Summary Basis for Regulatory Action

From: Annette Ragosta, Chair of the Review Committee

BLA STN#: 125314/50

Applicant Name: Alba Bioscience Limited (Alba)

Date of Submission: August 18, 2017; application received in CBER August 31, 2017

MDUFA Goal Date: July 1, 2018

Proprietary Name/ Established Name: ALBAclone®Anti-D *fusion* (Anti-D), Blood Grouping Reagent

Intended Use: (*Copied from page one of the Instructions for Use document for each of the Rh products)*

"This Anti-D reagent is for the *in vitro* detection and identification of human RhD blood group status in patient and donor samples by direct agglutination and the indirect antiglobulin test."

Recommended Action:
The Review Committee recommends approval.

Review Office(s) Signatory Authority(ies): Orieji Illoh, MD, Director of the Division of Blood Components and Devices, Office of Blood Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below (Table 1) indicates the material reviewed when developing the SBRA

TABLE 1

Document title	**Reviewer name, Document date**
Clinical	Annette Ragosta, OBRR/DBCD/DRB May 18, 2018
Non-Clinical Review	Annette Ragosta, OBRR/DBCD/DRB May 18, 2018
Statistical Review	Paul Hshieh, OBE/DB/TEB May 18, 2018
CMC Product Review	• Annette Ragosta, OBRR/DBCD/DRB May 18, 2018 • Claire Wernly, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden May 22, 2018
CMC Facility Review	Priscilla Pastrana OCBQ/DMPQ/BII May 14, 2018
Labeling Review	Annette Ragosta, OBRR/DBCD/DRB May 18, 2018
Lot Release Protocols/Testing Plans	Varsha Garnepudi, OCBQ, DBSQC May 25, 2018
Establishment Inspection Report	Not applicable for these submissions, inspection waived
Bioresearch Monitoring Review	Not applicable for these submissions

1. Introduction

Alba Bioscience Limited (Alba) submitted an Efficacy Supplement requesting approval to manufacture and distribute ALBAclone®Anti-D *fusion* (Anti-D), Blood Grouping Reagent. The manufacture and assembly of the product covered by this application is performed at Alba Bioscience Limited, 21 Ellen's Glen Road, Liberton, Edinburgh, EH17 7QT, Scotland, United Kingdom.

The Anti-D Blood Grouping Reagent is prepared from a blend of monoclonal antibodies from cell lines LDM1 and ESD1, which are manufactured by Alba and used in the manufacture of previouslyapproved US licensed products.

The Rh blood group system is one of thirty-five known human blood group systems. It is the second most important blood group system, after the ABO

blood group system. The Rh blood group system consists of 50 defined blood group antigens, among which the five antigens D, C, c, E, and e are the most important. The D antigen is highly immunogenic, and antibodies to the D antigen are associated with hemolytic transfusion reactions and hemolytic disease of the fetus and newborn. The prevalence of the D antigen is 85% in Caucasians, 93% in African Americans, and 99% in Asians. Together with ABO typing, it is routine practice to test blood donors, pregnant women and blood recipients for the D antigen.

Clinical laboratories commonly perform blood group determination using hemagglutination methods. The principle of the hemagglutination test dates back to the 1900's when Karl Landsteiner identified the A, B, and O blood groups. The same principle applies to the other blood group systems. When reagent antiserum is added to red blood cells containing the corresponding antigen, agglutination occurs.

2. Background

Meetings with FDA:

Alba did not request any pre-submission meetings for this product.

Marketing History:

There is no foreign marketing history for the above-mentioned blood grouping reagent.

Device Description:

The main components of this blood grouping reagent are an IgM antibody and an IgG antibody derived from the in vitro culture of the IgG and IgM secreting human/mouse heterohybridomas of cell lines LDM1 and ESD1. The blood grouping reagent also contains (b) (4) with(b) (4) bovine serum albumin and 0.1% (w/v) sodium azide.

Chronology:

CBER received this original submission on August 31, 2017, and received three amendments from Alba in response to two information requests (IRs).

3. Chemistry Manufacturing and Controls (CMC)

The application was submitted in accordance with the recommendations in FDA's Guidance for Industry: "*Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Biological In-Vitro Diagnostic Product*".

All manufacturing is carried out in a controlled environment.

a) Manufacturing Summary

In Vitro Substances (IVS)

The IVSs include two monoclonal antibodies manufactured by Alba at their Edinburgh location. The specificity of each monoclonal antibody along with the IVS product status, cell line, antibody class and the cell line origin are provided in Table 2, below.

