CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217064Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 070499

MEETING MINUTES

Ocuphire Pharma, Inc.
Attention: Barbara Withers, PhD
Vice President Clinical and Regulatory Strategy
37000 Grand River Ave., Suite 120
Farmington Hills, MI 48335

Dear Dr. Withers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for phentolamine ophthalmic solution (POS). We also refer to the meeting between representatives of your firm and the FDA on June 24, 2022. The purpose of the meeting was to discuss the development of POS for indication of "reversal of pharmacologically-induced mydriasis."

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

If you have any questions, call Lois Almoza, MS, Senior Regulatory Health Project Manager at (240) 402-5146.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 24, 2022 from 9:00am – 10:00am (EST)
Meeting Location: Teleconference

Application Number: IND 070499
Product Name: phentolamine ophthalmic solution
Indication: [redacted] reversal of pharmacologically induced mydriasis, [redacted]
Sponsor Name: Ocuphire Pharma, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Lois Almoza, MS

FDA ATTENDEES

Alex Gorovets, MD	Office of New Drugs (OND)/Office of Specialty Medicine (OSM)
Wiley Chambers, MD	Director, Division of Ophthalmology (DO)/OSM
William Boyd, MD	Deputy Director, DO/OSM
Jennifer Harris, MD	Clinical Team Leader, DO/OSM
Lucious Lim, MD	Clinical Reviewer, DO/OSM
Martin Nevitt, MD	Clinical Reviewer, DO/OSM
David Summer, MD	Clinical Reviewer, DO/OSM
Shilpa Rose, MD	Clinical Reviewer, DO/OSM
Ping Ji, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Priya Brunsdon, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
Greg Soon, PhD	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)
Abel Eshete, PhD	Statistical Reviewer, OB/DBIV
Chunchun Zhang, PhD	Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)/Division of New Drug Products (DNDP)/New Drug Products Branch VI(DNDPIII)
Anne Marie Russell, PhD	Product Quality Reviewer, OPQ/ONDP/DNDPIII/NDPB6
Vidya Pai, PhD	Supervisory Chemist, OPQ/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Ash Bekele, PhD	Microbiology Reviewer, OPQ) Office of Pharmaceutical Manufacturing Assessment (OPMA) Division of Microbiology Assessment I (DMAI) Branch III

Mukesh Summan, PhD	Director, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT- RPURM/SM)
Shiny Mathew, PhD	Acting Deputy Director, DPT-RPURM/SM
Maria Rivera, PhD	Pharmacology/Toxicology Reviewer, DPT-RPURM/SM
Deborah Myers, MBA	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)/Office of Medication Error Prevention and Risk Management (OMEPRM)/Division of Medication Error Prevention and Analysis1(DMEPA1)
Kimberly Peters, MS	Biomedical Engineer, OPQ
Bindi Nikhar, MD	Associate Clinical Director, Office of the Commissioner (OC)/ Office of Clinical Policy and Program (OCPP)/ Office of Combination Products (OCP)
Daniel Gottlieb	Senior Regulatory Counsel, Office of Regulatory Policy (ORP)
Judit Milstein	Director, Project Management Staff, Office of Regulatory Operations/Division of Regulatory Operations for Specialty Medicine (ORO/DROSM)
Diana Willard	Chief, Project Management Staff, ORO/DROSM
Lois Almoza, MS	Senior Regulatory Health Project Manager, ORO/DROSM

SPONSOR ATTENDEES

Mina Sooch, MBA.	Chief Executive Officer; Ocuphire Pharma Inc
(b) (4)	Regulatory Consultant; (b) (4)
Barbara Withers, PhD	VP, Clinical and Regulatory Strategy; Ocuphire Pharma Inc
Jay Pepose, MD, PhD	Chief Medical Advisor; Ocuphire Pharma Inc
Mitchell Brigell, PhD	Head of Clinical Development; Ocuphire Pharma Inc
Drey Coleman	VP, Clinical Operations; Ocuphire Pharma Inc
Chris Ernst	Global Head, QA and Manufacturing; Ocuphire Pharma Inc
Daniela Oniciu, PhD	Global Head of R&D, Chemistry & Product Development; Ocuphire Pharma Inc
Laura Gambino	Director, Project Management; Ocuphire Pharma Inc
Ronil A. Patel, MS	Director, Business Development and Market Strategy; Ocuphire Pharma Inc
Charlie Hoffmann	VP Corporate Development and Operations; Ocuphire Pharma Inc
Amar Khatri, MS, MBA	Manager, Market Research and Business Analysis; Ocuphire Pharma Inc
Bindu Manne	Head of Market Development and Commercialization; Ocuphire Pharma Inc
(b) (4)	Medical Advisor; (b) (4)
	Regulatory Consultant; (b) (4)
	Regulatory Consultant;
	CMC Consultant; (b) (4)

(b) (4) (b) (4) CMC Consultant; (b) (4) (b) (4)

BACKGROUND

Ocuphire Pharma, Inc. (Ocuphire) submitted a meeting request on April 21, 2022, to discuss the development of POS for indication of "reversal of pharmacologically-induced mydriasis" in preparation for a New Drug Application submission in late 2022.

DISCUSSION

Following, in **bold**, are the questions submitted in the May 24, 2022, meeting package. The FDA responses to these questions are in *italics.* Discussion that took place during the June 24, 2022, meeting are in regular font.

Chemistry Manufacturing and Controls Questions

1. **Ocuphire has used (b) (4) for analytical support of the development program and for release testing of good manufacturing practice (GMP) materials used in clinical and non-clinical studies, and for testing of the registration stability program samples conducted to date.**

   Ocuphire intends to utilize prior development data generated at (b) (4) in support of the planned NDA. An Official Action Indicated (OAI) classification is currently assigned to (b) (4) with the inspection and final Establishment Inspection Report pending. As a mitigation strategy, transition to an additional laboratory, (b) (4) site, for commercial product release will be conducted according to the technical transfer plan and timeline provided as an appendix (see Appendix 1).

   The technical transfer plan follows United States Pharmacopeia <1224> Transfer of Analytical Procedures and is consistent with Guidance for Industry – Analytical Procedures and Methods Validation for Drugs and Biologics July 2015. Comparability data from both laboratories will be provided in the NDA application at the time of the filing to demonstrate execution of the plan and confirmation of (b) (4) as a suitable alternate commercial product release laboratory as needed.

   a. **Ocuphire acknowledges that ultimate confirmation of the following question is a topic pending full review of the NDA and if significant items with respect to data integrity are identified they would be considered in any approval decision. Ocuphire would like to confirm agreement with the Agency that upon execution of the technical transfer plan provided herein, and demonstration of data comparability, (b) (4) would be a suitable alternate site to support process validation and commercial**

release for the product if the additional laboratory is needed. Does the Agency agree?

FDA Response: Your acknowledgement that the ultimate confirmation acceptability of analytical data generated at (b) (4) *would be pending full review of the NDA is in line with Agency thinking. We cannot review quality agreements and plans for technical transfer and/or their execution. The Agency does not comment either on the 'suitability' of alternate facilities during the IND stage. You can continue to include and qualify alternate facilities as proposed, but at the time of NDA approval, all facilities supporting commercial manufacturing and testing for the NDA need to be compliant.*

b. In the minutes of the Type C Meeting on February 14, 2022, the Agency included a Post Meeting Comment regarding the current OAI status at (b) (4) **Should the status remain unchanged at the time of the NDA application, i.e., the current Official Action Indicated (OAI) remains, due to the** (b) (4) **site having not been reinspected, does the Agency agree that prior development data generated at the** (b) (4) **site is reviewable in the NDA?**

FDA Response: Your acknowledgement that the ultimate confirmation of the prior development data would be pending full review of the NDA and if significant items with respect to data validity or integrity are identified, they would be considered in any approval decision is in line with Agency thinking.

