DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112952

MEETING MINUTES

River Vision Development Corporation
Attention: Liz Lucini, Pharm.D.
U.S. Regulatory Agent
One Rockefeller Plaza
Suite 1204
New York, NY 10020

Dear Dr. Lucini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RV001 (teprotumumab for injection).

We also refer to the meeting between representatives of your firm and the FDA on August 19, 2016. The purpose of the meeting was to discuss with the Agency the data generated in Study TED01RV and potential for this study to support a BLA filing.

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

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 19, 2016 from 9:30AM – 10:30AM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 112952
Product Name: RV001 (teprotumumab for injection)
Indication: treatment of moderate to severe thyroid eye disease (TED)
Sponsor/Applicant Name: River Vision Development Corporation

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

FDA ATTENDEES

Renata Albrecht, MD	Director, Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, MD	Deputy Division Director, DTOP
William Boyd, M.	Clinical Team Leader, DTOP
Sonal Wadhwa, MD	Clinical Reviewer, DTOP
Martin Nevitt, MD	Clinical Reviewer, DTOP
Sunita Shukla, MPH, PhD	Associate Director for Regulatory Science, Office of Antimicrobial Products (OAP)
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Abhay Joshi, PhD	Clinical Pharmacology Reviewer, OCP/DCPIV
Lori Kotch, PhD	Pharmacology/Toxicology Team Leader, DTOP
Maria Rivera, PhD	Pharmacology/Toxicology Reviewer, DTOP
Jee Chung, PhD	Product Quality Team Leader, Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research I (DBRRI)
Subramanian Muthukkumar, PhD	Product Quality Reviewer, OBP/DBRRI
Yan Wang, PhD	Statistical Team Leader, Office of Biometrics (OB)/ Division of Biometrics IV (DBIV)

Yunfan Deng, PhD	Statistical Reviewer, OB/DBIV
Lois Almoza, MS	Regulatory Health Project Manager, DTOP

SPONSOR ATTENDEES

Kathleen Gabriel, RN, MFT	Director, Clinical Operations
Guido Magni, MD, PhD	Chief Medical Officer
David Madden, MBA	Chief Executive Officer
Richard Woodward, PhD	Chief Scientific Officer
(b) (4)	Regulatory Consultant
	CMC Consultant
Liz Lucini, PharmD	Regulatory Consultant
(b) (4)	CMC consultant
Anne Rentz	Clinical consultant
Bent Hygum	VP Quality, CMC Biologics

BACKGROUND

A June 22, 2016, submission, from River Vision Development Corporation (River) requested a meeting for IND 112952 to discuss with the Agency the data generated in Study TED01RV and potential for this study to support a BLA filing for treatment of moderate to severe thyroid eye disease (TED).

A Meeting Request Granted letter issued on, July 5, 2016. The July 15, 2016, Meeting Package was received on July 15, 2016. Meeting Preliminary Comments were sent to River via e-mail on August 16, 2016.

River forwarded talking points and a graphic via e-mail on August 18, 2016. The talking points have been incorporated throughout the meeting minutes in bold italic font and the graphic is attached(see attachment 1) A question pertaining to the meeting was e-mailed from River on August 24, 2016, and the Division responded via e-mail on August 25, 2016(see attachment 2).

DISCUSSION

Following, in **bold font**, are the questions in the July 15, 2016, Meeting Package. The FDA responses to these questions are in *italic* font. Talking points from the Sponsor sent via e-mail on, August 18, 2016, are in ***bold, italic*** font. Discussions that took place during the August 19, 2016, teleconference are in regular font.

Clinical Questions:

1. **Does the Agency agree with the Sponsor's efficacy conclusions from study TED01RV; specifically,**
    a. **Does the Agency agree that the statistically significant results for the primary outcome measure of reduction ≥ 2 in the clinical activity score (CAS) and reduction ≥ 2 mm in proptosis in the study eye, without a similar degree of**

deterioration in CAS or proptosis in the non-study eye demonstrate the efficacy of teprotumumab in the treatment of moderate to severe active TED?

FDA Response: The results appear favorable; however, decisions regarding acceptability of the efficacy results for approval can only be made once the complete BLA package is reviewed.

Sponsor Comments: To address the points raised in the responses to questions 1 and 2, we will submit the CSR for Study TED01RV as soon as it is ready, which we currently anticipate to be in about 2 months as we are still waiting for the PK data. Would the Division find it helpful to receive datasets as well?

