CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166

MICROBIOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: **February 23, 2007**
To: Administrative File, **STN 125166/0**
From: Brenda Uratani, Ph.D., CDER/OC/DMPQ TFRB, HFD-328 2/23/07
Through: Patricia Hughes, Ph.D., CDER/OC/DMPQ/TRFB, HFD-328 2/23/07
Subject: Review of Biological License Application (BLA): new BLA
US License: 1743
Applicant: **Alexion Pharmaceuticals Inc.**
Facility: **Lonza Biologics Inc., Portsmouth, New Hampshire (FEI 3001451441)**
Product: **Soliris™ (eculizumab, h5G.1-mAb)**
Dosage: **Sterile parenteral solution for intravenous infusion (300 mg at 10 mg/ml)**
Indication: Paroxymal Nocturnal Hemoglobinuria (PNH)
Due date: March 17, 2007

Recommendation: The drug substance section of the application was reviewed from a microbiological product quality perspective. The application is recommended for approval.

Review Summary

Alexion Pharmaceuticals Inc. submitted this BLA in support of the manufacturing of eculizumab, a humanized monoclonal antibody that binds to the human complement protein C5. This drug is indicated for the treatment of PNH, a rare life threatening hemolytic disease. Eculizumab is produced from a mouse myeloma NS0 cell expression system. The drug substance is manufactured at Lonza Biologics in Portsmouth, New Hampshire and the drug product is manufactured at [redacted]

The drug substance CMC sections of the BLA were evaluated in this review for adequacy from a microbiology product quality perspective. The sections evaluated include in part 3.2.S.2, 3.2.S.4, 3.2.S.6, 3.2.S.7, and 3.2.A.1.

A pre-approval inspection of Lonza Biologics was conducted by TFRB (Brenda Uratani, Bo Chi), OBP/DMA (Kurt Brorson), and NWE-DO (Ellen Madigan) in January 8-12, 2007. The manufacture for eculizumab drug substance was found to be in good control and GMP compliance. No 483 observation was made.

The facility and equipment controls were conducted during the pre-approval inspection. In addition, microbial control of the manufacturing process for eculizumab was evaluated in-depth on site and was found to be adequate. Please refer to the inspection report (EIR) for details.

Review Narrative

Drug Substance

Manufacturer-3.2.S.2

Drug substance manufacturer:
Lonza Biologics Inc.
101 International Drive
Pease International Tradeport
Portsmouth
New Hampshire 03801, USA
FEI: 3001451441

Cell banking:
Lonza Biologics PLC
228 Bath Road
Slough, Bershire SL1 4DX
UK
FEI: 1000583959

Testing:

[redacted]

Alexion Pharmaceuticals, Inc. (drug substance release and stability tests)
352 Knotter Drive
Cheshire, Connecticut 06410
FEI: 3006031727

Description of Manufacturing Process and Process Controls, 3.2.S.2.2

Eculizumab drug substance is manufactured in a [redacted] scale production bioreactor. The cells used to inoculate the [redacted] production bioreactor originate from a single ampoule taken from the WCB. A single bioreactor harvest is purified as a single batch, yielding a nominal batch size of approximately [redacted] of drug substance.

1 Page(s) Withheld

✔ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Microbiology- 6

Bioburden samples are taken at appropriate points throughout the purification process steps. The bioburden and endotoxin in-process monitoring data for the [redacted], were evaluated on-site and found to be acceptable, showing that the process is adequately controlled.

Satisfactory

Filling, Storage, and Transportation- 3.2.S.2.2.4

The filling, storage and transportation process for the manufacture of eculizumab drug substance is comprised of [redacted] transportation.

