CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212520Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 116915

MEETING MINUTES

RevitaLid, Inc.
Attention: Joann Stavole
Sr. Director, Regulatory Affairs, CMC
400 Crossing Boulevard, 1st Floor
Bridgewater, NJ 08807

Dear Ms. Stavole:

Please refer to your Investigational New Drug Application (IND) file for RVL-1201 (oxymetazoline hydrochloride ophthalmic solution), 0.1%. We also refer to the teleconference between representatives of your firm and the FDA on June 3, 2019. The purpose of the meeting was to discuss and reach agreement on the content of the upcoming NDA submission.

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 Judit Milstein, Chief, Project Management Staff at 301-796-0763.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 3, 2019, 3:00-4:00 PM, EST
Meeting Format: Teleconference

Application Number: IND 116915
Product Name: RVL-1201 (oxymetazoline hydrochloride ophthalmic solution)
Indication: Treatment of acquired blepharoptosis
Sponsor Name: RevitaLid, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Judit Milstein

FDA ATTENDEES

Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products
William M. Boyd, Clinical Team Leader, DTOP
Jennifer Harris, Clinical Reviewer, DTOP
Maria Rivera, Pharmacology/Toxicology Reviewer, DTOP
Lori Kotch, Pharmacology/Toxicology Team Leader, DTOP
Wonyul Lee, Biometrics Reviewer, Division of Biometrics IV
Sharon Kelly, Product Quality Reviewer, Office of Pharmaceutical Quality (OPQ)
Shrikant Pagay, Product Quality Reviewer, OPQ
Daniel Obrzut, Product Quality Reviewer, OPQ
Renee Marcsisin-Rogers, Microbiology Reviewer, Division of Microbiology Assessment, OPQ
Chunchun Zhang, Pharmaceutical Assessment Lead, OPQ
Judit Milstein, Chief, Project Management Staff, DTOP

SPONSOR ATTENDEES

Brian Markison, Chief Executive Officer, RevitaLid, Inc.
J.D. Schaub, Executive Vice President and Chief Operating Officer, RevitaLid
Tina deVries, Executive Vice President, Research & Development, RevitaLid
David Jacobs, Vice President, Clinical Development & Medical Affairs, RevitaLid
George Wagner, Vice President, Regulatory Affairs, RevitaLid
Angela Dentiste, Vice President, Program Management, RevitaLid
Joann Stavole, Senior Director, Regulatory Affairs, RevitaLid
(b) (4) Consultant for RevitaLid, Inc.
(b) (4) Statistician, Consultant for RevitaLid, Inc.

BACKGROUND

RevitaLid (The Sponsor) has developed a sterile, non-preserved ophthalmic solution of oxymetazoline hydrochloride, 0.1% for the treatment of acquired blepharoptosis and intends to submit an 505(b)(2) application which relies upon literature and a relative bioavailability study that bridges RVL-1201 to RHOFADE (oxymethazoline hydrochloride), Cream.

The Sponsor requested this pre-NDA meeting to discuss the format and content of their upcoming NDA application.

Preliminary responses to the questions posted in the briefing document dated May 1, 2019, were sent to the Sponsor on May 24, 2019. In response to these comments, the Sponsor forwarded via e-mail a document, with a request for follow up on CMC questions 8, 2, 7, additional CMC comments 2 and 3 and Clinical questions 14 and 15. This document is included in these minutes as an attachment.

DISCUSSION

For the purposes of these minutes, the question posted by the Sponsor in their briefing document are in **bold format**, the preliminary responses are in *italics* and the summary of the meeting discussions are in normal font.

Regulatory

1. **RevitaLid will rely on the Agency's previous finding of safety for oxymetazoline in RHOFADE™ Prescribing Information (NDA 208552) with respect to carcinogenicity, mutagenicity and fertility.**

   Does the Division agree that comparative bioavailability Study RVL-1201-PKP01 provides a bridge to allow RevitaLid to rely on the Agency's previous finding of safety for oxymetazoline with respect to carcinogenicity, mutagenicity and fertility?