Meeting Discussion:

Ocuphire proposed to keep stability storage at the analytical facility (b) (4) which is currently in OAI status, awaiting inspection and asked about changing to another facility, (b) (4) for their commercial product. FDA advised that a facility that stores drug product stability samples is within scope of FDA facility assessment to support a pending application. FDA advised that an NDA may be submitted, but the acceptability to file or approve will be a review issue.

FDA noted that because the registration stability data from the stability program was conducted at (b) (4) if impacted by data integrity, it may not be reviewable, which could impact acceptability. Another option is to manufacture new lots and place them on stability at a new facility to provide stability data for the NDA.

2. Based on the risk profile of the proposed single entity drug-led combination product (single-use BFS (Blow-fill-seal vial), demonstration of compliance with the device Quality System regulations will be addressed by Ocuphire and (b) (4) **(the commercial manufacturing site), during any potential planned inspection on site. Documentation at the manufacturing site will be available to demonstrate compliance with 21 CFR Part 4 and the device**

Quality Management System (QMS) 21 CFR part 820 following the streamlined approach. The applicable GMP drug manufacturing documentation which supports the device QMS, will be identified in a cross-reference matrix format to indicate the 21 CFR part 820 section they support. The matrix and supporting discussion are included (see Appendix 2). This approach is in consideration of "Guidance for Industry Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4" March 2022.

Ocuphire considers that the reference matrix format outlined herein for presentation of the applicable sections of the device file is adequate to address compliance to 21 CFR Part 820 and 21 CFR part 4 in support of the drug-lead combination product NDA application. Does the Agency agree?

FDA Response: *As described in the Guidance for Industry Certain Ophthalmic Products: Policy Regarding Compliance with 21 CFR Part 4, FDA is evaluating how the 21 CFR part 820 requirements as set forth in part 4 apply to combination products that include single-use blow fill seal ampules that administer the drug directly to the eye. The briefing document on pages 33-34, includes Table 13 Documentation at the Manufacturing Site to Demonstrate Compliance with 21 CFR Part 4 and 21 CFR 820.*

Based on the limited information submitted, your proposal appears adequate. If you need more information for the submission of your application related to this issue, we would be happy to discuss this issue further.

Meeting Discussion:

Ocuphire noted that commercial facilities who manufacture constituent parts of the product (such as the (b) (4) and the (b) (4) will be listed in the Form 356(h). Oversight of those manufacturers of constituent parts as required by 21 CFR part 820 and 21 CFR Part 4 would be as specified by the (b) (4) (b) (4) being the product manufacturer) who directly interfaces with these vendors on behalf of Ocuphire. Ocuphire asked if the Agency agreed that this would be adequate to demonstrate compliance with 21 CFR 820 and/or 21 CFR Part 4? The Agency indicated that the requirements applicable to certain ophthalmic combination products are still being evaluated by the Agency and considering Ocuphire's product as a combination product is a new issue. The Agency is still processing how to handle these products. The Agency suggested that for now, Ocuphire should follow their current proposal (as noted in the FDA response) and guidelines. If there are any changes to these guidelines, the Agency will inform the Sponsor.

3. **Elements of the control strategy for commercial manufacture, packaging and testing of the proposed product is outlined in Section 16.2.1. The strategy is intended to ensure robust manufacture of the product and reproducible**

achievement of the product's quality attributes. Does the Agency concur that the outlined control strategy is adequate for assurance of the identity, purity, strength, safety, and quality of the product at release and throughout its shelf life?

FDA Response: *Your proposed drug substance and drug product specifications appear reasonable at this stage of development. For an NDA submission, upon evaluation of the data submitted, additional tests and/or tightening of the specification may be necessary. As your development proceeds towards an NDA, we have the following recommendations:*

1. *Provide photostability data to support the 30 day in use period when the product is stored out of the pouch.*

Meeting Discussion: Ocuphire described their plans for a (b) (4) day in-use study to evaluate the stability of the product both out of pouch and in an opened pouch at various light and temperature conditions. Ocuphire asked if the Agency concurred that the available photostability data and planned in-use study would adequately support the proposed (b) (4) day in-use instructions? The Agency asked w*hy* (b) (4) *days was chosen for the in-use study.* Ocuphire indicated that it is based on expected use for the product. The Agency felt that (b) (4) days was too arbitrary and recommended testing until product fails.

The Agency indicated that testing should be a combination of both ambient (real world) and ICH testing conditions with the goal of understanding the product as much as possible (i.e., potential conditions; plan for other indications for use). Testing needs to be on product aged in real-time near expiry. A bracketing approach (i.e., early, middle, end) may be proposed. Worst case (near expiry only) may also be acceptable, but is conducted at risk.

2. *Provide foil pouch leak detection data in your drug product stability program.*

Meeting Discussion: Ocuphire confirmed they would provide foil pouch leak detection data in their drug product stability program in the NDA.

3. *Provide a* (b) (4) *risk assessment.*

Meeting Discussion: Ocuphire confirmed they will include a (b) (4) risk assessment in the NDA.

4. *Include minimum fill volume in your drug product specifications.*

Meeting Discussion: Ocuphire indicated that the vial fill volume was controlled (b) (4) (b) (4) The values were 0.31 ± (b) (4) mL. Vials outside this range were rejected. This target fill volume adequately covers the intended dose from each single use vial (one or two drops per eye or approximately (b) (4) mL). Therefore, minimum fill was not a critical product quality attribute and is adequately controlled by

the process parameter setting for vial fill volume. Ocuphire also stated that vials are tested for uniformity of dosage units per USP <905>. The test involved determining the product volume per vial and determining the average fill volume.

Ocuphire proposed that the dosage uniformity test and the fill volume parameter are adequate to control the minimum fill volume and a finished product specification for minimum fill was not required. Ocuphire asked if the Agency concurred with the proposal to omit minimum fill volume from the drug product specifications. The Agency asked that if there is a 0.31 ± (b) (4) mL fill volume, then the minimum fill is (b) (4) why not just list the minimum fill? Ocuphire clarified the intention is to state approximately (b) (4) mL on the label. Content uniformity and minimum fill volume are required specs. The Agency asked how the minimum fill volume is currently being tested if it is based on weight (rather than a volume measurement).

Ocuphire clarified that given the small fill volumes and the fact that phentolamine in solution is a “true solution”, a measurement based on weight was more accurate. Ocuphire further clarified that weight measurements are done after the fill; if fill weights were “off” the product was rejected. Ocuphire asked if they could declare a minimum fill volume on the label using a minimum fill volume spec based on a weight measurement. The Agency noted that is a review issue.

5. *Include assay of phentolamine mesylate as an in-process test for bulk formulation with appropriate specification.*

We note that the Blow-fill-seal (BFS) primary containers are 100% leak tested prior to pouching during the in-process testing using a “Manual test method.” However, the stated “Manual test method” used to test the integrity of the BFS container closure system is not clear. Note that the BFS containers are expected to be subjected to 100% leak testing with a reliable and sensitive method capable of identifying defective units (i.e., leakers). It is expected that the NDA submission include a description of the specific test method, the acceptance criteria, limit of detection along with validation data. The acceptability of the test method and the validation data will be determined during the NDA review. For additional information, see Appendix 2: Blow-Fill-Seal Technology in the FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. 2004.