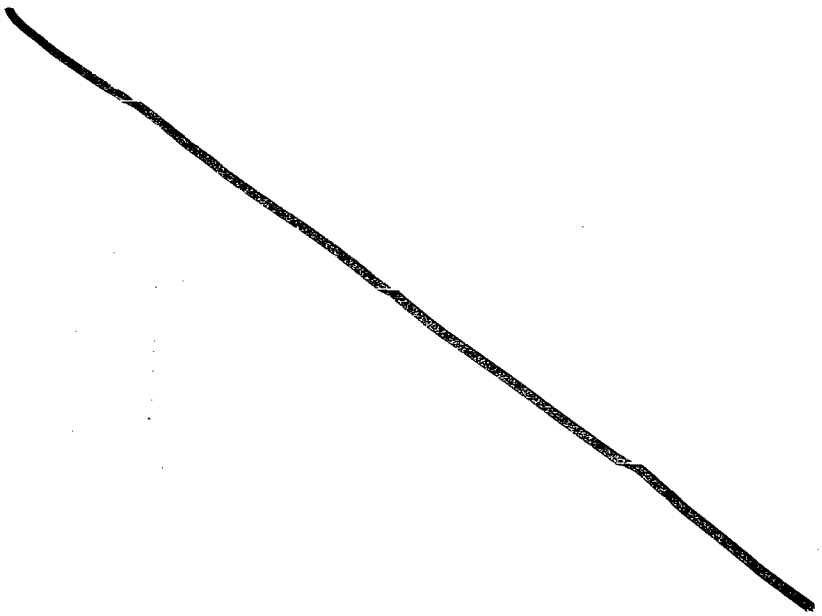
The concentrated and [redacted] production in final formulation buffer is [redacted] After [redacted] and integrity tested using the bubble point method. The [redacted] The drug substance containers are [redacted] packaging [redacted] and shipped.

Satisfactory

Control of Materials- 3.2.S.2.3

This is reviewed by OBP/DMA reviewers.

Controls of Critical Steps and Intermediate- 3.2.S.2.4



Satisfactory

Process Validation and/or Evaluation- 3.2.S.2.5

The microbiological validation [redacted] was evaluated during the pre-approval inspection and was found to be acceptable.

Process validation summary reports on the drug substance manufacturing process are review by OBP/DMA.

Characterization- 3.2.S.3; Control of Drug substance- 3.2.S.4; Reference Standards or Material- 3.2.S.5

This is evaluated by OBP/DMA reviewers.

Container and Closure System- 3.2.S.6 and 3.2.A.1

Eculizumab drug substance is dispersed into [redacted] containers with an [redacted] and associated filling tubes and fitting. The storage vessels are adequately described in the BLA and were inspected in the preapproval inspection in January 8-12, 2006.

Satisfactory

Stability- 3.2.S.7

This is evaluated by OBP/DMA reviewers.

Environmental Assessment

The BLA letter states that "As pursuant to 21 CFR 25.31(b). Alexion requests a categorical exclusion from providing an environmental assessment for the commercial manufacture, distribution and use of SOLIRIS."

cGMP Status

A pre-approval inspection was conducted for the manufacture of eculizumab drug substance at Lonza Biologics Inc (FEI 3001451441) January 8 through 12, 2007. No 483 was issued. The facility was found to be in good GMP compliance. There are also no pending or ongoing compliance actions to prevent approval of STN 125166/0 at this time.

A GMP inspection was conducted for the drug substance release testing lab at Alexion (FEI 3006031727) by NEW-DO, January 17 through 19. The inspection is classified VAI for minor GMP issues and the District recommend approval.

Conclusion

I. The drug substance section of the application is acceptable from a microbiology product quality perspective. The microbial controls for the manufacturing process were evaluated during the pre-approval inspection and are found to be adequate. The application is recommended for approval.

II. The drug substance control of Source and Starting Materials of Biological Origin, Generation of Cell Substrate, Cell banking System, Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections are reviewed by OBP/DMA.

III. GMP compliance-

- Lonza Biologics, New Hampshire (manufacturer of the drug substance) was inspected and is found to be in good GMP compliance.
- Alexion Pharmaceuticals, Connecticut (release testing) was inspected by ORA and is found in acceptable GMP compliance.

Cc: HFD-328, Uratani
HFD-328, Hughes
HFD-320, Harper-Velazquez
HFD-320, Friedman
HFD-328, TFRB Blue Files (STN 103836)

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