



Late-Cycle Meeting Summary

Application type and number: STN BL 125488/0
Product name: Crotalidae Immune Fab2 Equine Intravenous
Applicant: Instituto Bioclon S.A. de C.V.
Meeting category: Late-Cycle Meeting (LCM)
Meeting date & time: November 21, 2013, 2 p.m. to 3 p.m.
Meeting format: Teleconference
Meeting Chair/Leader: Howard Chazin, MD
Meeting Recorder: Edward Thompson

LCM package sent: November 8, 2013

FDA Participants:

Karen Campbell, Biologist, Division of Biological Standards and Quality Control, OCBQ
Howard Chazin, MD, MBA, Deputy Director of Medical Affairs, Division of Hematology, OBRR

John Dennis, DVM, Director, Division of Veterinary Services, OM

Robert Fisher, PhD, Staff Fellow, Division of Hematology, OBRR

Basil Golding, MD, Director, Division of Hematology, OBRR

Ravi Goud, MD, MPH, Medical Officer, Division of Epidemiology, OBE

Cheryl Hulme, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ

Nisha Jain, MD, Chief, Clinical Review Branch, Division of Hematology, OBRR

Chris Joneckis, PhD, Senior Advisor, Office of the Director, CBER

Michael Kennedy, PhD, Biologist/Team Leader, Division of Hematology, OBRR

Xue Lin, PhD, Mathematical Statistician, Division of Biostatistics, OBE

Erin McDowell, Consumer Safety Officer, Division of Inspections and Surveillance, OCBQ

Ginette Y. Michaud, MD, Deputy Director, OBRR

Paul D. Mintz, MD, Deputy Director of Medical Affairs, Division of Hematology, OBRR

Renee Rees, PhD, Mathematical Statistician, Division of Biostatistics, OBE

Evi Struble, PhD, Pharmacologist, Division of Hematology, OBRR

Kimberly Taylor, MBA, MPH, Operations Research Analyst, Office of Program & Strategic Analysis, OSP/CDER

Edward Thompson, Regulatory Project Manager, OBRR

Iliana Valencia, MS, Chief, Regulatory Project Manager Branch, OBRR

Maria Luisa Virata-Theimer, PhD, Chemist, Division of Hematology, OBRR

Nancy Waites, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ

Yonggang Wang, PhD, Visiting Associate, Division of Hematology, OBRR

Lilin Zhong, Biologist, Division of Hematology, OBRR

Contractor Participant:

Christopher Sese, Independent Assessor, Eastern Research Group, Inc.

Instituto Bioclon Attendees:

Jennifer Spinella, MT (ASCP), RAC, VP Regulatory Affairs & Quality Assurance, Rare Disease Therapeutics, Inc.

Tomas Gonzalez, MS, MBA/TM, Director, Regulatory Affairs, Rare Disease Therapeutics, Inc.

Michelle Taylor, Senior Director, Regulatory Affairs, Rare Disease Therapeutics, Inc.

Jude McNally, RPh, DABAT, VP, Medical Science Liaison, Rare Disease Therapeutics, Inc.

Walter Garcia, MD, Medical Director, Instituto Bioclon

Rita Mancilla, Plant Manager, Instituto Bioclon

Alexandra Sanchez, Drug Safety Coordinator, CCRP, Instituto Bioclon

(b) (4)

Background and Objectives:

FDA informed Instituto Bioclon S.A. de C.V. (Bioclon) on September 4, 2013, of the date for the late-cycle meeting. The purpose of the meeting is to share information, to discuss substantive review issues, and to communicate our objectives for the review cycle of STN BL 125488/0 for Crotalidae Immune Fab2 Equine Intravenous for the proposed indication of:

Management of patients with pit viper envenomation and prevention of late or recurrent coagulopathies

FDA sent the Late-Cycle Meeting package to Instituto Bioclon on November 8, 2013.