Additionally, the release specification includes container closure integrity testing; however, the test method stated as “USP <1207>” and the acceptance criteria are not clear. In the NDA submission, the release specification should include the specific method (i.e., dye or microbial ingress, vacuum decay, etc.) and the acceptance criteria used to differentiate integral and non-integral BFS units.

For additional information, refer to the following two guidance documents regarding the Agency’s expectations for filing an NDA submission for aseptically filled including

blow-fill-seal products.

- *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. 2004*
- *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.*

Meeting Discussion: Ocuphire clarified Phentolamine Ophthalmic Solution was a true solution and was homogenous once the active pharmaceutical ingredient (API) was fully dissolved. The manufacturing process parameters such as (b) (4) (b) (4) (b) (4) throughout the manufacturing process. Similar testing would be performed during process validation prior to commercialization.

Therefore, Ocuphire believed an in-process phentolamine mesylate assay test for the bulk formulation was not required to assure product potency and quality. Ocuphire asked if the Agency concurred with the proposal to omit (b) (4) (b) (4) of phentolamine ophthalmic solution? The Agency indicated that it is a review issue and for the Agency to fully understand, all details should be included in the NDA.

Regarding leak testing Ocuphire emphasized that they were (b) (4) (b) (4)

Ocuphire plans to provide a full description of these methods in the NDA submission and asked for Agency agreement. The Agency stated that this is a review issue.

Nonclinical Questions

4. **The non-clinical development program is described in Section Error! Reference source not found.. Completed studies at the time of NDA submission include repeat dose ocular non- Good Laboratory Practice (GLP) toxicology studies in rabbits of up to 10 days dosing duration, GLP-compliant 28-day, and GLP 6-month ocular toxicology studies in Dutch Belted (pigmented) rabbits.**

Given that the proposed clinical dosing is a single administration of 1 to 2 drops to be instilled in each dilated eye following the completion of the ophthalmic examination to reverse the mydriasis (i.e., acute), does the Agency agree that the Sponsor's non-clinical development program is sufficient to support the NDA?

FDA Response: *Agree.*

Meeting Discussion: None

Clinical Pharmacology Questions

5. **The Sponsor plans to fulfill the requirements for clinical pharmacology and pharmacokinetic (PK) data for the planned NDA for POS via the following:**
    - **PK characterization of the to-be-marketed formulation in the OPI-NYXRM-302 (MIRA-3) Study**
    - **Drug-Drug Interactions and Use in Specific Populations (pregnancy and lactation) from the listed drug (OraVerse)**
    - **Use in Specific Populations (pediatric use) from the MIRA-4 pediatric study**
    - **Mechanism of Action (ocular; reversal of mydriasis) from peer-reviewed literature and POS clinical trials.**

    Does the Agency agree that the clinical pharmacology program is sufficient and that no additional clinical pharmacology or pharmacokinetic studies beyond those outlined herein will be required to support the proposed indication and acceptance for review of the NDA?

FDA Response: Agree.

Meeting Discussion: None

6. **The POS NDA is being submitted for approval via the 505(b)(2) regulatory pathway and relying on the listed drugs, Regitine (NDA 008278) and OraVerse (NDA 022159) to support elements of the nonclinical and clinical safety and clinical pharmacology of phentolamine.**

    Findings in the nonclinical 6-month GLP ocular toxicology study in rabbits demonstrated phentolamine systemic exposure levels less than those with OraVerse (administered by submucosal administration) or less than when administered intravenously (Regitine). Interpretation of the preliminary PK data from the MIRA3 clinical study suggests that plasma concentration curves following topical ophthalmic administration of phentolamine for independent patients are lower than those observed with the OraVerse data. Therefore, to justify reliance on the proposed listed drugs, the Sponsor's proposed bridging strategy is to conduct a "scientific bridge" to demonstrate lower systemic

exposure from the POS product compared to historical exposure data from the listed drugs (submucosal or IV/IM phentolamine).

Does the Agency agree that the Sponsor may bridge to the listed drugs by demonstrating lower systemic levels of phentolamine in Sponsor studies of POS compared with historical data for the listed drugs?

FDA Response: Agree.

As described in table 17 of the briefing package, you are proposing to utilize information from the OraVerse clinical pharmacology review to establish a bridge with FDA's previous findings for the listed drug. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs (see 21 C.F.R. 314.430(e)(2)). The Summary Basis of Approval and FDA reviewers' public summaries, however, do not constitute full reports of investigations. A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug. If the OraVerse study information you seek to utilize are described in the listed drug's labeling or the published literature, you may be able to reference those sources.

Meeting Discussion: None

Clinical Questions

7. **Ocuphire proposes not to include an ISS in the NDA. However, an integrated safety analysis of all relevant completed clinical studies, the content of which is described further in Section 19.4, will satisfy the requirements of an ISS. The structure proposed for presentation of the pooled safety analyses in this application is as follows:**

    - **A text summary will be provided in Module 2.7.4 (Summary of Clinical Safety)**
    - **Appendices (tables, listings, and figures) and datasets will be included in Module 5.3.5.3.**

    Does the Agency agree with the proposed integrated safety analysis and the presentation of the analyses in the NDA?

    FDA Response: The Agency has no objection to the proposed integrated safety analysis and the presentation of the analyses in the NDA.

    Meeting Discussion: None

8. **Ocuphire proposes not to include an ISE in the NDA. However, a pooled analysis of the two pivotal Phase 3 studies (OPI-NYXRM-301 and OPI-NYXRM-302) will be conducted using a hierarchical analysis of RM endpoints and included in the NDA and will satisfy the requirements of an ISE. The structure and location in the NDA of the components of the pooled analysis is as follows:**

- **A text summary will be provided in Module 2.7.3 (Summary of Clinical Efficacy)**
- **Appendices (tables, listings, and figures) and datasets will be included in Module 5.3.5.3.**

a. Does the Agency agree with the proposed integrated efficacy analysis and the presentation of the analyses in the NDA?

FDA Response: *Analysis of the pooled data is acceptable provided the study reports, data and relevant SAS codes are presented for each individual study separately.*

Meeting Discussion: None

b. Does the Agency agree that statistical findings from the hierarchical analysis of the pooled data (b) (4)

FDA Response: *No.* (b) (4)

(b) (4)

(b) (4)

Meeting Discussion: (b) (4)

(b) (4)

9. The structure and content for the BIMO data and files is provided in Section 20.3.

Does the FDA agree with the proposed NDA location and content for the BIMO data files?

FDA Response: *Agree*

Meeting Discussion: None

Regulatory Questions

10. **Ocuphire plans to submit an NDA for POS for the "reversal of pharmacologically-induced mydriasis" indication via the 505(b)(2) regulatory pathway which was confirmed as the appropriate pathway by the Agency in the End-of-Phase 2 (EOP2) Meeting Minutes, (Reference ID: 4617304, response to question 18).**

    The Sponsor proposes to establish a scientific bridge (see question 6) through the demonstration of lower phentolamine exposure between the proposed topical ophthalmic product and the approved listed drugs, OraVerse (NDA 022159; Setptodont, Inc) and Regitine (NDA 0080278; Novartis).