Table 2: Overview information on monoclonal antibody material

Specificity	**Anti-D**	**Anti-D**
Product status	Concentrate	Concentrate
Cell line ID	LDM1	ESD1
Antibody/isotype class	IgM	IgG1
Cell line origin	Human	Human

Both cell lines are negative for (b) (4) . Anti-D from Cell line (b) (4) can detect a variety of weak and rare RhD phenotypes with the exception of the DVI phenotype by direct hemagglutinati0n at 37 degrees Celsius . Anti-D from Cell line (b) (4) reacts by

indirect hemagglutination at 37 degrees Celsius using the indirect agglutination test (IAT) to detect the D antigen. Anti-D from Cell line (b) (4) can detect the DVI phenotype but not the DIV phenotype.

Both cell lines were produced by the (b) (4) Ownership of the cell lines and production of the relevant antibodies were then transferred from the (b) (4) to Alba Bioscience Ltd. as part of a commercial agreement.

LDM1 and ESD1 hybridoma cell lines were prepared as follows: (b) (4) to create the monoclonal cell line. Master and Working Cell Banks are then prepared and stored in (b) (4) for future production of monoclonal antibodies. During the cell bank preparation, (b) (4) .

Manufacture of monoclonal antibodies is performed by expansion of the cell line in culture. The monoclonal antibodies produced are then harvested and concentrated. The monoclonal concentrates are tested for specificity and potency as detailed in Tables 3 and 4 below.

Table 3 – Specificity Testing

Specificity	**Anti-D**	**Anti-D**
Cell Line ID	LDM1	ESD1
Test Method	(b) (4)	(b) (4)
Acceptance Criteria	Reactive with RhD positive RBCs Non-reactive with RhD negative RBC	Reactive with RhD positive RBCs Non-reactive with RhD negative RBCs

Table 4 – Potency Testing

Specificity	**Anti-D**	**Anti-D**
Cell Line ID	LDM1	ESD1
Test Method	(b) (4)	
RBCs		
Acceptance Criteria		

The acceptable (b) (4) ranges for the IVS materials are presented in Table 5 below:

Table 5 – Biochemistry ranges for the IVS materials

Specificity	Anti-D	Anti-D
Cell Line ID	LDM1	ESD1
(b) (4)		

The IVS materials are considered intermediate products and therefore do not undergo (b) (4) . Post concentration, (b) (4) until required for formulation to the final product. At the time of (b) (4) sodium azide (0.1% w/v) is added to individual production lots to minimize the potential for bacterial growth.

Results from a 2005 validation study demonstrate that the stability of concentrated (b) (4) The stability of (b) (4) material was determined to be (b) (4) Following FDA approval of the product subject of this application, the first (b) (4) lots of IVS materials manufactured from cell lines LDM1 and ESD1 will be placed on full real- time stability. In subsequent years, (b) (4) of IVS will be placed on limited real-time stability.

In Vitro Products (IVPs)

Alba manufactures the IVP at their licensed facility, located at 21 Ellen's Glen Road, Edinburgh, UK.

The process includes formulation (b) (4) , filling, and in-process and final Quality Control (QC) testing. (b) (4) testing of (b) (4) water and (b) (4) water is carried out by a subcontractor. As with the IVS, multiple products are manufactured in the same rooms as the

Anti-D IVP; Alba provided a comprehensive list of these products in the submission. Cross contamination of the products is controlled by campaign manufacturing; full line clearance is required before commencing production steps. All raw materials used for the manufacture of the Anti-D IVP are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

Manufacturing Process Description

The minimum and maximum batch volumes for the Anti-D reagent are (b) (4) respectively. Alba does not perform reprocessing or sublotting, as described in 21 CFR 660.21(a)(3), for the Anti-D reagent.

If necessary, the IVS materials (LDM1 and ESD1) (b) (4)

The IVP undergoes further (b) (4) with a (b) (4) and is filled into the final container using validated filling workstations in a Class (b) (4) clean room. The filling machine is a semi-automatic filling machine and dropper/caps are applied then tightened using a capping machine. The product is labeled and placed in the appropriate packaging together with the Instructions for Use (IFU) document. Specificity and potency testing are performed on the filled product. (b) (4) and bioburden testing are also performed on the filled product. The product is stored at 2 to 8 °C until it is released for distribution by Quality Assurance.