   FDA Response: *Please refer to the response to Question 10.*

Chemistry, Manufacturing and Controls

2. **The drug product stability data package will be submitted on six (6) registration batches manufactured utilizing two (2) different oxymetazoline hydrochloride API sources** (b) (4) **These six batches were manufactured at the intended commercial batch scale and utilized the intended commercial container closure system. At the time of submission, stability data will consist of the following:**

- **Three registration batches manufactured with (b) (4) API: 24 months (m) at 25ºC/60% RH, 12 m at 30ºC/75% RH, and 6 m at 40ºC/75% RH;**
- **Three registration batches manufactured with (b) (4) API: One (1) batch with 12 m at 25ºC/40% RH and 25ºC/60% RH, 12 m at 30ºC/75% RH, and 6 m at 40ºC/25% RH and 40ºC/75% RH; Two (2) batches with 9 m at 25ºC/40% RH and 25ºC/60% RH, 9 m at 30ºC/75% RH, and 6 m at 40ºC/25% RH and 40ºC/75% RH.**

Does the Division agree that since we will have four registration batches of finished product with at least 12-months stability data, that the 12 month data points on two of the three registration batches manufactured with (b) (4) API can be submitted no later than one month after the submission of the NDA and still be acceptable for filing?

FDA response:

a. *Please confirm if the stability data submitted in the briefing package for the registration batches were manufactured at the intended commercial site.*

b. *Also, confirm if you plan to include both API sites ((b) (4)) as API drug substance manufacturers for the NDA/commercial market.*

c. *We expect the NDA at the time of submission should provide at least 12 months of long-term and 6-months accelerated stability data for three registration batches in the intended commercial configuration from the commercial manufacturing site. Any data submitted during review may or may not be reviewed depending on resources available.*

3. **Does the Division require that all six executed registration batch records be provided in the NDA or is it acceptable to provide one representative executed registration batch record?**

   FDA response: We expect all executed registration batch records to be submitted in the NDA per 21 CFR 314.50(d)1(ii)(b).

4. **Would it be acceptable to provide one representative excipient manufacturer's certificate of analysis (COA) and the corresponding CMO (b) (4) COA for each excipient instead of providing copies of all COAs for all excipient lots utilized in the six drug product registration batches?**

   FDA Response: Yes.

5. Does the Division agree with the proposed drug substance specification for oxymetazoline hydrochloride (Table 3)?

FDA Response: The proposed drug substance specification appears reasonable; however, final determination is an NDA review issue.

In support of your proposed limits on impurities, provide in the NDA information on impurities as per current revisions of ICH guidance's Q3A, Q3C, Q3D, and M7.

6. Does the Division agree with the proposed drug product release specification (Table 6) and proposed drug product stability specification (Table 7)?

FDA response: The proposed specifications provided in Table 6 and Table 7 appear to be reasonable. For an NDA submission, upon evaluation of the data submitted, additional tests and/or tightening of the specification may be required. Provide a combined table to include the release and the stability specifications in the NDA submission.

All six registration batches do not meet the current stability limits for related substances at 6 months at 40C/75%RH, therefore we are proposing that RVL-1201 accelerated stability data be generated only up to 3 months at 40C/75%RH. For post approval changes typically requiring 3 months at 40C/75%RH at submission, RevitaLid is proposing to provide 3 months at 40C/75%RH (which will be the last test interval) at submission. Additional data from subsequent intervals (6, 9, 12 etc.) tested at 25C/60% RH and 30C/65%RH (as applicable) will be submitted as requested or in the next annual report.

7. Does the Division agree that it is justified to study the accelerated condition of 40C/75%RH up to 3 month test interval only and that submission of 3 months accelerated data at submission with subsequent data from room temperature and intermediate testing as applicable will be acceptable for post-approval changes?

FDA response: Please submit all the stability data as per FDA response to Q.2(long term, intermediate and accelerated) in the NDA. If the batch has failed under the accelerated condition, refer to ICH Guidance on Stability Studies ICH Q1A (R2) for explanation of the data. We do learn about product quality when exposed to accelerated conditions and is a valuable component of the stability study.