    For the POS NDA and as detailed further in Section 20.1, the Sponsor proposes to rely on the following information to support product approval:

    - **Nonclinical**
        - **Nonclinical safety information from Sponsor-conducted nonclinical studies**
        - **Nonclinical safety information from the approved labeling for the listed drugs, OraVerse and Regitine**
        - **Nonclinical safety information from published literature**
    - **Clinical Pharmacology**
        - **Clinical pharmacology information from Sponsor-conducted clinical studies**
        - **Clinical pharmacology information from the approved labeling of the listed drugs, OraVerse and Regitine**
        - **Clinical pharmacology safety information from the published literature (ocular mechanism)**
    - **Clinical Safety**
        - **Clinical safety information from Sponsor-conducted clinical studies**
        - **Clinical safety information (systemic) from the approved labeling of the listed drug, OraVerse**
    - **Clinical Efficacy**
        - **Clinical efficacy information from Sponsor-conducted pivotal studies (MIRA-2 and MIRA-3)**

- **Chemistry Manufacturing and Controls**
  - **Sponsor-generated pharmaceutical development data**

Based on the information provided herein, will the Agency confirm that the Sponsor's proposed plan for data reliance appears to be appropriate for the submission of the POS NDA submitted in accordance with part 505(b)2 of FD&C Act?

FDA Response: *Acceptable.*

Meeting Discussion: None

11. **Ocuphire is not planning to submit a Risk Evaluation and Mitigation Strategy (REMS). Phentolamine has been approved in the United States (US) since 1952 (Regitine®, NDA 008278), and hence has a well-established and well understood systemic safety profile. Furthermore, for the indication understudy, POS is administered as a single dose in the doctor's office. Ocuphire does not consider a REMS for this NDA to be necessary.**

    Does the Agency agree a REMs is not necessary for this NDA?

    FDA Response: *The Agency does not anticipate requesting a REMs for this NDA at this time.*

    Meeting Discussion: None

12. **The proposed content and electronic Common Technical Document (eCTD) structure of the NDA is presented in Section 20.1.**

    Does the Agency have any overall comments on this proposed content and eCTD structure of the NDA?

    FDA Response: *The Agency has the following additional comments.*

ADDITIONAL INFORMATION
(I). DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)
From a medication error perspective, we concur that you do not need to submit human factors such as a comparative analysis, use-related risk analysis, or data from a human factors validation study to support the marketing application at this time.

(II). Combination Product comments:

a. For location of information on the device constituent part see the FDA eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" October 2021 accessible at

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

b. In your future submission, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.

c. For general information on discussing the combination product and its constituent parts, see FDA guidance on Requesting FDA Feedback on Combination Products (December 2020) accessible at https://www.fda.gov/media/133768/download.

Meeting Discussion: Ocuphire asked if there was a reason for mentioning the October 2021 version of the "Guidance for Industry Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" which has been superseded. The Agency clarified that citing the October 2021 Guidance (instead of the most current version) was in error.

Ocuphire confirmed that in the NDA they will be compliant with the requirements for combination products in the most current version of the Technical Conformance Guide at the time of submission.

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

/s/

WILEY A CHAMBERS
07/20/2022 01:23:44 PM

IND 070499

MEETING REQUEST-
WRITTEN RESPONSES

Ocuphire Pharma, Inc.
Attention: Mina Sooch
CEO
37000 Grand River Ave
Suite 120
Farmington Hills, MI 48335

Dear Ms. Sooch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Phentolamine Ophthalmic Solution. We also refer to your April 23, 2021, correspondence requesting a meeting to the CMC development plan.

The enclosed document constitutes our written responses to the questions contained in your May 10, 2021, background package. If you have any questions, call Kelly Ballard at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief
Division of New Drug Products III
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: End of Phase 2

Application Number: IND 070499

Product Name: Phentolamine Ophthalmic Solution

Indications: Treatment of [redacted] reversal of pharmacologically-induced mydriasis, [redacted]

Applicant Name: Ocuphire Pharma, Inc.

1.0 BACKGROUND

The purpose of the requested meeting was to discuss the Sponsor's CMC development plan.

2.0 QUESTIONS AND RESPONSES

Question 1:
The Sponsor has provided information on the control of the Drug Substance (DS), phentolamine mesylate, USP, which is under DMF # [redacted] in the briefing package. The DMF is active, and a Letter of Authorization is on file with the FDA dated June 3, 2019 from the Holder to Ocuphire who is the Applicant of the NDA and Sponsor of the clinical investigations. Phentolamine mesylate, USP is used as drug substance for NDA 008278 Regitine and NDA 022159 Oraverse. The Holder of the DMF, [redacted] has filed annual reports with the FDA, has met the reported stability commitment, and there have been no substantive unvalidated changes. The Sponsor believes that the controls and the Specification for the DS are adequate to support the planned NDA. Does the FDA agree the DS controls are adequate to support the planned NDA?

FDA Response to Question 1:
Comments on the adequacy of the drug substance specification in the DMF will be conveyed to the DMF holder after our review of it in support of your NDA. Provide the following information in your NDA: Authorized reference to the applicable DMF, a brief section on the general properties of the drug substance, regulatory specification of the

drug substance (i.e., for the drug substance upon receipt by the drug product manufacturer), certificates of analysis and/or batch release data of drug substance batches used to manufacture the drug product primary stability batches, information on impurities as per ICH M7 as appropriate for your drug product, retest period, and comparability information on the commercial drug substance and the drug substance used in biobatches of the pivotal clinical studies if there is any significant difference in the synthesis, manufacturing process, or manufacturing facility.

Question 2:

The Sponsor has provided information on the Drug Product (DP) to be produced at (b) (4) (formerly part of (b) (4) The DP will be a sterile, non-preserved product in single-dose blow-fill-seal (BFS) vials for topical administration that maintain sterility. The Sponsor believes that the proposed release and stability specifications are appropriate for the planned NDA. Does the FDA agree with the release and stability specifications presented to support the planned NDA?

FDA Response to Question 2:

The acceptability of your specifications will be an NDA review issue, based on the product characteristics and the data submitted to support the methods and acceptance criteria. We remind you impurities/degradants should be reported per ICH Q3B (R2).

Question 3:

The stability studies conducted to date, at the (b) (4) site, indicate that the drug product packaged in low-density polyethylene (b) (4) vials, (b) (4) and sealed in a foil pouch (see IND SN0025) is stable at refrigerated conditions 5°C/Ambient RH for at least two years (b) (4) (b) (4) Stability studies in BFS vials from a feasibility batch produced at the (b) (4) site are currently ongoing. Although the BFS vial container-closure system includes a foil overwrap to create a container-closure system which is impermeable to moisture and air transmission, the stability program will be conducted at the 25°C/40%RH condition specified for semi-permeable containers, as was previously conducted at the (b) (4) site. Accelerated stability at the 40°C/NMT25%RH condition will also be conducted along with the corresponding intermediate and refrigerated conditions. Does the FDA agree on the use of the stability conditions as specified by ICH Guidelines for semi-permeable containers for ophthalmic drug products in support of the planned NDA?

FDA Response to Question 3:

We agree that the ICH Guidelines for semi-permeable containers set forth in Section 2.2.7.3 of ICH Q1A are appropriate for your BFS container closure system stability studies, e.g., 25°C ± 2°C/40% RH ± 5% RH, 30°C ± 2°C/35% RH ± 5% RH and 40°C ± 2°C/not more than (NMT) (b) (4)% RH. We acknowledge that weight loss is included in your stability protocol.