DISCUSSION SUMMARY:

Introductory Comments:

FDA introduced the agenda items, which are listed herein.

1. Chemistry, manufacturing and controls, facilities & equipment, non-clinical pharmacology/toxicology, clinical pharmacology, clinical, bio-research monitoring, pharmacovigilance, risk evaluation and mitigation strategy, and labeling.
2. Outstanding Information Requests.
3. Post Marketing Requirements (PMR)/Post Marketing Commitments (PMC).
4. Questions from Instituto Bioclon.
5. Summarization by Instituto Bioclon.

FDA explained that the meeting is not intended to discuss the pending regulatory decision on the application. After the meeting discussion, FDA may request Bioclon to submit additional data or analyses. Submission of significant additional information may be considered a major amendment, and therefore could extend the user fee goal date 3 months beyond the current date of March 18, 2014.

Chemistry, Manufacturing and Controls:

1. Please commit to (b) (4) [redacted]
[redacted] production lots of Anavip and/or identically manufactured products with different specificities.

Additional discussion:

Bioclon agreed to do this after (b) (4) additional Anavip batches.

2. Per pharmacology/toxicology concerns regarding possible worst case scenario cresol exposure to patients (b) (4) [redacted]
[redacted]

Additional discussion: (refers also to Questions 8 and 20)

(b) (4) [redacted]
[redacted]

3. Bioclon does not have critical reagents for their potency assay (snake venom standards and internal positive control) on an ongoing stability program.

Additional discussion:

Bioclon agreed to start stability with internal controls on the next lot of Anavip and will submit the draft proposal and stability information.

4. Bioclon has agreed to (b) (4) [redacted] but the validation will not be completed until the end of March 2014 so this will need to be a PMC.

Additional discussion:

Bioclon agreed to the PMC for (b) (4) testing and agreed to a possible date of April 2014. FDA will include this PMC in the final action letter for the application.

5. Bioclon has not provided any (b) (4) [redacted]
[redacted]

Additional discussion:

Bioclon agreed to present the proposal after (b) (4) additional lots. FDA advised Bioclon to compare this (b) (4) data to historical data on other products. Bioclon accepted the recommendation and the information will be sent in June or July 2014.

6. The stability data suggest that they need shorten the dating period for both drug substance and drug product.

Additional discussion:

FDA informed Bioclon that this information was received today by an amendment to the application. The information is pending review. FDA suggested that the data cover (b) (4) for the bulk drug substance and (b) (4) months for the final drug substance. FDA advised Bioclon to generate more data in order to have the expiration date of the product extended. FDA noted a concern that the potency of the product (b) (4)

Facilities and Equipment:

7. No substantive issues at this time and no PMCs at this time.

Additional discussion:

No further discussion with this item.

Non-Clinical Pharmacology/Toxicology:

8. Worst case scenario exposure calculations raise concerns regarding possible exposures to cresol that are higher than other approved products. At these amounts there is potential for adverse reactions due to cresol such as generalized myalgias. (b) (4)

Additional discussion:

(b) (4). See also Item #3 above.

Clinical Pharmacology:

9. There are no substantive review issues at this time.

Additional discussion:

No further discussion with this item.

Clinical:

10. The pre-specified primary endpoint for superiority over CroFab with regard to prevention of recurrent coagulopathy was not met with statistical significance. Additional assessment of efficacy parameters is ongoing.

Additional discussion:

FDA noted that the pre-specified superiority endpoint was not met; hence that claim cannot be made. FDA also noted the unmet medical need for this product in this rare disease. FDA is currently reviewing other clinical outcomes such as snakebite severity score and will also consider a non-inferiority statistical margin.

Bioresearch Monitoring:

11. There are no substantive review issues at this time.

Additional discussion:

No further discussion with this item.

Pharmacovigilance:

12. There are no substantive review issues at this time.

Additional discussion:

No further discussion with this item.

