

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166

CHEMISTRY REVIEW(S)



Review Cover Sheet

BLA STN 125166/0

SOLIRIS™ (Eculizumab)

Alexion Pharmaceuticals Inc.

Michelle Frazier-Jessen, Ph.D.

Joseph Kutza, Ph.D.

Gurpreet Gill-Sangha, Ph.D.

Kurt Brorson, Ph.D.

Division of Monoclonal Antibodies, HFD-123



CMC Review Data Sheet

- 1. **BLA#** STN 125166/0
- 2. **REVIEW #:** 1
- 3. **REVIEW DATE:** 01-MAR-2007
- 4. **REVIEWERS:** Michelle Frazier-Jessen, Ph.D.
Joseph Kutza, Ph.D.
Gurpreet Gill-Sangha, Ph.D.
Kurt Brorson, Ph.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS¹:**

<u>Previous Documents</u>	<u>Document Date²</u>
Pre-BLA Meeting	28-MAR-2006
Filing Review (45 days)/Deficiency Com.	21-NOV-2006
E-com	15-NOV-2006
E-com	22-NOV-2006
T-com	29-NOV-2006
E-com	05-DEC-2006
T-com	18-DEC-2006
E-com	08-JAN-2007
E-com	11-JAN-2007
T-com	16-JAN-2007
E-com	18-JAN-2007
T-com	24-JAN-2007
E-com	26-JAN-2007
E-com	29-JAN-2007
E-com	30-JAN-2007
E-com	01-FEB-2007
T-com	02-FEB-2007
E-com	05-FEB-2007
T-com	27-FEB-2007
E-com	28-FEB-2007

¹ Chronology of previous CMC communications between CDER and the firm and/or reviews

² Applicant's letter date or date of review and/or communication with applicant

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	
STN 125166/0	Original Submission	19-SEPT-2006
STN 125166/0002	Resp to CMC IR	27-OCT-2006
STN 125166/0003	Stability Update, Resp to CMC IR	21-DEC-2006
STN 125166/0005	Resp to CMC IR	26-JAN-2007
STN 125166/0006	Labeling	21-FEB-2007
STN 125166/0007	Resp to CMC IR, Stability	28-FEB-2007



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7. NAME & ADDRESS OF APPLICANT:

Name: Alexion Pharmaceuticals, Inc.
Address: 352 Knotter Drive, Cheshire, CT
Representative: Nancy C. Motola, Ph.D, RAC
Telephone: 203-271-8241

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Soliris™
- b. Non-Proprietary Name: eculizumab
- c. Code name: h5G1.1-mAb
- d. Common name: anti-(human complement C5 a-chain) monoclonal antibody
- e. Drug Review Status: Priority Review
- f. Chemical Type: recombinant humanized immunoglobulin G2/G4 kappa mAb

9. PHARMACOL. CATEGORY: Therapeutic monoclonal antibody to human complement C5 a-chain.

10. DOSAGE FORM: Sterile parenteral solution.

11. STRENGTH/POTENCY:

- a. The concentration of Soliris™ (eculizumab) Drug Product is 10.0 +/- 1.0 mg/ml
- b. Potency is defined as a passing result of <50% hemolysis at 6.25 mcg/ml of eculizumab in a proprietary hemolytic assay. A proprietary C5 Binding assay, with a result of   BU/mg supports the Hemolytic potency assay.
- c. Dating period for vial drug product is 24 months when stored at 2°C -8°C. Following dilution into saline, the diluted drug product is stable for 24 hours post-dilution when stored at 2-8°C or at 18-25°C.

12. ROUTE OF ADMINISTRATION: Intravenous infusion after dilution to a final concentration of 5 mg/mL.

13. ANIMAL- AND HUMAN-DERIVED RAW MATERIALS

The animal-derived raw materials used in the manufacturing process of eculizumab are only used in cell culture and cell banking.