Question 4:

The (b) (4) site has the capability to perform either manual or automatic leak detection testing on the individual BFS vials depending on whether the specific manufacturing suite is equipped with automatic leak detection equipment and whether the product has been qualified on that equipment. The Sponsor has presented the procedures for both automatic leak detection and manual leak detection and believes that both methods ensure 100% leak detection on the BFS vials. Does the FDA agree that both methods ensure 100% leak detection of the BFS vials?

FDA Response to Question 4:

The FDA agrees that either manual leak detection or automatic leak detection on the BFS vials appears reasonable. It is expected that the NDA submission contains leak test validation data using containers that are representative of production BFS vials. Please note that the final acceptability of the leak test will be determined during the review of the NDA.

Question 5:

The sterility assurance validation program for the BFS DP manufactured at (b) (4) will include:

(b) (4)

Does the FDA agree that this program is acceptable and comprehensive to support the planned NDA?

FDA Response to Question 5:

The overall sterility assurance validation program proposed by the applicant for the manufacturing of the Phentolamine Ophthalmic Solution at the (b) (4) facility appears reasonable. Please note that the final acceptability of the manufacturing process and controls will be determined during the review of the NDA.

Please refer to the to the FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice for validation, monitoring and testing information.

Question 6:
Sponsor intends to use DP from 3 cGMP batch(es) for both clinical and registration functions. The batch(es) will be manufactured and tested identically. A portion of each batch will be packaged in (b) (4) foil to simulate packaging artwork and placed on stability (long-term, intermediate, and accelerated). The remainder of each batch will be packaged in (b) (4) foil to be used for clinical studies. Does the FDA agree that these three batches are acceptable for use in the NDA registration program and as clinical supply?

FDA Response to Question 6:
Since the three cGMP batches were not submitted in your meeting package, we cannot advise on the acceptability of their use in the NDA registration program and as clinical supply. However, we can advise that, in concept, it is reasonable to supply your clinical studies with a portion of your registration batches. If there is any change, they must be treated as individual batches in your quality system and follow standard release and stability programs. And the impact of changes, such as to the immediate package (b) (4) foil versus (b) (4) foil), should be evaluated on release and monitored on stability. If you choose to make no changes, e.g., all (b) (4) foil, then they are not individual batches.

Question 7:
Extractables & Leachables (E&L) testing on the primary container closure system, including the BFS vials and the foil pouch, is required. The E&L program will include the following studies prior to performing leachables testing on stability of 3 batches through expiry:

(b) (4)

(b) (4)

g. Risk assessment evaluation

Does the FDA agree that this E&L program is acceptable to support the planned NDA?

FDA Response to Question 7:
Your proposed extractable and leachable program appears reasonable, except that it is incomplete. We recommend you perform leachables/extractables on the proposed commercial container/closure including (b) (4) *etc. We acknowledge your plan to use screening analytical methods (such as HPLC, GC etc.) and conduct studies on at least three stability batches through expiry. Refer to USP <1663>, <1664> for recommendations.*

Question 8:
Sponsor is planning on providing the following registration batches and supportive stability data at the time of NDA submission:

(b) (4)

Does the FDA agree that the available registration batch and supportive stability data available at time of submission, with the commitment to provide additional data as specified per each stability protocol, is adequate to support the planned NDA?

FDA Response to Question 8:
No, we do not agree with your proposal. We recommend that you follow ICH Q1A(R2) guidance for stability. At the time of submission, the NDA should include release and stability data for three registration batches, manufactured and packaged as proposed for the commercial product in your NDA. The stability data should include results through to at least 12 months under long term storage conditions for each of the three registration batches, as well as in-use and stress studies (photostability, extractables and freeze/thaw), to support your proposed in-use period and expiry. The primary and secondary packaging must be the same as your proposed commercial product. Stability studies should be conducted in the worst-case orientation.

Question 9:
Data presented in the DS DMF # (b) (4) (see question 1 of this document) includes batch history of replicate batches of product on various scales that range from (b) (4) KG to (b) (4) KG, and one batch of (b) (4) KG also reported and with a stability study conducted (see modules 3.2.S.4 Batch Analysis, which conforms to the specification stated in 3.2.S.4, and reported stability in 3.2.S.7). The Sponsor believes that these controls and specifications for the DS, along with continuing manufacturing batch history (e.g., year over year in batch sizes of (b) (4) KG several times a year within specification) are adequate to demonstrate appropriate consistency and reproducibility. The DS is adequate to produce consistent DP that will be demonstrated in 3 DP registration batches. With the understanding of recommended guidelines supporting Registration batches, the Sponsor requests consideration of the following options given the supporting referenced Regulatory File DMF # (b) (4)

A. Utilize DS material from 1 batch record, that would be used to prepare 3 independent DP Registration batches.

b. Utilize DS material from 1 batch record that would be used to prepare DP Registration batch 1. Utilize DS material with a separate batch record that would be used to prepare DP Registration batch 2. A portion of DS material 1 and of DS material 2 would be aliquoted by weight and used to prepare DP Registration batch 3.

Does the FDA agree that the sponsor can proceed with either option 1 or option 2 to provide DS material(s) for the preparation of 3 Registration DP batches to support the planned NDA?

FDA Response to Question 9: *Per ICH Q1A, primary batches of drug product (DP) should be manufactured using different batches of the drug substance (DS), so we do not recommend that you utilize DS material from one batch record to prepare three independent DP Registration batches.*

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

/s/

DANAE D CHRISTODOULOU
06/24/2021 07:55:09 AM

IND 070499

MEETING MINUTES

Ocuphire Pharma, Inc.
Attention: Mina Sooch, MBA
CEO
37000 Grand River Avenue
Suite 120
Farmington Hills, MI 48335

Dear Ms. Sooch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Phentolamine Ophthalmic Solution. We also refer to the telecon between representatives of your firm and the FDA on May 11, 2020. The purpose of the meeting was to discuss the Sponsor's development plan for an eventual NDA submission for one or more indications.

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

If you have any questions, call Lois Almoza, M.S., Senior Regulatory Health Project Manager at (240) 402 - 5146.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: May 11, 2020 from 4:00pm – 5:00pm (EST)
Meeting Location: Teleconference

Application Number: 070499
Product Name: Phentolamine Ophthalmic Solution
Indication: [redacted (b) (4)] reversal of pharmacologically-induced mydriasis, [redacted (b) (4)]
Sponsor Name: Ocuphire Pharma, Inc.
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

Meeting Chair: Wiley A. Chambers, M.D.
Meeting Recorder: Lois Almoza, M.S.