8. **RVL-1201 is a LDPE vial individually packaged in a foil pouch that provides a non-permeable barrier. Evaluation of the stability data at 25ºC/60% RH is comparable to stability data at 25ºC/40% RH. RevitaLid is proposing to utilize the standard stability storage condition of 25C/60% RH instead of the semi-permeable condition 25C/40% RH for future stability studies.**

   Does the Division agree with the proposed stability testing protocol and proposed stability conditions of 25C/60%RH, 30C/65%RH, and 40C/75%RH (Table 8, Table 9 and Table 10 respectively) in support of post-approval commitments?

   FDA response: We recommend that you follow ICH Q1A(R2) guidance for stability. Drug product stability study should be conducted under low relative humidity since the drug product is packaged in a semi-permeable container.

9. **Based on the available stability data, we will propose a 2-year expiration date for the drug product, does the Division concur?**

   FDA response: Shelf life of the drug product will be assessed after reviewing quality and amount of the data submitted in the NDA.

Pharmacology/Toxicology

10. **The submission will include a 28-Day Topical Ocular Toxicity Study in New Zealand white rabbits (Study 12c145q2r3g25), a 26-Week Topical Ocular Toxicity Study in New Zealand white rabbits (Study 74041B), and reference to the Agency's previous finding of safety for oxymetazoline in RHOFADE™ with respect to carcinogenicity, mutagenicity and fertility.**

    The amount of all of the excipients in RVL-1201 are at or below the approved levels indicated in the Inactive Ingredient Database (IID), see Table 5.

    Does the Division agree that these studies represent a complete nonclinical package for filing this NDA?

    FDA Response: Based on the information provided in the briefing document, we agree that no additional nonclinical studies are needed for filing.

    As previously recommended, all nonclinical elements should be provided, either directly (original studies or published literature) or by relying on the FDA's findings of safety and effectiveness for a listed drug. If literature is being relied upon to support the NDA, include a summary of all published nonclinical literature being relied upon and a copy of all publications cited. The nonclinical summary is typically organized to address each of the nonclinical elements (e.g. pharmacology, pharmacokinetics, ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.). See Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals for further information regarding required nonclinical elements.

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf

Clinical Pharmacology

11. RevitaLid conducted a Phase 1 comparative bioavailability Study RVL-1201-PKP01 comparing the approved dose of RHOFADE (oxymetazoline HCl) cream, 1%, to the proposed dose of RVL-1201. The results from this study demonstrate that the oxymetazoline systemic exposure (AUC and Cmax) from RVL-1201 is less than the exposure from RHOFADE.

Does the Division agree that the results from Study RVL-1201-PKP01 provides a bridge to the Agency's previous finding of safety for RHOFADE?

FDA Response: The information provided from Study RVL-1201-PKP01 appears adequate to provide a bridge. A final determination will be made upon review of the complete application.

12. The Clinical Pharmacology section of the NDA will be prepared from two primary information sources: 1) one single-dose clinical study conducted to provide the bioavailability data required to support this 505(b)(2) submission and 2) a summary of relevant human pharmacokinetic (PK) data extracted from the open scientific literature on oxymetazoline, including absorption, distribution, metabolism, excretion (ADME), etc. as available.

A literature search was performed on the clinical pharmacology, PK, and pharmacodynamics (PD) of oxymetazoline. Oxymetazoline exposures were observed in general to be lower following ocular dosing than by other routes of administration (nasal or topical). In a relative bioavailability study, systemic oxymetazoline exposure following administration of a clinical dose of RVL-1201 to both eyes was shown to be substantially lower than after topical application of a therapeutic dose of RHOFADE™.

Oxymetazoline is moderately bound in human plasma and is metabolized by CYP2C19 and UGT1A9, although plasma concentrations of oxymetazoline after ocular administration are well below those that would be required for biotransformation by either of these enzymes. It has been suggested that, at the low concentrations achieved after ocular administration, oxymetazoline is primarily excreted unchanged in the urine. Oxymetazoline volume of distribution and clearance are influenced by body weight based on an allometric relationship, whereas age and gender do not appear to be important determinants of oxymetazoline disposition. The likelihood of oxymetazoline being involved in clinically relevant DDIs mediated by effects on major drug metabolizing enzymes as either a perpetrator or victim is minimal.