Meeting Discussion: Yes. The Division would find it helpful to receive datasets as well.

b. Does the Agency agree that the statistically significant results for the secondary endpoints of Graves' Ophthalmopathy quality of life scale (GO-QOL), proptosis, and CAS provide further evidence of the efficacy of teprotumumab in the treatment of moderate to severe active TED?

FDA Response: While the results appear favorable, we would need to see the data supporting the validation of the GO-QOL before commenting on its interpretation. See also response to Question #1.

Sponsor Comments: We would like to clarify this point further. Our plan would be to provide information on the psychometric properties of the GO-QOL to show that the reliability and validity information is sufficient. Would this approach be acceptable to the Division? Can you please also confirm that the intent is to validate vs. qualify this instrument, as we recognize the terms mean different things and we'd like clarification on the guidance to follow.

As GO-QOL is a secondary endpoint, is validation of the endpoint a requirement for labeling or for another purpose?

Meeting Discussion:

The Sponsor asked for confirmation that the intent is to validate versus qualify this instrument, as they recognize the terms mean different things. They plan to provide information from the published literature on the psychometric properties of the GO-QOL to show that its reliability and validity are sufficient.

The Division recommended that the Patient-Reported Outcomes(PRO) Guidance be followed and the Sponsor noted that if their intent is to include results of the GO-QOL in the USPI, they would validate the GO-QOL in accordance with the 2009 Guidance document "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" and submit a PRO dossier for this scale. The Division noted that without validation, single questions are more likely to be accepted for the USPI than results from a multiple component endpoint.

2. **Based on the safety data from Study TED01RV, the Sponsor has identified hyperglycemia as an AE of Special Interest.**

    a. **Does FDA have any comments on the proposed risk mitigation for this event?**

FDA Response: No, not at this time; we may have additional comments once we see a final CSR (Clinical study report).

Meeting Discussion: None

    b. **Does FDA have any other comments regarding the safety profile of teprotumumab observed in Study TED01RV?**

FDA Response: No, not at this time; we may have additional comments once we see a final CSR (Clinical study report).

Meeting Discussion: None

3. **Does the Agency agree with the proposed safety database for teprotumumab, including utilizing the solid tumor safety data from the oncology program as supportive safety information?**

FDA Response: Potentially, provided the safety database for teprotumumab utilized the same product dosing or greater product dosing than that proposed for TED.

Sponsor Comment: The dosing in the oncology indication was similar or greater than the dosing proposed for TED. Most of the patients in the oncology studies received 9 mg/kg/week.

Meeting Discussion: None

4. **Does the Agency agree that the statistically significant and clinically meaningful results from study TED01RV and the safety profile of teprotumumab support proceeding with a BLA filing for teprotumumab for the unmet medical need of moderate to severe active TED?**

FDA Response: No. The Agency expects at least two adequate and well-controlled trials to support the safety and efficacy of a product. In addition, at least one of these trials should have used the-to-be marketed final formulation.

Sponsor Comments: We would like to clarify this point further.

Meeting Discussion:

The Agency advised that while the Sponsor could file a BLA based on the single trial, this approach is not recommended as it would be unlikely to support an approval. The Agency clarified that the intent of a second study would be to both provide corroborative evidence of efficacy as well as provide clinical exposure with the proposed commercial product. The Agency

agreed that a new trial could begin with the currently available [redacted] (b) (4) product and switch to use of the new process [redacted] (b) (4) product when available.

The Sponsor noted several challenges it would anticipate in conducting an additional placebo-controlled trial, including the reluctance of investigators to participate given the efficacy seen in the TED01RV trial and the likelihood that placebo subjects would be withdrawn early from the study for lack of efficacy. The Sponsor stated that a potential new trial would likely not be the same as the TED01RV trial in either design or size. The Agency acknowledged that a second trial may differ in design (number of subjects, duration, etc.) and expressed willingness to review and discuss the acceptability of any proposed new study.

The Agency suggested that the Sponsor consider submitting the new protocol under a Special Protocol Assessment (SPA); however, the Sponsor stated that they did not feel this would be necessary.

Additional Comments:
In any future TED trials, randomization should include stratification for baseline factors which can significantly impact the outcome (ie. level of TED at onset of trial).