Item	
Process Stage	
Vendor	
Source	
Adventitious Agent Control	
Item	
Process Stage	
Vendor	
Source	
Adventitious Agent Control	

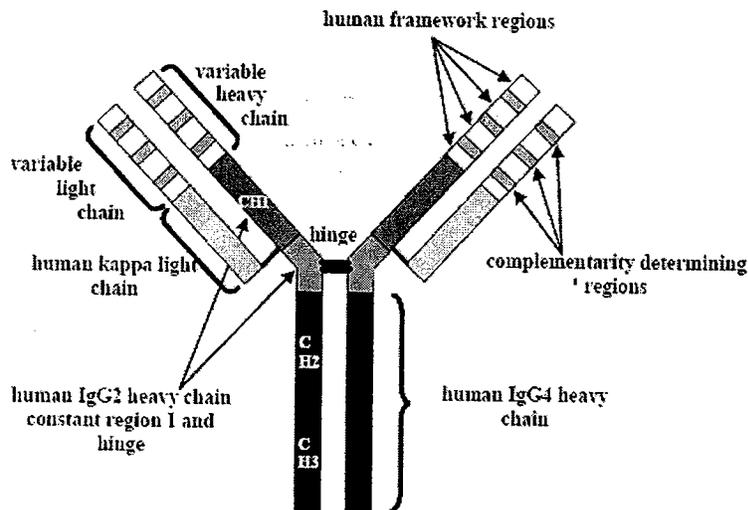
	[REDACTED]
Item	
Process Stage	
Vendor	
Source	[REDACTED]
Adventitious Agent Control	

14. **PRIMARY STRUCTURE, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

The drug substance, eculizumab, is a humanized IgG_{2/4} kappa antibody, consisting of two 448 amino acid heavy chains and two 214 amino acid light chains. The heavy chains are comprised of human IgG₂ sequences in constant region 1, the hinge, and the adjacent portion of constant region 2, and human IgG₄ sequences in the remaining part of constant region 2 and 3. The light chains are comprised of human kappa sequences. The variable chains consist of human framework regions with grafted murine complementarity-determining regions, which form the antigen binding site.

[REDACTED]

MALDI-TOF mass spectrometry has indicated the molecular weight of the molecule to be within 1% of the expected molecular mass of 148,523 Da.. The mature eculizumab protein is expressed in a murine myeloma NS0 cell line.





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The amino acid sequence of eculizumab is shown:

Heavy Chain
Light Chain

15. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	V			4	Adequate	26-FEB-2007	Sufficient information in BLA for review
	V			4	Adequate	26-FEB-2007	Sufficient information in BLA for CMC review; Facility-specific issues reviewed by TFRB (G. Salud)
	III			4	N/A	N/A	Meets USP/Ph. Eur. Standards
	III			4	N/A	N/A	Meets USP/Ph. Eur. Standards



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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
BB IND	11075	Eculizumab development for PNH

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approve	Pending	Colleen Hoyt
Labeling Nomenclature Committee/Office of Drug Safety	Approve	Pending	DMETS
OPDRA#	Approve	Pending	DMETS
Environmental Assessment	Approve	Pending	Brenda Uratani, TFRB
TFRB	Approve	Pending	Brenda Uratani Gilbert Salud

[#] Review trade name for medical error avoidance

17. CMC Inspectional Activities

Two pre-approval inspections were performed and one pre-approval inspection was waived as part of the approval process for eculizumab.

- a. A pre-approval inspection of Lonza Biologics, PLC licensed biologics bulk drug substance manufacturing facility was conducted following a request by the Therapeutics and Facilities Review Branch, Office of Compliance, CDER. The inspection covered the manufacturing operations for BLA STN 125166 for the Soliris (Eculizumab) drug substance at Lonza Biologics, PLC (101 International Drive, Portsmouth, NH 03801) and was limited to the manufacturing of eculizumab drug substance as part of the product review.