Does the Division agree that Study RVL-1201-PKP01 and the literature information are sufficient to support filing of this NDA?

FDA Response: *Agree*

Clinical

13. **Does the Division agree with the proposed structure and content of the Statistical Analysis Plan (SAP) for Integrated Summary of Efficacy and Integrated Summary of Safety?**

    FDA Response: *The SAP for Integrated Summary of Efficacy (ISE) appears reasonable. Regarding Integrated Summary of Safety (ISS), the SAP states that "most frequent AEs are defined as AEs occurring in ≥ 2% of subjects of the RVL-1201 treatment group". We recommend that you also report AEs occurring in ≥ 1% of subjects in the RVL-1201 treatment group. The SAP should clearly define pooled RVL-1201 treatment group and pooled placebo group for the AE reports. In addition, please submit all integrated ADaM datasets and SAS programs used to generate the analysis results for the ISE and ISS.*

14. **Enrollment in Study RVL-1201-202 and Study RVL-1201-203 was open to subjects greater than 9 years of age. One subject in Study RVL-1201-202, and 3 subjects in Study RVL-1201-203 were younger than 18 years old.**

    Osmotica intends to submit a waiver request for all pediatric age groups. Does the Division concur?

    FDA Response: *A waiver request may be submitted to the Agency for review.*

15. **Draft prescribing information for Oxymetazoline HCl Ophthalmic Solution 0.1% has been provided. Does the Division have any comments on the proposed labeling statements?**

    FDA Response: *Labeling is a review issue. Comments will be provided once the NDA is submitted and reviewed.*

Additional Agency Comments:

1. *Regarding submission of study data in your planned NDA, please see the Agency's 'Study Data Technical Conformance Guide' document (https://www.fda.gov/media/119807/download). We further recommend that you provide a 'reviewers-guide.pdf' document and a 'define.pdf' document for both the analysis and tabulation datasets of the Phase 3 studies. The programming codes (preferably SAS codes) used to create the analysis datasets and the efficacy and safety tables for each individual Phase 3 study should also be provided.*

2. *Please include information in the NDA on extractable obtained by interaction of the drug product solution with the container using USP <1663> test methods (HS/GC/MS, GC/MS/, LC/MS and ICP/MS) for the volatile, SEMI VOLATILE AND NON-VOLATILE EXTRACTABLE. Based on the extractable information, provide leachable obtained in the 3 registration stability batch samples stored through the shelf life of the drug product. Please follow testing as per USP<1664> using the same test methods.*

3. *It is acknowledged that the formulation maximum hold time is 72 hours.* (b) (4) *validation of its microbiological quality at the maximum holding time is expected in the NDA submission.*

4. *Regarding the container-closure system integrity validation, if a dye immersion method is utilized, please consider the following Agency expectations:*

   a. *It is recommended that a description of the study that was performed to determine the limit of detection (LOD) is included in the marketing application. The container closure integrity test method should be capable of detecting ~1 µl of dye ingress.*
   b. *Vacuum and/or pressure conditions should be applied during integrity testing.*
   c. *Positive and negative controls should be included in the integrity test method and a breached positive control is recommended.*

SUMMARY OF THE MEETING DISCUSSION:

1. The Sponsor clarified that the API at both sites has comparable manufacturing process and profile. The Sponsor proposed to submit 3 registration batches for 24 months at standard relative humidity with (b) (4) API and 3 registration batches for 12 months at low relative humidity and standard relative humidity with (b) (4) API. The division expected that the proposed bridging stability data would be acceptable for review. (Question 2)

2. The Division reiterated the recommendation to submit 3 batches with 12-month long term stability data *under the low humidity condition* at the time of NDA submission. (Questions 2 & 8)

3. The Sponsor proposed to only conduct three months accelerated testing at 40°C and to not repeat 6-month time-points for the accelerated stability studies because the product previously failed at the 6-month accelerated conditions. The division found the proposal acceptable. (Question 7)