Meeting Discussion: None

Clinical Pharmacology Question

5. **Does the Agency agree that the clinical pharmacology data generated to date with teprotumumab are adequate to support registration for the treatment of moderate to severe active TED, with respect to the following elements?**
    a. **ADME profile**
    b. **Drug-drug interaction potential**
    c. **TQT potential**
    d. **Renal and hepatic impairment**

FDA Response: Yes, we agree for item d. However, with regard to items a, b and c, only brief summaries are provided without the teprotumumab pharmacokinetic data in TED patients. Once the complete study report for Study TED01RV is submitted, adequacy of the Clinical Pharmacology data will be reassessed.

Sponsor Comment: We have no points for further discussion on this question.

We will also look into conducting the PK and PK/PD analyses noted in additional points 2 and 3 but note we do have limited PK data.

Meeting Discussion: None

Nonclinical Questions

6. **Does the Agency agree that further fertility studies are not necessary for teprotumumab?**

FDA Response: We agree that fertility studies might not be warranted. However, based on mechanism of action and literature information, an effect on fertility cannot be excluded. The BLA should include an integrated summary and a copy of all published literature used to support a role of IGF/IGF-1R in fertility and any adverse effects related to IGF/IGF-1R inhibition, and a formal waiver should be submitted, as noted under Question 7.

Sponsor Comment: We have no points for further discussion on the nonclinical questions and will plan to submit waivers for fertility and carcinogenicity studies to the IND.

Meeting Discussion: None

7. **Does the Agency agree that the overall nonclinical program conducted to date with teprotumumab is sufficient to support registration for the treatment of moderate to severe active TED?**

FDA Response: The overall nonclinical program conducted to date appears adequate to support registration, with the following recommendations:

a. *Please submit formal waiver requests to the Division to omit fertility and peri-postnatal studies. They should include your rationale, a summary of all safety data to support your rationale, and a copy of all literature referenced in the summaries.*
b. *If you believe that carcinogenicity studies are not needed, you should also submit a formal waiver to the Division for review providing your rationale to omit the studies.*

A final decision as to the adequacy of the data to support registration will be determined upon review of the waiver requests and the BLA.

In addition, based on the manufacturing changes, additional nonclinical studies may be required if biological comparability is not demonstrated for the drug substance and/or the drug product.

Meeting Discussion: None

Pediatrics Question

8. **Does the Agency agree with River Vision's rationale that a waiver of pediatric requirements would apply for teprotumumab?**

FDA Response: If teprotumumab has been granted orphan designation for the treatment of active TED, PREA would not apply to this orphan-designated indication.

Sponsor Comment: We have no points for further discussion on this question.

Meeting Discussion: None

CMC Questions

Given the breakthrough status recently granted to teprotumumab, we strongly encourage you to request a CMC only meeting to discuss product development, including product characterization, process development, analytical methods development, and stability studies. The current meeting package is incomplete and contains substantial errors, e.g., mislabeled, incomplete, and inaccurate figures and tables, an unclear description of the bioassay bridging strategy, etc. (see specific responses to your questions below). To enable effective meetings with meaningful discussions and efficient receipt of substantially informative advice, please ensure that subsequent meeting packages contain complete and accurate information (with appropriate data) to describe and support the questions posed.

Sponsor Comments: Considering the recently granted breakthrough status, the Sponsor does intend to request a CMC meeting to discuss and achieve concurrence in aspects of product development, including product characterization, process development, analytical methods development, and stability studies related to the program. What additional briefing materials would be needed by the Agency in order to make this meeting as productive as possible?

The Sponsor acknowledges and apologizes for the incomplete nature of the current meeting package.

Meeting Discussion: See Meeting Discussion for Question 9.

9. The manufacturing of teprotumumab is being changed (site transfer and process adaptions) for both the drug substance and drug product. Does the Agency agree that the proposed program to demonstrate biological comparability is adequate and sufficient to support a BLA filing?

FDA Response: No; insufficient information was provided to support the proposed comparability program. A number of potential issues with the proposed program have been identified.

While it is appropriate to implement many of the previous FDA CMC recommendations for the current comparability program, the expectations regarding comparability change over the course of product development; protocols and data determined to be acceptable during early stages of product development are often not sufficient to support comparability during or after completion of pivotal clinical studies. Ultimately, the determination of comparability will be a BLA review issue.

Meeting Discussion:

The Sponsor provided an overview of the planned CMC activities and intent to meet with FDA in the future to discuss the comparability protocol. The Agency recommended having a meeting

to review the comparability protocol, lots to be compared, and the bridging strategy for the bioassay. The Agency recommended requesting the meeting before the comparability data are available after the Sponsor stated their comparability data would not be available until the beginning of 2017.