REMS or other risk management actions:

13. No issues were identified that would require a *Risk Evaluation and Mitigation Strategy* (REMS).

Additional discussion:

No further discussion with this item.

Labeling:

14. APLB will perform a secondary review of the proprietary name within 90 days of the Action Due Date.

Additional discussion:

No further discussion with this item.

15. Recommendations to the *Prescribing Information* and the vial and carton labels will be provided as part of the labeling review.

Additional discussion:

No further discussion with this item.

Advisory Committee Meeting:

16. Presentation of the BLA at the Blood Products Advisory Committee meeting is not planned.

Additional discussion:

No further discussion with this item.

PMR/PMC:

17. Bioclon commits to (b) (4) [redacted] production lots of Anavip and/or identically manufactured products with different specificities.

Additional discussion:

Bioclon agreed to the PMC.

18. Bioclon commits to provide the test method standard operating procedures (SOPs), method validation protocols, and method validation study reports (including all test results) for the detection of cytopathogenic and/or hemadsorbing agents (as described in 9 CFR 113.46) and the detection of extraneous viruses by the fluorescent antibody technique (as described in 9 CFR 113.47).

Additional discussion:

Bioclon agreed to the PMC one year after approval. FDA will take this into consideration.

19. Bioclon commits to (b) (4) [redacted] product lots of Anavip and/or identically manufactured products with different specificities.

Additional discussion:

Bioclon agreed to the PMC.

20. Bioclon commits to (b) (4) [redacted] (b) (4) [redacted] in the final drug product and performing the appropriate process validation to support the necessary manufacturing changes related to the (b) (4) [redacted] (b) (4) [redacted].

Additional discussion:

Bioclon agreed to the PMC.

21. Bioclon commits to completing the validation of their (b) (4) and providing CBER the final validation report by April 30, 2014.

Additional discussion:

Bioclon agreed to the PMC.

22. Bioclon commits to provide stability updates for the conformance lots manufactured in support of STN 125488/0 (lots (b) (4), plus one lot to be initiated during the pre-licensure inspection). These updates will be submitted annually as a PMC Annual Report, and the final stability report will be submitted as a PMC Final Study Report within 3 months of the final time-point.

Additional discussion:

Bioclon agreed to the PMC.

Outstanding Information Requests:

23. An information request was sent to Instituto Bioclon on November 6, 2013. Instituto Bioclon acknowledged receipt of this request. The response is expected on November 21, 2013.

Additional discussion:

FDA noted that the response to the information request was received today and the material has not yet been reviewed. Additional information requests have been sent out since November 7, 2013, by FDA. Bioclon acknowledged the information requests and agreed to provide responses as amendments to the application.

Decisions made and/or agreements reached:

1. Bioclon:

- a. Agreed to all PMCs
- b. Agreed to (b) (4) and will send in a proposed study
- c. Agreed to draft a stability protocol
- d. Agreed to (b) (4)
- e. Agreed to submit data regarding potency/shelf life/expiration date

Issues requiring further discussion:

1. The clinical review branch will discuss with Bioclon any outstanding clinical issues.

Action items:

1. Bioclon agreed to submit historical data for Item #5.

End

Concurrence Page

Application Number: STN 125488/0

Letter Type: Late Cycle Meeting Summary (LCMS)

Cc: EDR

History: Drafted/Revised Edward Thompson / November 24, 2013
Reviewed/Revised Michael Kennedy/December 13, 2013
Reviewed/Revised Nisha Jain/ December 12, 2013
Reviewed/Revised Howard Chazin/ December 13, 2013
Reviewed/Revised Sunday L. Kelly/ December 16, 2013
Reviewed/Revised Trevor Pendley/ December 11, 2013

Minutes verified:

(for attendees) _____
Michael Kennedy, PhD

Nisha Jain, MD

Howard Chazin, MD

Summary Received: _____
Basil Golding, MD

Concurrence box

Office	Name/Signature
OBRR	Edward Thompson
OBRR	Basil Golding