4. The Division did not object to the Sponsor's plan for extractables data with 3 registration batches (CMC *additional* Comment 2) and to the proposal to submit

data on 1 [redacted] batch to support 72- hour hold time. (CMC *additional* Comment 3)

5. The Division clarified that the agreed initial Pediatric Study Plan (iPSP) was adequate and there is no need to revise the iPSP. The Sponsor can submit a request for a waiver for all pediatric ages in the NDA submission. (Question 14)

6. The Division indicated that review of the data at the time of the NDA submission will determine the appropriateness of including the distance from the central pupillary light reflex to the central margin of the upper eyelid (MRD) data to [redacted]. (Question 15)

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
The Division will issue the minutes of the meeting within 30 days

ATTACHMENTS AND HANDOUTS
Sponsor's request for follow up on Question 8, 2, 7, additional CMC comments 2 and 3 and Clinical Questions 14 and 15.

ADDITIONAL INFORMATION

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[2] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance

on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ATTACHMENT

Regulatory

1. **RevitaLid will rely on the Agency's previous finding of safety for oxymetazoline in RHOFADE™ Prescribing Information (NDA 208552) with respect to carcinogenicity, mutagenicity and fertility.**

   Does the Division agree that comparative bioavailability Study RVL-1201-PKP01 provides a bridge to allow RevitaLid to rely on the Agency's previous finding of safety for oxymetazoline with respect to carcinogenicity, mutagenicity and fertility?

   FDA Response: *Please refer to the response to Question 10.*

   RevitaLid response: We acknowledge the response; further clarification is not needed.

Chemistry, Manufacturing and Controls

2. **The drug product stability data package will be submitted on six (6) registration batches manufactured utilizing two (2) different oxymetazoline hydrochloride API sources (b) (4)). These six batches were manufactured at the intended commercial batch scale and utilized the intended commercial container closure system. At the time of submission, stability data will consist of the following:**

   - **Three registration batches manufactured with (b) (4) API: 24 months (m) at 25ºC/60% RH, 12 m at 30ºC/75% RH, and 6 m at 40ºC/75% RH;**
   - **Three registration batches manufactured with (b) (4) API: One (1) batch with 12 m at 25ºC/40% RH and 25ºC/60% RH, 12 m at 30ºC/75% RH, and 6 m at 40ºC/25% RH and 40ºC/75% RH; Two (2) batches with 9 m at 25ºC/40% RH and 25ºC/60% RH, 9 m at 30ºC/75% RH, and 6 m at 40ºC/25% RH and 40ºC/75% RH.**

   Does the Division agree that since we will have four registration batches of finished product with at least 12-months stability data, that the 12 month data points on two of the three registration batches manufactured with (b) (4) API can be submitted no later than one month after the submission of the NDA and still be acceptable for filing?

   FDA response:

   a. *Please confirm if the stability data submitted in the briefing package for the registration batches were manufactured at the intended commercial site.*

RevitaLid response: Yes, all six registration batches were manufactured at [redacted](b) (4), which is the commercial manufacturing facility.

b. *Also, confirm if you plan to include both API sites* [redacted](b) (4) *as API drug substance manufacturers for the NDA/commercial market.*

RevitaLid response: Yes, both API manufacturers [redacted](b) (4)) will be included in the NDA.

c. *We expect the NDA at the time of submission should provide at least 12 months of long-term and 6-months accelerated stability data for three registration batches in the intended commercial configuration from the commercial manufacturing site. Any data submitted during review may or may not be reviewed depending on resources available.*

RevitaLid response: We intend to submit at least three registration batches with 12 months of long-term and 6 months accelerated stability data in the intended commercial configuration from the commercial manufacturing site in the original NDA submission.

3. **Does the Division require that all six executed registration batch records be provided in the NDA or is it acceptable to provide one representative executed registration batch record?**

FDA response: We expect all executed registration batch records to be submitted in the NDA per 21 CFR 314.50(d)1(ii)(b).

RevitaLid response: We acknowledge the response; further clarification is not needed.