The Agency noted the importance of using testing results from material used in the clinic when setting acceptance criteria. Sponsor clarified the plan to generate acceptance criteria by using the (b) (4) material, both of which were used in the TED01RV trial. The Agency requested that the future meeting briefing packages include information on which lots were used in the TED01RV trial.

The Sponsor stated its intent to make a future side-by-side comparison using the (b) (4) material for comparison to the new material. The Sponsor noted that to start a new study using the new material, use of 2 (b) (4) produced lots to establish comparability rather than 3 would be preferable from a timing perspective.

Sponsor Comments: The Sponsor acknowledges the Agency's comments and intends to seek concurrence on the comparability protocol for the drug substance and drug product manufactured (b) (4) respectively.

Regarding the proposed comparability study, we have the following comments:

a. *The changes to both the drug substance (DS) (b) (4) and the drug product (DP) manufacturing process are significant. It is not clear why only one lot of DS manufactured (b) (4) at the new site (b) (4) (b) (4) will be compared to the current DS lots, rather than performing testing side-by-side all three DS lots manufactured (b) (4). In order to evaluate and understand any potential differences in DS quality, more than a single lot should be used in the comparability study.*

Sponsor Comment: The Sponsor intends to demonstrate comparability of the drug substance manufactured (b) (4) using multiple lots derived from the new manufacturing process.

b. *The comparability study states that only DS lots will be used to conduct stressed stability studies for comparison of the rate and pathways of degradation of the materials. Because changes are also proposed for the DP manufacturing process, the comparability study should also include stressed stability studies for the DP batches from previous and current manufacturing process if the (b) (4) DP stability data are intended to provide any support for the (b) (4) process and expiry period.*

Sponsor Comment: The Sponsor intends to perform stressed stability studies under accelerated conditions to compare the rates and degradation pathways associated with the drug product manufactured (b) (4).

c. *You indicated on page 9 of Appendix 1 that the old bioassay is not reliable and that side-by-side testing using this assay will not be performed. To identify potential product*

differences due to the manufacturing changes, samples should be tested in a side-by-side manner to minimize variability due to issues with the old bioassay. In addition, there is insufficient support for not performing side-by-side testing using the new bioassay. The use of combined historical and current data can lead to the inability to interpret the data, for example, if different early development reference standards are used or if there are instabilities in the reference standard(s).

Sponsor Comments: The current (old) bioassay is currently performed by (b) (4) on behalf of the Sponsor. (b) (4) has reported that the current assay repeatedly fails to meet the system suitability criteria associated with the test method resulting in repeated assay failures. The Sponsor, together with (b) (4), has developed a new bioassay based on an AlphaLISA assay format. This assay is currently being validated at (b) (4) (b) (4) and is intended to be used for the release of drug substance and products. The bioassay test method, validation protocol, and validation report will be submitted to the Agency for review in the BLA.

See also response to Question 11.

d. *Acceptance criteria should not be based on Roche data and small-scale studies. The key comparisons should be to the pivotal clinical study material (b) (4) (b) (4). The product quality attributes of the manufacturing-scale materials should be characterized and an evaluation of critical quality attributes should be used to inform the comparability acceptance criteria.*

Sponsor Comments: The Sponsor acknowledges the Agency's guidance. Acceptance criteria established to date have been based on the Roche (b) (4) material, two lots of which were used in the TEDRV01 study. The data from the (b) (4) process will be incorporated together with the Roche (b) (4) data to establish acceptance criteria. For clarity, no small-scale data was used in the development of the criteria presented in the briefing document. Considering that there were only two batches of the (b) (4) material produced, it would be difficult to create acceptance criteria on the basis of only those two batches.

e. *Where new methods are being implemented to replace the current methods due to issues with the current methods, the new methods should be an integral part of the comparability study, with acceptance criteria more informative than "report results."*

Sponsor Comment: The Sponsor acknowledges the Agency's guidance and will incorporate any new methods into the comparability protocol and implement numerical limits as part of the acceptance criteria associated with these methods.

f. *"Report results" is generally not an acceptable acceptance criterion for a comparability study. Similarly, for methods such as oligosaccharide mapping, "chromatogram comparable to reference," is not a sufficient acceptance criterion. Although teprotumumab glycosylation might not significantly impact in vitro potency, the*

oligosaccharide profile can impact PK and immunogenicity and should be assessed with appropriate consideration of these potential impacts.