The firm was previously inspected by CDER Office of Compliance/ DMPQ/ TFRB on March 12-15, 2006, covering 101B, a different manufacturing suite than the one covered during this inspection (101A). No observation Form FDA 483 was issued for the March 2006 inspection.

The team inspection was conducted by: Kurt Brorson, Ph.D. (Division of Monoclonal Antibodies), Ellen Madigan (ORA Boston District Office), Bo Chi, Ph.D. (TFRB) and



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Brenda Uratani, Ph.D. (TFRB) The inspection covered the six elements for a Robust Quality System: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, Packaging and Labeling, and Laboratory Controls. No Refusals were encountered during the inspection. No sample collection was needed. No 483 was issued at the conclusion of this inspection.

- b. An abbreviated pre-approval inspection was performed at Alexion Pharmaceuticals, located at 352 Knotter Drive, Cheshire, CT 06410, where the majority of in-process and lot release testing for eculizumab is performed. Alexion Pharmaceuticals has not been inspected previously; eculizumab is the first BLA submission for Alexion .

An objectionable observation was found regarding the hemolytic potency assay used for lot release of eculizumab drug substance and drug product. Specifically, a complete investigation has not been done to determine the root cause of initial OOS results and to initiate the appropriate corrective and preventative actions. A critical reagent used in the hemolytic assay had not been appropriately characterized. The sponsor plans to re-validate the hemolytic potency assay as part of a post-marketing commitment, which will help to address the objectionable observation (see **PMC #6**). No samples were collected and no refusals were encountered during the inspection. The lead investigator recommended that the inspection be classified as VAI.

- c. The PAI for Soliris DP at _____ was waived. This waiver was based on the criteria as required per SOPP 8410, "Determining When Pre-licensing/pre-approval Inspections(PLI/PAI) are Necessary." Information available from recent Pre-Approval and biennial GMP inspections performed at the _____ manufacturing facility were acceptable. The review committee felt that the best utilization of CDER resources at this time indicated an inspection was not warranted. These reasons justified waiving the inspection. Soliris DP batch records should be reviewed during the next biennial inspection.

**Appears This Way
On Original**

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Eculizumab is well controlled, and leads to a product that is pure and potent. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .

The sponsor has agreed to the following post-marketing commitments related to the product:

1. Alexion commits to developing a validated and quantitative assay for the measurement of human anti-human antibodies (HAHA) for the detection of antibody formation to Eculizumab. This assay will assess potential immune responses to the whole Eculizumab molecule. Description of the validated assay will be submitted to the BLA as a CBE 30 by July 9, 2008.
2. Alexion commits to developing a validated and sensitive assay for the measurement of neutralizing HAHA to Eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BLA by July 9, 2008.
3. Alexion commits to revalidating the linearity and accuracy of the Osmolality method across the full specification range using a combination of product samples diluted to lower osmolality and product samples spiked with osmolality standards. The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.
4. Alexion commits to revalidating the linearity of the IEF method across a load range of . The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

5. Alexion commits to revising the IEF method SOP to specify that the method is validated only for a [REDACTED]. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.
6. Alexion commits to improving and revalidating the existing hemolytic assay. Improvements include increasing the number of sample replicates and qualifying the chicken erythrocytes reagent. The revised method SOP and revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.
7. Alexion commits to developing a new quantitative biological activity assay to replace the existing hemolytic assay, or submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed. This information will be submitted to the BLA as a CBE 30 by February 29, 2008. Validation of the quantitative biological activity assay will be submitted by July 9, 2008.
8. Alexion commits to providing FDA with a completed drug substance and drug product container closure system leachables evaluation using end-of-shelf-life, long-term 2 – 8°C stability samples. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.
9. Alexion commits to develop a suitable [REDACTED] assay and subsequently confirm [REDACTED] on three drug substance batches. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance

- SOLIRIS™ is a sterile, clear, colorless liquid formulation composed of 10 mg/ml eculizumab buffered to a target of pH 7 in a formulation containing [REDACTED] sodium phosphate, [REDACTED] sodium chloride, [REDACTED] Polysorbate 80 and Water for Injection. Soliris does not contain preservatives. The eculizumab drug product is filled into 30 cc Type I [REDACTED] vials with a target fill volume of [REDACTED], to allow for complete withdrawal of labeled contents. The eculizumab antibody is designed for infusion by diluting into commercially available intravenous solutions, such as normal saline, (0.9% sodium chloride), half normal saline (0.45% sodium chloride), Ringer's solution, or 0.5% Dextrose in Water (D5W).
- The eculizumab manufacturing process has undergone several changes throughout product development. There have been five drug substance manufacturing processes used over the development of eculizumab. These processes are referred to as Process A, B, C, D, and E. Process E is the commercial process. Process A was only used for the

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Deliberative Process

must receive the meningococcal vaccine at least 2 weeks prior to receiving SOLIRIS™ therapy. The therapy consists of 600 mg via 25 to 45 minutes intravenous infusion every 7 ± 2 days for the first 4 weeks followed by 900 mg for the fifth dose 7 ± 2 days later and then 900 mg every 14 ± 2 days thereafter. Intravenous push or bolus injection is prohibited.

The preparation for administration is to be performed ——— Each vial contains 300 mg of active ingredient in 30 mL of product solution. The required amount of SOLIRIS is transferred into an infusion bag or infusion vial and diluted to a final concentration of 5 mg/mL by addition of the appropriate amount (equal volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP. The final volume of a 5 mg/mL diluted SOLIRIS solution is 120 mL for 600 mg doses or 180 mL for 900 mg doses. Diluted solutions of SOLIRIS may be stored at 2-8°C (36-46°F) or at room temperature (18-25°C) for up to 24 hours prior to administration. Diluted solutions stored at 2-8°C should be allowed to warm to room temperature prior to administration.

Eculizumab vials must be stored in the original carton until time of use under refrigerated conditions at 2-8°C (36-46°F) and protected from direct light. Eculizumab vials should not be frozen or shaken. The recommended expiration dating period for eculizumab DP is 24 months at 2-8°C (36-46°F).

C. Basis for Approvability or Not-Approval Recommendation

- Soliris (eculizumab) is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Eculizumab is manufactured consistently, resulting in a safe and effective product and should be approved for the proposed indication.
- Post-marketing commitments described in the recommendation section above will provide additional information to assure the continued safety of the product.



SUMMARY



III. Administrative

A. Reviewers' Signature

Product Reviewers:

Patrick Swann
Joseph Kutza, Ph.D. (Drug Substance)

Michelle Frazier-Jessen 2/26/07
Michelle Frazier-Jessen, Ph.D. (Drug Product/Analytical Laboratory Facility)

Gurpreet Gill-Sangha 2/27/07
Gurpreet Gill-Sangha, Ph.D. (Analytical Methods/Methods Validation)

Kurt Brorson 2/27/07
Kurt Brorson, Ph.D. (DS Facility/Adventitious Agents)

B. Endorsement Block

Product Branch Chief: Patrick Swann, Ph.D. *Patrick Swann* 2/27/07

Product Division Director: Kathleen Clouse, Ph.D. *Kathleen Clouse* 2/27/07

C. CC Block

Office Director: Steve Kozlowski, M.D.
Division of Monoclonal Antibodies File/BLA STN 125166/0

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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: March 13, 2007
To: Administrative File, STN 125166/0
From: Gilbert Salud, CMC Reviewer, CDER/OC/DMPQ TFRB, HFD-328 *As. 3/13/07*
Through: Patricia Hughes PhD, Acting Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328 *PH 3/13/07*
Subject: Review Memo: Biologic License Application: Original Application for treatment of Treatment of paroxysmal nocturnal hemoglobinuria (PNH).