4. **Would it be acceptable to provide one representative excipient manufacturer's certificate of analysis (COA) and the corresponding CMO** [redacted](b) (4) **COA for each excipient instead of providing copies of all COAs for all excipient lots utilized in the six drug product registration batches?**

FDA Response: Yes.

RevitaLid response: We acknowledge the response; further clarification is not needed.

5. **Does the Division agree with the proposed drug substance specification for oxymetazoline hydrochloride (Table 3)?**

   FDA Response: *The proposed drug substance specification appears reasonable; however, final determination is an NDA review issue.*

   In support of your proposed limits on impurities, provide in the NDA information on impurities as per current revisions of ICH guidance's Q3A, Q3C, Q3D, and M7.

   RevitaLid response: We acknowledge the response; further clarification is not needed.

6. **Does the Division agree with the proposed drug product release specification (Table 6) and proposed drug product stability specification (Table 7)?**

   FDA response: The proposed specifications provided in Table 6 and Table 7 appear to be reasonable. For an NDA submission, upon evaluation of the data submitted, additional tests and/or tightening of the specification may be required. Provide a combined table to include the release and the stability specifications in the NDA submission.

   RevitaLid response: We acknowledge the response; further clarification is not needed.

All six registration batches do not meet the current stability limits for related substances at 6 months at 40C/75%RH, therefore we are proposing that RVL-1201 accelerated stability data be generated only up to 3 months at 40C/75%RH. For post approval changes typically requiring 3 months at 40C/75%RH at submission, RevitaLid is proposing to provide 3 months at 40C/75%RH (which will be the last test interval) at submission. Additional data from subsequent intervals (6, 9, 12 etc.) tested at 25C/60% RH and 30C/65%RH (as applicable) will be submitted as requested or in the next annual report.

7. **Does the Division agree that it is justified to study the accelerated condition of 40C/75%RH up to 3 month test interval only and that submission of 3 months accelerated data at submission with subsequent data from room temperature and intermediate testing as applicable will be acceptable for post-approval changes?**

   FDA response: Please submit all the stability data as per FDA response to Q.2 (long term, intermediate and accelerated) in the NDA. If the batch has failed under the accelerated condition, refer to ICH Guidance on Stability Studies ICH Q1A (R2) for explanation of the data. We do learn about product quality when

exposed to accelerated conditions and is a valuable component of the stability study.

RevitaLid response: We plan to submit the 6 month accelerated stability data for all 6 registration batches along with the intermediate and long-term data in the original NDA submission.

To support post approval changes, we are proposing to conduct 3 month long-term and accelerated testing at 40ºC and to not include a 6 month time-point for the accelerated stability studies. Based on our current stability data, 6 month accelerated testing at 40ºC will not pass the current impurity specifications. Will this be acceptable for post-approval changes?

8. **RVL-1201 is a LDPE vial individually packaged in a foil pouch that provides a non- permeable barrier. Evaluation of the stability data at 25ºC/60% RH is comparable to stability data at 25ºC/40% RH. RevitaLid is proposing to utilize the standard stability storage condition of 25C/60% RH instead of the semi-permeable condition 25C/40% RH for future stability studies.**

   Does the Division agree with the proposed stability testing protocol and proposed stability conditions of 25C/60%RH, 30C/65%RH, and 40C/75%RH (Table 8, Table 9 and Table 10 respectively) in support of post-approval commitments?

   FDA response: We recommend that you follow ICH Q1A(R2) guidance for stability. Drug product stability study should be conducted under low relative humidity since the drug product is packaged in a semi-permeable container.

   RevitaLid response: The primary container (with product contact) is a LDPE (b) (4) vial that is semi-permeable. This vial is then packaged into an impermeable foil pouch. As the vial in the foil pouch is what is tested in the stability studies, we consider this an impermeable container closure and are proposing stability testing at standard relative humidity (e.g. 60, 65 or 75% RH). Is this acceptable?

9. **Based on the available stability data, we will propose a 2-year expiration date for the drug product, does the Division concur?**

   FDA response: Shelf life of the drug product will be assessed after reviewing quality and amount of the data submitted in the NDA.