Sponsor Comments: The Sponsor acknowledges the Agency's guidance. Where applicable, numerical limits will be applied to test methods.

g. *Small-scale model data will not support comparability evaluations. Small-scale models of DS* (b) (4) *manufacturing are typically not fully representative of the manufacturing-scale process and product.*

Sponsor Comments: The Sponsor provided small-scale data in the briefing document solely for information purposes and as an indication of what might be expected in evaluating comparability between the drug substance derived from the (b) (4) ***processes once completed. The Sponsor intends to establish comparability using multiple lots manufactured at scale using the*** (b) (4) ***process***.

h. *The data presented in figures 8-15 are not clear. In future submissions, text should not cover the data, full-scale and enlarged images should be provided, and overlays of chromatograms, electropherograms, peptide maps, etc. should be provided where appropriate.*

Sponsor Comments: The Sponsor acknowledges the Agency's request and apologizes for the technical issues in reproducing chromatograms and will provide full-scale and enlarged images, overlays of chromatograms, electropherograms, peptide maps, etc. in future submissions.

Meeting Discussion: None

10. Does the Agency agree to the control strategy proposed for both drug substance and drug product?

FDA Response: No. We do not agree. The proposed control strategy for the DS and DP shown in Appendix 2 appears to include only one aspect of product control strategy, (b) (4) (b) (4) *. The control strategy for your DS and DP should include consideration and understanding of* (b) (4) (b) (4) *how these factors contribute to the overall product quality.*

Sponsor Comment: The Sponsor acknowledges the Agency's guidance and will provide a description of the entire control strategy for the drug substance and product at future meetings.

Regarding the testing aspect of your control strategy, limited specific advice can be provided at this time because the commercial specifications tables, Table 14 and Table 15, appear to be mislabeled; they are incomplete and inconsistent with the Appendix. In addition, the

specifications need to be evaluated in the context of the complete historical clinical lot data and product characterization data and information. The BLA should include justifications and supporting data for not including testing of excluded product quality attributes as part of lot release and stability specifications. It is not clear that the proposed potency assay is fully representative of the teprotumumab mechanism of action; detailed information and data to demonstrate that the surrogate endpoint is appropriate to use to control potency should be included in the BLA. Container closure integrity testing should be performed in lieu of sterility testing for DP stability.

Sponsor Comments: The Sponsor apologizes for mislabeling of the referenced tables. The Sponsor acknowledges the Agency's guidance regarding the justification of quality attributes with respect to lot release and stability specifications in light of historical data. In addition, a justification of the potency assay will be provided. Container closure integrity will be employed in lieu of sterility testing.

Meeting Discussion: None

11. Does the Agency agree with the Bioassay bridging strategy?

FDA Response: No. It appears that the only information included is the "sponsor rationale," and based only on this comment, the strategy for bridging the bioassays is not clear. Although the samples to be used in the new assay are not clear, it appears that it would not be acceptable to only compare historical values derived from the existing assay to results generated by the new assay. The most appropriate bridging strategy is a direct side-by-side comparison of existing (b) (4) *samples,* (b) (4) (b) (4) *, and all available proposed commercial product material, using both current and new methods. The strategy used should be able to attribute any differences observed in the results to differences between the methods and not to differences in product quality. With respect to the use of any historical data, the reference standard(s) used and the stability of these materials should be considered.*

Sponsor Comments: See response provided to Question 9c. The Sponsor intends to compare the results of the current bioassay with the new bioassay. Unfortunately, given issues currently experienced with the assay, this may not be possible due to the failed system suitability criteria. The Sponsor will provide all data produced in this comparison to the Agency for its review.

Meeting Discussion:

The Sponsor explained the issues that have been experienced in using the old bioassay, leading to assay failures and therefore a new assay has been developed. The Agency expressed that they would like to see the old assay and the new assay tested side-by-side with the same samples. The Sponsor noted that it may no longer be possible to get valid results from the old assay. The Agency recommended providing the details of their issues with the old bioassay with data to support alternative approaches in a future meeting package. Sponsor clarified that they will use (b) (4) samples from (b) (4) lots to establish comparability and for bridging the new bioassay with the

current bioassay. The Agency also stated that if only the new bioassay is used to test retain samples, then the stability of the old (b) (4) samples should be addressed in the bridging study proposal.