FDA ATTENDEES

Wiley A. Chambers, M.D. Acting Director, Division of Ophthalmology (DO)
William Boyd, M.D. Clinical Team Leader, (DO)
Lucious Lim, M.D. Clinical Reviewer, DO
David Summer, M.D., Clinical Reviewer, DO
Chunchun Zhang, Ph.D., Product Quality Team Leader, Office of Product Quality (OPQ)
Sithamalli Chandramouli, Ph.D., Chemist, CMC – Drug Substance Reviewer/ONDP, Division of New Drugs API.
Catherine Gilbert, Ph.D., Product Quality Microbiology Reviewer, OPQ
Lori Kotch, Ph.D., Nonclinical Supervisor, Division of Pharm/Tox of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT-RPURM)
Maria Rivera, Ph.D. Pharm/Tox reviewer, DPT-RPURM
Yunfan Deng, Ph.D. Mathematical Statistician
Priya Brunsdon, Pharm.D. Clinical Pharmacology Reviewer, Division of Immunology and Inflammatory Pharmacology (DIIP)
Lois Almoza, M.S. Senior Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine

SPONSOR ATTENDEES

Ocuphire Pharma, Inc.(Ocuphire)
Kostas Charizanis, Ph.D., R&D/Clinical
Charlie Hoffmann, M.B.A., Operations/Finance
Reda Jaber, M.D., M.B.A., Clinical/Operations
Seth Klapman, M.B.A., R&D/Clinical

Richard Messmann, M.D., M.H.S., M.Sc., R&D/Clinical
Al Meyer, M.B.A., Board Director
Mina Sooch, M.B.A., President and CEO, Board Director
Jonah Yousif, R&D/Clinical
(b) (4)

BACKGROUND

Phentolamine Ophthalmic Solution (POS) is intended for topical use (b) (4) (b) (4) POS is a sterile solution comprised of the drug s Phentolamine Mesylate, USP; mannitol, USP; Sodium Acetate Trihydrate, USP; water for injection, USP; and reagents to adjust the pH ((b) (4) Sodium Hydroxide, NF and (b) (4) Hydrochloric Acid, NF). The formulation is preservative-free. With regard to clinical trials completed to date, the Phentolamine Mesylate drug product has been packaged in a single-use low-density (b) (4) with a (b) (4) as the primary container closure system.

DISCUSSION

Following, in **bold** font, are the question in the March 17, 2020, Meeting Package. The FDA response to these questions are in *italic* font. Discussions that took place during the May 11, 2020, teleconference are in regular font.

Chemistry, Manufacturing and Control:

1. **(From IND Amendment SN#0016, 15 October 2019, page 9, in response to the Agency's IND review comments dated August 31, 2011 and request to provide justification of some specifications): "Ocuphire recognizes that USP <905> Uniformity of Dosage Units is a test applicable to dosage forms packaged in single-unit containers and should be implemented for the drug product Phentolamine Mesylate Ophthalmic Solution (PMOS). Does the agency agree that this test and associated acceptance criteria may be implemented at such time as the registration stability program is initiated?"**

FDA Response:
Yes, implementing USP <905> test for the proposed drug product (by weight variation) at time your stability program is initiated appears reasonable.

Meeting Discussion: None

2. **(From IND Amendment SN#0016, 15 October 2019, page 9, in response to the Agency's request to implement a specification for endotoxins - FDA comment #14 of communication dated 31 August 2011): "Does the agency agree that the Bacterial Endotoxins Test (BET) is not required as part of the specifications for Phentolamine Mesylate (b) (4) 1% ophthalmic solution in light of the current guidelines?"**

FDA Response:
Yes, we agree that the BET is not required for a topical-use, ophthalmic solution.

Meeting Discussion: None

3. **(From IND Amendment SN#0016, 15 October 2019, page 13, in reference to the Agency's requests for additional CMC information - Pre-IND meeting minutes, May 25, 2005): "Does the agency agree that a specification for (b) (4) is not necessary if the drug substance suppliers provide a specification for appropriate in-process impurities?"**

FDA Response: You reference two different vendors with DMFs as your drug substance source. Of those, you have stated in your 10/15/2019, IND amendment (SD 22) that one vendor (with DMF (b) (4) uses (b) (4) with a (b) (4) ppm limit in the drug substance specification. This is acceptable at this stage.

For the second vendor (with DMF (b) (4), after review of all the recent DMF amendments we are not able to find any in-process control information or drug substance specification and batch analysis data showing how (b) (4) and (b) (4) (b) (4) levels are controlled. Provide that information in the briefing package for the proposed CMC-specific End of Phase 2 meeting; or, ask the DMF holder to provide the information in an amendment to the DMF.

Meeting Discussion: None

4. **In our IND Amendment SN#0016, 15 October 2019, we answered several questions from FDA during the development of this product. These were comments #11−#19 (Section 1.11.1.2.2 and 1.11.1.2.3). Does FDA concur that the Sponsor has addressed those questions adequately?**

FDA Response:
Yes, the previous questions have been addressed (or committed to) adequately at this stage of development.

Meeting Discussion: None

5. **To date, the container-closure system used by th a single-use low-density (LDPE) and a with a mL fill volume specification, while the label claim for the drug product packaging is mL. The proposed drug product for the latter Phase 3 is intended to be packaged in a blow-fill-seal (BFS) container closure system made of a similar LDPE with an aluminum foil overwrap impermeable to water and oxygen. The change to a BFS container closure system provides for technological improvements in the packaging, while reducing the excess fill volume. To support the BFS container closure system, the Sponsor intends to provide data supporting the protective properties, compatibility, safety, and performance in the NDA such as sterility assurance, evaluation of extractables/leachables, and delivered volume in accordance with FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics. Does the Agency agree that this data is sufficient to support the implementation of the BFS as the new container closure system? We intend to request a CMC focused Type B meeting to further discuss these topics.**

FDA Response:
The data supporting the change in container closure system (CCS) should be provided in an IND quality amendment to facilitate the proposed CMC-only EOP2 meeting.
In addition, specifically include the following test on CCS in accordance with added USP reference:

a. Freeze-thaw cycling studies (3 cycles)
b. Weight loss through expiry on primary stability batches
c. Leachables/extractables on container/closure system (including primary and, secondary packaging components such as etc. on at least three stability batches through expiry, Refer to USP <1663> and <1664> for recommendations.

From the quality microbiological perspective, the proposal to use BFS as the new container closure system appears reasonable, however the adequacy of these data to support the use of the BFS is a review issue. An IND amendment should be provided prior to making this cha
manufacturing process

Meeting Discussion: None

6. **In IND Amendment SN#0016, 15 October 2019, Table 2, page 7, The Sponsor discloses the Release Specifications of its Drug Product PMOS for both 1% (also referred to as 0.75% Phentolamine Ophthalmic Solution, or POS) (b) (4) (b) (4) Does the Agency agree that the release specifications presented in that amendment (and replicated in this briefing document) are acceptable for the release of the Phase 3 clinical material, irrespective of packaging modifications (BFS instead of (b) (4) ?**

FDA Response:
The proposed specifications seem reasonable at this stage of development. For an NDA submission, upon evaluation of the data submitted, additional tests and/or tightening of the specification may be necessary. We recommend that you report degradants in the drug product specification per ICH Q3B(R2) guideline (i.e., specified unidentified, specified identified, unspecified, and total degradation products).

The provided release specification regarding the microbiological quality of the drug product appear reasonable.

Meeting Discussion: None

7. **In IND Amendment SN#0016, 15 October 2019, Table 3, page 11 the Sponsor d (b) (4) oses the current Stability Specifications of its Drug Product PMOS for (b) (4) 1% (also referred to as 0.75% POS) (b) (4) (b) (4) Does the Agency agree that the stability specifications presented in Table 3 in that amendment (and replicated in this briefing document) are acceptable for Phase 3 clinical material, irrespective of packaging modifications (BFS instead of (b) (4) ?**

FDA Response:
Refer to the response to Question #6.