   RevitaLid response: We acknowledge the response; further clarification is not needed.

Pharmacology/Toxicology

10. **The submission will include a 28-Day Topical Ocular Toxicity Study in New Zealand white rabbits (Study 12c145q2r3g25), a 26-Week Topical Ocular Toxicity Study in New Zealand white rabbits (Study 74041B), and reference to the Agency's previous finding of safety for oxymetazoline in RHOFADE™ with respect to carcinogenicity, mutagenicity and fertility.**

    The amount of all of the excipients in RVL-1201 are at or below the approved levels indicated in the Inactive Ingredient Database (IID), see Table 5.

    Does the Division agree that these studies represent a complete nonclinical package for filing this NDA?

    FDA Response: *Based on the information provided in the briefing document, we agree that no additional nonclinical studies are needed for filing.*

    As previously recommended, all nonclinical elements should be provided, either directly (original studies or published literature) or by relying on the FDA's findings of safety and effectiveness for a listed drug. If literature is being relied upon to support the NDA, include a summary of all published nonclinical literature being relied upon and a copy of all publications cited. The nonclinical summary is typically organized to address each of the nonclinical elements (e.g. pharmacology, pharmacokinetics, ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.). See Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals for further information regarding required nonclinical elements. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc es/UCM073246.pdf

    RevitaLid response: We acknowledge the response; further clarification is not needed.

Clinical Pharmacology

11. RevitaLid conducted a Phase 1 comparative bioavailability Study RVL-1201-PKP01 comparing the approved dose of RHOFADE (oxymetazoline HCl) cream, 1%, to the proposed dose of RVL-1201. The results from this study demonstrate that the oxymetazoline systemic exposure (AUC and Cmax) from RVL-1201 is less than the exposure from RHOFADE.

Does the Division agree that the results from Study RVL-1201-PKP01 provides a bridge to the Agency's previous finding of safety for RHOFADE?

FDA Response: *The information provided from Study RVL-1201-PKP01 appears adequate to provide a bridge. A final determination will be made upon review of the complete application.*

RevitaLid response: We acknowledge the response; further clarification is not needed.

12. The Clinical Pharmacology section of the NDA will be prepared from two primary information sources: 1) one single-dose clinical study conducted to provide the bioavailability data required to support this 505(b)(2) submission and 2) a summary of relevant human pharmacokinetic (PK) data extracted from the open scientific literature on oxymetazoline, including absorption, distribution, metabolism, excretion (ADME), etc. as available.

A literature search was performed on the clinical pharmacology, PK, and pharmacodynamics (PD) of oxymetazoline. Oxymetazoline exposures were observed in general to be lower following ocular dosing than by other routes of administration (nasal or topical). In a relative bioavailability study, systemic oxymetazoline exposure following administration of a clinical dose of RVL-1201 to both eyes was shown to be substantially lower than after topical application of a therapeutic dose of RHOFADE™.

Oxymetazoline is moderately bound in human plasma and is metabolized by CYP2C19 and UGT1A9, although plasma concentrations of oxymetazoline after ocular administration are well below those that would be required for biotransformation by either of these enzymes. It has been suggested that, at the low concentrations achieved after ocular administration, oxymetazoline is primarily excreted unchanged in the urine. Oxymetazoline volume of distribution and clearance are influenced by body weight based on an allometric relationship, whereas age and gender do not appear to be important determinants of oxymetazoline disposition. The likelihood of oxymetazoline being involved in clinically relevant DDIs mediated by effects on major drug metabolizing enzymes as either a perpetrator or victim is minimal.

Does the Division agree that Study RVL-1201-PKP01 and the literature

information are sufficient to support filing of this NDA?

FDA Response: *Agree*

RevitaLid response: We acknowledge the response; further clarification is not needed.