US License #1743

Applicant Alexion Pharmaceuticals, Inc.
352 Knotter Dr.
Cheshire, CT 06410

Facility

Product Eculizumab (Soliris)

Indication BLA - treatment of paroxysmal nocturnal hemoglobinuria (PNH)

Due date: March 17, 2007

Recommendation: The drug product manufacturing information referenced by Alexion Pharmaceutical Inc. in _____ for eculizumab drug product manufacturing has been reviewed and is deemed adequate to support _____ from a sterility assurance perspective. The submission is recommended for approval.

Summary

- Alexion Pharmaceutical Inc. submitted this BLA in support the drug product manufacturing of Eculizumab at _____
- The CMC sections related to drug product manufacturing were all deferred to _____ Volume 1 and 2. There was very little information regarding drug product manufacturing in the submitted Application (STN 125166.0). All related items associated with the drug product manufacture of eculizumab were reviewed in _____. A letter of authorization to reference _____ is included in the BLA.
- Drug product quality related issue such as product specifications, container closure leacheables, stability, and analytical methods were deferred to the Office of Biotech Products (OPS/OBP/DMA).
- Information to support _____; of the drug product is contained in _____ and is adequate from a sterility assurance perspective.

Manufacturer

The drug manufacturing site is

- No formulation or compounding steps are performed at _____. All formulation steps occur during the drug substance manufacturing process.
- General design of the drug product manufacturing process has remained fundamentally the same through out the clinical development. All ingredients are added during the manufacturing of the drug substance. The drug product manufacturing steps contains no formulation step. The formulated drug substance is stored in 2-8°C and transferred to a _____ and gently mixed prior to drug product manufacturing. The drug substance is _____ environment.

- Drug product manufacturing process consists of filling, labeling and packaging operations.

Container Closure System.

The primary container closure is USP Type _____ : Type 1 _____ vial,
_____ Stopper, _____ seals with _____

Eculizumab is light sensitive and Stability Studies completed was claimed to have been completed in accordance to ICH Guidelines. This study was based on the protectiveness of the secondary packaging carton. Ability of the secondary packaging to protect from light excludes the primary packaging to be light protective. Verify the types of tests performed.

Eculizumab drug product is filled into _____ 30cc vials stoppered with _____ stoppers and sealed with _____ seals
_____. These vials/stoppers and Seals are supplied by and are accompanied with vendor certification.

The vials are supplied by:

The stoppers and seals are supplied by:

Alexion Response:

[REDACTED]

Satisfactory.

Stability

The stability studies that were deferred to OPS/OBP are drug product Physical Description, General Characteristic, Quantity, Identity, Identity /Purity and Impurities, Potency, and Safety.

Stability studies were also conducted for [REDACTED]. Accelerated studies were also conducted. Long term stability studies were conducted at 2-8°C and protected from light.

The stability plan included monitoring for the secondary light protecting cartons to be placed at 2-8C and Tested [REDACTED]

Stability Review

There was no mention of Container Closure Integrity Testing conducted at any of the specified product testing time points. Additional information was requested on March 5, 2007 to Alexion to provide a rationale for not conducting container closure integrity tests during stability.

[REDACTED]

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Deliberative Process

cGMP Status

A compliance check was conducted on January 9, 2007 by Ms. Colleen Hoyt. The compliance check at that time was deemed VAI. A compliance re verification was conducted by MR. Anthony Charity and he indicated the following:

“There has not been any change from what Colleen has provided you. The firm is acceptable.”

Conclusion

- I. The drug product section of the application as it relates to sterile manufacturing validation is deemed acceptable. This application based on the information submitted in ~~_____~~ is recommended for approval.
- II. Review of product specifications, process specifications, and analytical methods were not part of this review. These sections were deferred to the product office (OPS/OBP/DMA/DTP).
- III. No additional inspectional follow-up items were identified.

Cc: HFD-328, Hughes
HFD-180, Moore
HFD-328, Harper-Velasquez
HFD-328, TFRB Blue Files (STN125166)

Archived File: S:\archive\BLA\125166\125166.0.rev.mem.BLA.March 13, 2007.doc