Meeting Discussion: None

Nonclinical

8. (b) (4)

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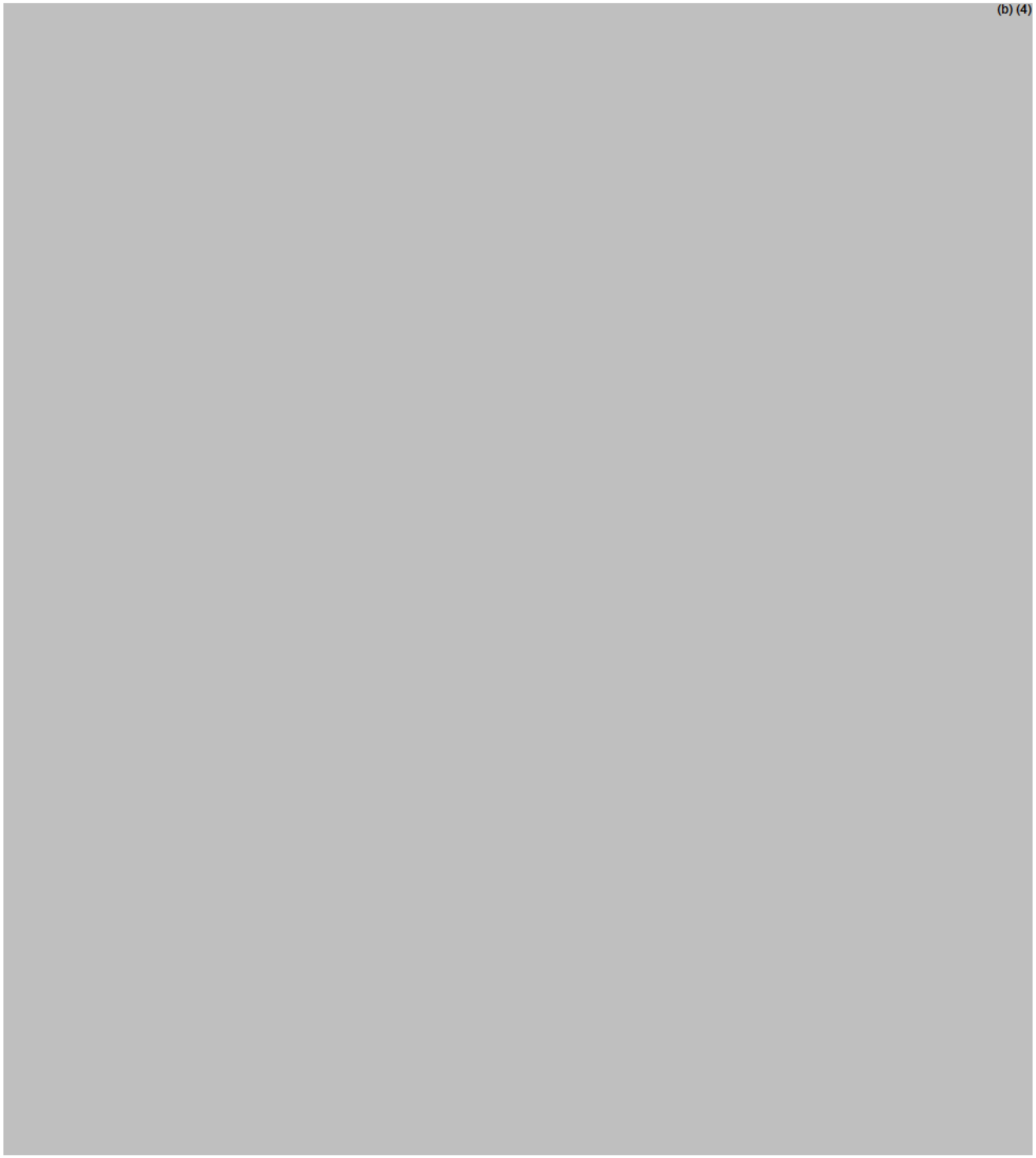

11. **Reversal of pharmacologically-induced mydriasis: The Sponsor intends to evaluate POS for the indication "the treatment of pharmacologically-induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination thereof." In pivotal clinical studies, primary efficacy will be determined using a**

continuous analysis of pupil size at a single time point after instillation of POS (e.g., 2 hours) in a pre-designated study eye.

a. Efficacy would be concluded if there was a statistically significant improvement of POS over placebo. Other time points will be measured as secondary measures. Does FDA concur?

FDA Response:
Potentially. We may have further comments when the full protocol and statistical analysis plan are submitted to the IND.

The Agency has the following comments on study design for studies evaluating reversal of pupillary dilation:

i. Safety and efficacy are expected to be demonstrated in at least two adequate and well-controlled trials.

Meeting Discussion: None

ii. To demonstrate efficacy, we expect the study drug treatment group to demonstrate a statistically significant difference in the number of patients who have a pupillary diameter that returns to its baseline (within 0.2 millimeters of baseline) under defined and controlled lighting conditions as compared to the vehicle group.

Meeting Discussion: None

iii. We recommend that efficacy in reversing pupillary dilation be demonstrated within 60 minutes of product administration and that duration of the treatment effect be evaluated.

Meeting Discussion: Ocuphire asked if efficacy in reversing pupillary dilation could be demonstrated within 90 minutes of product administration and that duration of the treatment effect be evaluated rather 60 minutes recommended by the Agency. The Agency strongly preferred 60 minutes or less.

iv. *Safety evaluations are expected to continue for at least 1 days after the end of the treatment effect.*

Meeting Discussion: None

v. *The study population is expected to include adult and pediatric subjects.*

Meeting Discussion: None

vi. *Randomization should include stratification for baseline factors, including iris pigmentation which can significantly impact the outcome.*

Meeting Discussion: None

vii. *If repeated use in the same eye is planned, endothelial cell count examinations should be performed in a minimum of 100 eyes at baseline and at the end of a trial in one study of at least 6 months duration. The baseline endothelial cell count examination should be compared with the 6-month examination of eyes treated with the proposed drug product.*

Meeting Discussion: Ocuphire asked if they needed to look at endothelial cell counts for this acute indication of reversal of mydriasis since there will only be a one-day application at time of eye examination. The Agency stated probably not, assuming the only indication being sought was an acute use such as reversal of mydriasis.

b. The Sponsor intends to evaluate accommodation as a secondary efficacy endpoint. The Sponsor considers that efficacy would be shown by statistically significant improvement of POS over placebo in a categorical analysis of percent of subject study eyes with unchanged accommodation from baseline by time point (e.g., 2 hours) and mydriatic agent (e.g., tropicamide). Unchanged accommodation from baseline is defined as a change from baseline value ≥ -1 D, as measured in diopters. Does FDA have any comment?

FDA Response:
The time to a return of full amount of accommodation would be an acceptable endpoint as long as the amount of accommodation is measured at multiple timepoints.

Meeting Discussion: Ocuphire sought clarification on the definition of "full amount of accommodation". The Agency clarified that "full amount of accommodation" means within 1 diopter of baseline measured at recommended multiple timepoints. Based upon the time-course of the loss of accommodation caused by the cycloplegic, Ocuphire proposed evaluation at 1, 2, 3, 4, and 6 hours, with an expectation like MIRA-1 study (OPI NYXRM-201) to see effects starting at 2 hours. The Agency noted that the evaluation periods were acceptable.

The Agency also suggested evaluating phentolamine in reversal of mydriasis after using the combination of phenylephrine/tropicamide, given this is a commonly used mydriatic product in practice. Ocuphire responded it has not studied that combination mydriatic agent to date (b) (4)

c. The Sponsor conducted the previously completed Phase 2 study OPI-NYXRM-201 with a single drop of POS per eye. The Sponsor is

considering dosing with up to two drops of POS separated by 5 minutes. Does FDA have any comment?

FDA Response:
The dosing regimen that demonstrates safety and efficacy is expected to be reflected in the labeling. We encourage the evaluation of multiple different dosing regimens to determine the one with the best benefit/risk profile.