12. Does the Agency agree that the proposed strategy to qualify commercially available assay reagents for HCP quantitation is acceptable and the generation of (b) (4) specific reagents is not necessary?

FDA Response: It is unclear from the rationale provided in the meeting package how the commercial kit coverage of HCPs will be demonstrated. However, if sufficient coverage is demonstrated using the commercially available reagents, then (b) (4) specific reagents will not be necessary. (b) (4) (b) (4) (b) (4) *. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum.* (b) (4) (b) (4)

Sponsor Comments: The Sponsor intends to seek concurrence with the Agency on the HCP assay reagent qualification protocol prior to its execution. If sufficient coverage is achieved using the commercial kit, then the assay will be used as part of the control strategy for the commercial drug substance manufactured by (b) (4) for the Sponsor.

Meeting Discussion: None

13. Does the Agency agree with the proposed outline for the process validation strategy for both drug substance and drug product?

FDA Response: An outline of the proposed process validation strategy was not provided.

The proposal to base the process validation approach on the FDA and ICH guidance documents sited as background to this question is appropriate. However, the adequacy of your process validation studies will depend on the data generated and will be a BLA review issue.

Sponsor Comments: The Sponsor apologizes for this error in the briefing document. The Sponsor intends to provide the Agency with validation protocols and a more detailed planning of the process validation strategy for concurrence at future meetings.

Meeting Discussion: None

Additional Comments:
We are providing additional product quality microbiology comments for you to consider for the preparation of your BLA 351(a) submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

a. *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
b. *Three successful consecutive product* (b) (4) *validation runs at manufacturing scale. Bioburden and endotoxin levels* (b) (4) (b) (4) *should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
c. *Provide* (b) (4) *study protocols and acceptance criteria. During the* (b) (4) *studies, bioburden and endotoxin samples should be taken* (b) (4) *(3.2.S.2.5).*
d. *Bioburden and endotoxin data obtained during manufacture of at least three performance qualification lots (3.2.S.2.5).*
e. *Information and summary results from the shipping validation studies (3.2.S.2.5).*
f. *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
g. *Summary report and results from bioburden and endotoxin test methods qualification performed for* (b) (4) *the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*
h. *Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect* (b) (4) *on endotoxin recovery should be assessed* (b) (4) (b) (4) *(3.2.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support (b) (4)*. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation* (b) (4) (b) (4)

The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

(b) (4)

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

a.

b. (b) (4)

c. (b) (4) *Three successful product* (b) (4) (b) (4) *validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels* (b) (4) *should be monitored and bioburden and endotoxin limits provided.*

d. (b) (4)

e.

f. (b) (4) *validation demonstrating maintenance of container closure integrity.*

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

a. Container closure integrity testing. System integrity (b) (4) (b) (4) *should be demonstrated initially and during stability. Container*

closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ (b) (4) microns). Container closure integrity testing should be performed (b) (4) for stability samples (b) (4) (b) (4).

b. *Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.*
c. *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).*
d. *Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect (b) (4) on endotoxin recovery should be assessed (b) (4)*

(b) (4)

Sponsor Comment: The Sponsor acknowledges the Agency's guidance in these additional comments and in each case will provide the relevant data and reports to the BLA.

Meeting Discussion: None

14. The first batches of the 500 mg/vial drug product strength manufactured (b) (4) (b) (4) are expected to be available in Q1/2017. These will be put on stability according to ICH Q1A(R2). Data evaluation/extrapolation in line with ICH Q1E is planned to be used to determine an initial shelf life for the marketed drug. As additional data will become available, shelf life of the drug is planned to be extended upon submission of these data. Does the Agency agree with this approach for defining an initial shelf life for teprotumumab?

FDA Response: No. The shelf-life for the DP should be based on real time stability data from DP batches manufactured using a process that is fully representative of the intended commercial

process, (b) (4) (b) (4) (b) (4). The DS and DP stability programs should include stress stability studies performed under appropriate conditions to assist in elucidating the potential degradation pathways and identifying stability-indicating test methods. Please refer to ICH Q5C "Stability Testing of Biotechnological/Biological Products" for additional guidance.

Sponsor Comment: The Sponsor acknowledges to Agency's guidance regarding the definition of a shelf-life for the drug product and the need for the stability programs to include stress conditions.

