

   Meeting Discussion:
   - The sponsor stated that cataract surgery is a rare event in the pediatric population and the punctum plug product is not sized for pediatric patients
   - The Division stated that the purpose of PREA is for sponsors to assess the drug product in the pediatric population. The Division also referred the sponsor to the recent approval of Durezol®.
   - The Division stated that efficacy may be extrapolated from the adult study, but a safety study will need to be conducted. The study should enroll at least 30 patients in each arm.
   - The sponsor agreed to revisit how they can address the required pediatric study plan.

3. ACTION ITEMS
- The sponsor agreed to provide an update on impurity levels
- The sponsor agreed to provide initial pediatric study plan

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
10/15/2013