Meeting Discussion: None

d. Depending upon the design of the Phase 3 study (OPI-NYXRM-301), is it possible the completed Phase 2 study OPI-NYXRM-201 could serve as one of the two pivotal efficacy studies for this indication?

FDA Response:
Potentially. See response to Question 11a.

Meeting Discussion: None

(b) (4)

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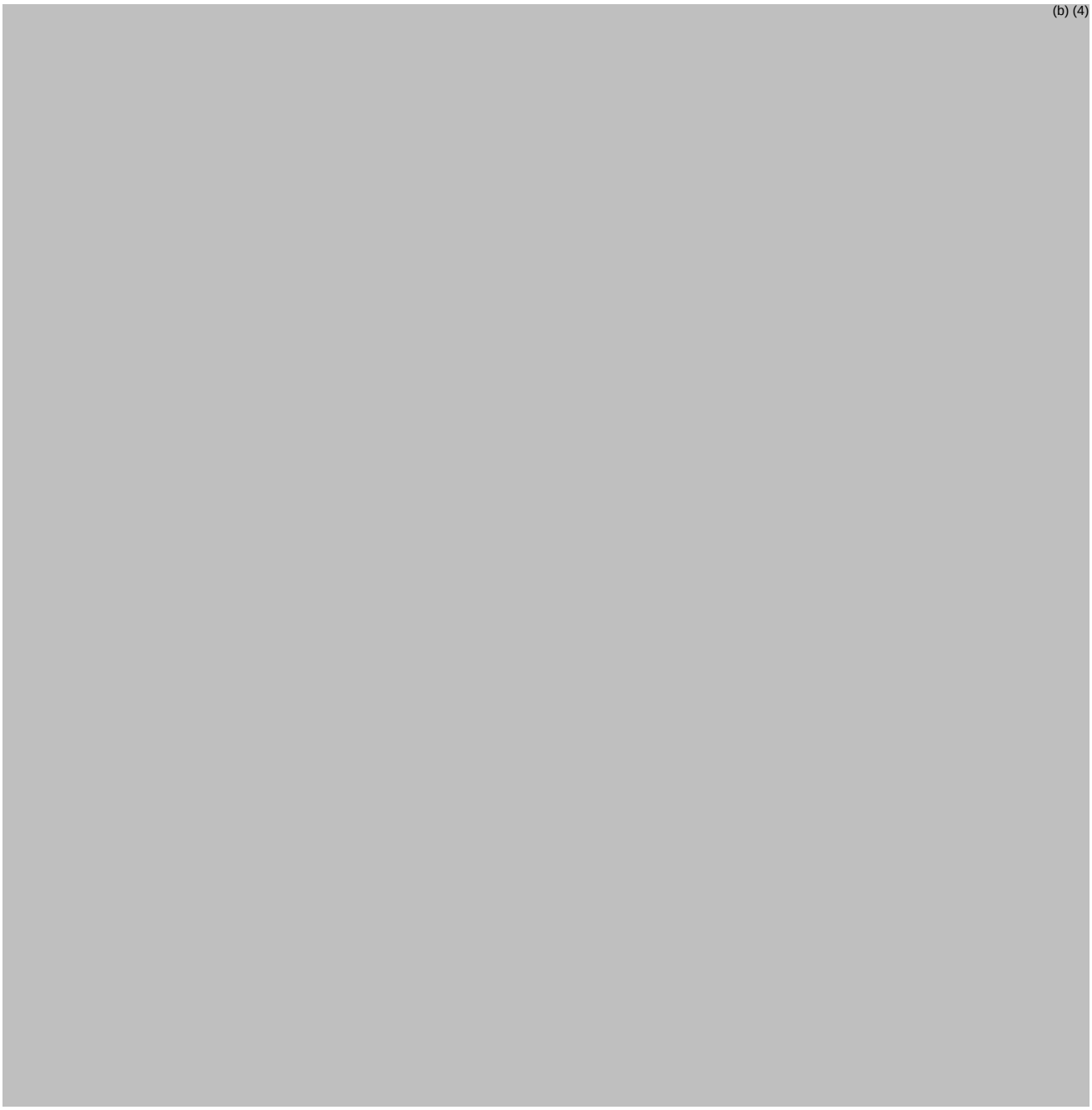

c. The Sponsor considers the indication of Reversal of Pharmacologically-induced Mydriasis to be an acute indication, and thus the exposure for the safety population can be limited to up to two drops of POS separated by 5 minutes in each eye with a one-day follow-up. Does FDA concur?

FDA Response:
Potentially. We may have further comments when the full protocol and statistical analysis plan are submitted to the IND.

Meeting Discussion: Ocuphire sought to clarify the safety exposure for the acute indication of reversal of mydriasis. Ocuphire suggested at least 300 subjects for 24 hours. The Agency concurred.

d. Based upon the preclinical and safety data in the literature, approved products, and as investigated by the Sponsor, no clinical studies are planned to evaluate the systemic exposure to POS after ophthalmic instillation. Does FDA concur?

FDA Response:
No. We recommend you collect sparse PK sampling to characterize the systemic exposure of phentolamine following ocular administration of the to-be-marketed product.

Meeting Discussion: Ocuphire sought clarification if the evaluation of systemic exposure might alternatively be as in some previously approved ophthalmic products. This might be a study in ~12-18 healthy volunteers looking at blood levels after one day and one week of dosing at selected time points.

FDA clarified that time points in humans selected might be informed by the nonclinical pharmacokinetics to hopefully capture C_{max}. Further, that either approach – i.e., sparse sampling in patients with the indication(s) OR a separate study in 12-18 healthy normals could be adequate to address the question of systemic exposure after ocular dosing. Regardless of the approach, blood levels would be measured after one day and one week of dosing at selected timepoints.

16. All indications: Pediatric: The Sponsor understands that FDA policy requires submission of a Pediatric Study Plan (PSP) within 60 days of this (b) (4) erstand that for the indication of (b) (4) Reversal of Pharmacologically-induced Mydriasis, there is potential pediatric use.

FDA Response:
We agree that pediatric patients of all ages would potentially use this product. You should submit an initial pediatric study plan (iPSP) [redacted] (b) (4) after the End of Phase 2 meeting. Waivers are not granted until after NDA submission and review.

Meeting Discussion: None

Regulatory

17. The Sponsor intends to continue evaluating POS for various clinical indications under a single IND. Does FDA concur?

FDA Response:
Yes. It is acceptable to study more than one indication under an IND.

Meeting Discussion: None

18. The Sponsor intends to reference FDA's previous finding of safety and efficacy on the products Regitine® (Phentolamine Mesylate Injection, NDA 008278) and Oraverse® (Phentolamine Mesylate Injection, NDA 22159) through the 505(b)(2) regulation for a potential NDA for POS. Does FDA concur?

FDA Response:
It is acceptable to reference the Agency's previous findings of the NDAs you cited.

Meeting Discussion: None

Additional Agency comments:
1. For DMF [redacted] (b) (4) please remind the DMF holder to submit complete CMC information to the FDA in an electronic format to avoid any delay in our review.

2. Regarding Table 4 and Table 5 in the meeting package, provide clarification for these items in the CMC-specific End of Phase 2 meeting package:

- [redacted] (b) (4)

3. Provide the proposed regulatory specification for the drug substance that will be included in the future NDA and that the drug product manufacturer will use to evaluate drug substance batches received from suppliers.

Meeting Discussion: None

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download

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