It is not clear why DS manufactured using the (b) (4) process was not placed into a stability program. The stability data derived from the Roche product will not provide support for the commercial expiry. In addition, the (b) (4) DP data will provide limited support for the (b) (4) (b) (4) DP expiry period.

The expiry period can be (b) (4) (b) (4)

Sponsor Comments: The drug substance manufactured by (b) (4) was not placed on a formal stability program, since at the time of manufacture, the Sponsor planned to convert the entire batch to the drug product to provide sufficient clinical trial material for the TED study.

The Sponsor acknowledges the Agency's guidance with respect to the value of the (b) (4) drug product stability data in support of the definition of a commercial expiration date.

Meeting Discussion: None

Additional Comments:

1. *We note that the dosing rationale is based on the results that >90% IGF receptor occupancy is expected at 20 µg/mL, which was estimated with the SP2/0 material. If available, please provide the information on the IGF receptor occupancy comparison between SP2/0 and CHO material.*

Sponsor Comment: We will provide a response in the future to address this point.

2. *We note that PK analysis is pending for Study TED01RV and you had also planned for biomarker assessment(s). Upon completion of the planned analyses, we recommend that you attempt to develop an integrated population PK model utilizing the PK data from all studies (including oncology studies). We also recommend that you attempt to characterize the effects of major covariates (e.g., disease presence, weight, immunogenicity), relevant intrinsic and extrinsic factors (e.g., concomitant drugs, hepatic and/or renal impairment) on the PK of teprotumumab.*

3. *In addition, upon completion of the planned analysis in Comment 2 above, we also recommend that you characterize the exposure response relationships (e.g., dose-response, concentration-response) for safety. You may also consider including the safety data from other indications (e.g., oncology; DME) in determining the exposure/dose-response relationships for safety risk(s) (e.g., hyperglycemia).*

Sponsor Comment: Points 2 and 3 addressed in clinical pharmacology above.

Meeting Discussion: None

ATTACHMENTS AND HANDOUTS

Attachment 1 – CMC Timelines and Milestones graphic from Sponsor sent via e-mail on, August 18, 2016

Attachment 2 – August 24, 2016, e-mail from Sponsor containing post-meeting related question, and the August 25, 2016, response from Division.

Attachment 1

CMC Timelines and Milestones

Q4 2016	1H 2017	2H 2017	2018
• GMP batches (1,2) (b) (4)	• GMP batches (3,4) (b) (4) • Comparability for DS and DP completed	• Validation batches (b) (4) (b) (4)	
	• Q1 DP batch 1 (b) (4) • Q2 Validation batches (b) (4)	• Q3 Validation batches (b) (4)	
• Initiate FMEA and CQA	• (b) (4) model validation		• Complete FMEA and CQA assessments
			• Data compilation and report writing, BLA preparation and filing

Attachment 2

From: Almoza, Lois
Sent: Thursday, August 25, 2016 10:02 AM
To: 'Liz Lucini'
Subject: RE: IND 112952: RV001EOP2 Sponsor meeting minutes and one question for the Division

Hi Liz,

It is acceptable to the Division to finalize the CSR using SI units.

Thanks,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

From: Liz Lucini (b) (4)
Sent: Wednesday, August 24, 2016 2:45 PM
To: Almoza, Lois
Subject: IND 112952: RV001EOP2 Sponsor meeting minutes and one question for the Division

Hi Lois,

As discussed the other day on the phone, please find attached a copy of the sponsor's meeting minutes from last week's RV001 EOP2 meeting. We will also plan to submit these to the IND for the administrative record.

There was one comment in the EOP2 preliminary feedback that we didn't discuss, but that the team would appreciate the Division's feedback on as it impacts our plans for finalization of the TED01RV clinical study report. On page 14 of the feedback, there was a comment regarding Laboratory Test Units for Clinical Trials that noted the potential need to report laboratory tests in both US conventional units and SI units and recommended obtaining input from the Division. The TED01RV CSR is currently being written using SI units, leading to the question: **Is it acceptable to the Division to finalize the CSR using SI units or would it be preferable to also convert laboratory test results to US conventional units?**

Please let me know your thoughts on how soon we may be able to receive clarification on the laboratory units question, as that factors into the Sponsor's plans for CSR finalization.

Many Thanks and Best Regards,
Liz

Liz Lucini, Pharm.D. (b) (4)
(b) (4)
M (b) (6)
(b) (4)

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

/s/

WILEY A CHAMBERS
09/13/2016