Specifications and Test Methods

The following tables include the specifications (Table 6) and required release tests and acceptance criteria (Table 7) for the Anti-D reagent:

Table 6 IVP Specifications for Anti-D

	Anti-D
Description of Product	Clear straw colored liquid
Unit Volume	10 mL
Primary Packaging	10 mL clear glass vials with dropper assemblies and black caps
Secondary packaging	Single, three, and 10 vial packs
Storage Temp	2-8 °C
Transport temp	Ambient temperature
Expiry Date/Shelf Life	Two years from the start date of the last group of potency testing of the bulk; i.e., prefill

TABLE 7 IVP Testing and Acceptance Criteria

Positive Specificity	(b) (4)
Negative Specificity (b) (4)	
Negative Specificity (b) (4)	
Exclusion of	

contaminating antibodies (b) (4)	(b) (4)
Potency	
Microbiology	
(b) (4)	
(b) (4)	

Microbiology

The Anti-D blood grouping reagent is a microbiologically controlled product and is considered a non-sterile, multiple use device. The acceptable level of micro-organisms which the product may contain is (b) (4) .

Microbiological control of the final product is accomplished as follows:

- Environmental and in-process controls are in place to limit the presence of micro-organisms, and therefore limit potential contamination of the product through environmental control and aseptic technique. The filling process is performed under Class (b) (4) conditions with a Class (b) (4) background environment.
- The final product is (b) (4) to remove microorganisms and tested with a validated bioburden method.
- The final products contain the preservative (bacteriostatic agent) sodium

azide at a concentration of 1 g/L, to inhibit growth of micro-organisms.

- Final product closures undergo sterilization (b) (4)

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the PAS were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Albaclone® Anti-D fusion [Human Monoclonal IgG/IgM Blend (Clones LDM1/ESD1) Product Code Z043U] is listed in the table below.

Name/Address	FEI Number	DUNS Number	Results/Justification
in vitro Substance *in vitro Product* *Release Testing* Alba Biosciences Limited 21 Ellen's Glen Road Edinburgh EH17 7QT Scotland, UK	3003580203	719392867	ORA May 2017 NAI

ORA performed a surveillance inspection of the Edinburgh, Scotland, UK facility May 22 to 25, 2017. No FDA 483 form was issued and the inspection was classified as No Action Indicated.

No pre-approval inspection was performed as there were no changes to the approved application that would require such an inspection.

d) Environmental Assessment

The supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

e) Container/ Closure

The in vitro Product is filled into 10mL (b) (4) borosilicate glass vial with 18mm screw neck manufactured by (b) (4) and 10 mL glass dropper assembly cap manufactured by (b) (4). Alba conducted the container closure integrity testing at the Edinburgh, UK facility, employing (b) (4); all acceptance criteria were met.

4. Analytical Studies

Analytical studies included accuracy studies for weak D and D variants, stability, anticoagulant, and precision studies.

Accuracy Studies for weak D and D variants

Alba's Anti-D IFU that the reagent will directly agglutinate most weak D and partial RhD samples except for DVI, and will detect DVI and weak D by IAT. In an IR communication, dated January 29, 2018 and a telecom dated March 26, 2018, FDA requested that Alba submit data to substantiate these claims.

Alba confirmed the performance of the Anti-D blood grouping reagent using weak D and rare D variant well-characterized red blood cell samples at both Alba and at the (b) (4)

Summary of Internal Alba Study:

- *Test Method*: (b) (4)
- *Red blood cell types used*: (b) (4)
- *Acceptance Criteria*: (b) (4)
- *Assessment***:** Results met the acceptance criteria and validate the claims made in the package insert.

Summary of (b) (4) **Study:**

- *Test Method*: (b) (4) .
- *Red blood cell types used:*
  - (b) (4)
- *Acceptance Criteria*: (b) (4)
- *Assessment:* Results met the acceptance criteria and validate the claims made in the package insert.

Stability Studies

A stability study was performed to validate the Anti-D product shelf life of 24 months. All three conformance lots of Anti-D were included in the real-time stability studies. Vials were opened briefly at the start of the study and then stored at 2-8 °C until testing at the following time points: day zero, and 3, 6, 9, 12, 15, 18, 21, 24, (b) (4) months.

Specificity was performed using (b) (4) The test method included (b) (4) . Real-time potency testing was performed using (b) (4) The test method included (b) (4)

Microbiology testing was performed at day zero (post-fill), 6, 12 , 24, (b) (4) month time points to demonstrate integrity of the closure system and verify effectiveness of the preservative included in the formulation of the IVP.