Clinical

13. **Does the Division agree with the proposed structure and content of the Statistical Analysis Plan (SAP) for Integrated Summary of Efficacy and Integrated Summary of Safety?**

FDA Response: *The SAP for Integrated Summary of Efficacy (ISE) appears reasonable. Regarding Integrated Summary of Safety (ISS), the SAP states that "most frequent AEs are defined as AEs occurring in ≥ 2% of subjects of the RVL-1201 treatment group". We recommend that you also report AEs occurring in ≥ 1% of subjects in the RVL-1201 treatment group. The SAP should clearly define pooled RVL-1201 treatment group and pooled placebo group for the AE reports. In addition, please submit all integrated ADaM datasets and SAS programs used to generate the analysis results for the ISE and ISS.*

RevitaLid response: We acknowledge the response; further clarification is not needed.

14. **Enrollment in Study RVL-1201-202 and Study RVL-1201-203 was open to subjects greater than 9 years of age. One subject in Study RVL-1201-202, and 3 subjects in Study RVL-1201-203 were younger than 18 years old.**

Osmotica intends to submit a waiver request for all pediatric age groups. Does the Division concur?

FDA Response: *A waiver request may be submitted to the Agency for review.*

RevitaLid response: We acknowledge the response and would like clarification regarding the currently agreed iPSP (that stipulates a waiver for the children under 9 years of age). Is it acceptable to submit the current agreed iPSP with the waiver for all pediatric age groups in the NDA submission or should a revised iPSP be created to indicate that we are requesting a waiver for all age groups? Does a revised iPSP need to be submitted to the IND?

15. **Draft prescribing information for Oxymetazoline HCl Ophthalmic Solution 0.1% has been provided. Does the Division have any comments on the proposed labeling statements?**

FDA Response: *Labeling is a review issue. Comments will be provided once the*

NDA is submitted and reviewed.

RevitaLid response: We acknowledge the response. Topline results were shared, and RevitaLid would be interested in the Division's impression of MRD data [redacted (b) (4)].

Additional Comments:

1. *Regarding submission of study data in your planned NDA, please see the Agency's 'Study Data Technical Conformance Guide' document (https://www.fda.gov/media/119807/download). We further recommend that you provide a 'reviewers-guide.pdf' document and a 'define.pdf' document for both the analysis and tabulation datasets of the Phase 3 studies. The programming codes (preferably SAS codes) used to create the analysis datasets and the efficacy and safety tables for each individual Phase 3 study should also be provided.*

   RevitaLid response: We acknowledge the response; further clarification is not needed.

2. *Please include information in the NDA on extractable obtained by interaction of the drug product solution with the container using USP <1663> test methods (HS/GC/MS, GC/MS/, LC/MS and ICP/MS) for the volatile, SEMI VOLATILE AND NON-VOLATILE EXTRACTABLE. Based on the extractable information, provide leachable obtained in the 3 registration stability batch samples stored through the shelf life of the drug product. Please follow testing as per USP<1664> using the same test methods.*

   RevitaLid response: We acknowledge the comment and will include extractable data to support the components (LDPE vial/foil) of the container/closure system using model solvents e.g. water, 2-propanol, hexane, and 95% ethanol. Leachable data will be provided on the drug product solution for the shelf-life for 3 of the 6 registration batches. Is this acceptable?

3. *It is acknowledged that the formulation maximum hold time is 72 hours. [redacted (b) (4)] validation of its microbiological quality at the maximum holding time is expected in the NDA submission.*

   RevitaLid response: We acknowledge the response and have developmental data that supports the 72 hour hold time that we will submit in the NDA. Process validation batches will be manufactured closer to the time of approval as they will be intended for commercialization.

4. *Regarding the container-closure system integrity validation, if a dye immersion method is utilized, please consider the following Agency expectations:*
   a. *It is recommended that a description of the study that was performed to determine the limit of detection (LOD) is included in the marketing application. The container closure integrity test method should be capable of detecting ~1 µl of dye ingress.*

      RevitaLid response: We acknowledge the response and confirm that the method is capable of detecting ~1 µl of dye ingress.

   b. *Vacuum and/or pressure conditions should be applied during integrity testing.*

      RevitaLid response: We acknowledge the response and confirm that vacuum conditions are being applied.

   c. *Positive and negative controls should be included in the integrity test method and a breached positive control is recommended.*

      RevitaLid response: We acknowledge the response and confirm that positive and negative controls are included.

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/

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