Alba provided 24 months of potency and specificity test results for the real-time stability study. For specificity: the results met the acceptance criteria for each time point in that there were clear positive results (b) (4) reaction grade) with the R_0r and R_1r cells, and for weak D and DVI cells there were clear positive macroscopic results when tested with the indirect antiglobulin test, and the RhD antigen negative cells gave clear negative reactions. For potency: each time point met the acceptance criteria of (b) (4) For the microbiological assessment: the results were (b) (4) .

In addition to the real-time stability study on the IVP, Alba also performed a simulated transport stability study on (b) (4) conformance (b) (4) to determine the impact of extreme temperature conditions which could potentially occur during transportation of the product between Alba and the end user. Testing is performed on the vials after the initial exposure to the simulated conditions and at the proposed expiry (24 months). Potency and specificity testing include the same tests, red blood cells, and acceptance criteria as the real-time stability study. The vialled reagent underwent the following simulated worst case conditions:

- (b) (4) and the vial stored at 2-8 °C until testing.
- (b) (4) then stored at 2-8 °C until testing.
- (b) (4), and then stored at 2-8 °C until testing.

In summary, specificity and potency results for the simulated transport stability demonstrate that extreme temperature conditions have no significant impact on the performance of the Anti-D reagent.

Anticoagulant Studies

The package insert includes the following sample limitations:

- Clotted samples and samples collected in EDTA should be tested within 14 days from collection.
- Donor blood collected in ACD, CPD, CPDA-1, CP2D, CP2D with AS-3, CPD with AS-1, and CPD with AS-5 may be tested until the expiration date of the donation.

The validation study included all samples types listed in the package insert and

addressed specimen collection limitations. The samples were stored at 2 to 8 °C for the duration of the study. (b) (4) donor samples were selected for the study and included (b) (4) antigen positive donors and (b) (4) antigen negative donor. Specificity testing was performed in accordance with the test methods listed in the package insert. Test results demonstrate that the reagent is not affected by the recommended anticoagulants and sample ages listed in the labeling.

Precision Studies

The Reproducibility and Repeatability study was performed to demonstrate that the test reagent generates reproducible and accurate results using a panel of well-characterized samples across different sites, using different operators, and on different days. The acceptance criterion stated that there should be 100% agreement between the test outcomes and the expected results.

The external study was performed at three external sites, using three lots of test reagent against a panel of (b) (4) reagent red blood cells (b) (4) positive cells: R1r and R1R2 and (b) (4) negative cells: rr cells). The testing was performed by three operators over (b) (4) non-consecutive days, with replicate testing performed by each operator within each run. There were no discordant results; all expected positive tests generated unequivocal positive reactions and all expected negative tests generated unequivocal negative reactions.

Alba also conducted an internal lot-to-lot study cells using three lots of the investigative reagent and the same panel used in the external precision study. (b) (4) lots of blood bank saline were also assessed for its effect on the results. Three operators performed testing over (b) (4) non-consecutive days. There were no discordant results; all expected positive tests generated unequivocal positive reactions and all expected negative tests generated unequivocal negative reactions.

5. Clinical Studies

a) Clinical Program

ALBAclone®Anti-D *fusion* was tested in parallel with currently licensed US products using de-identified leftover clinical samples at the following four sites:

- Alba Bioscience Limited (internal site, non-US site)
- Gulf Coast Regional Blood Center
- Memorial Blood Center
- Blood Center of Wisconsin

The three US study sites were selected for the diversity of their locations and donor populations. Two lots of the ALBAclone®Anti-D Fusion reagent were tested against the US licensed comparator. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents.

The following disease state samples were included in the study (see Table 8 below):

TABLE 8: *(copied from Section 6.5 of the Performance Evaluation Report)*

Disease state	Number of samples tested
Multiple Myeloma	10
Autoimmune Hemolytic Anemia	5
Pregnant women	53
Lymphoma	7
Leukemia	10
Lipemic	10
Hemolysed	10
Icteric	5
Sickle cell	10
Elderly >80 years	10
Neonate/Cord blood	7

Using the Clopper-Pearson exact calculation method, the one-sided 95% lower confidence limits for positive and negative percentage agreement are as follows (see Table 9 below):

TABLE 9 *(copied from Section 6.3.3 of the Performance Evaluation Report)*

ANTI-D		Comparator Reagent			Point Estimate	One sided 95% Lower Confidence Limit
		Positive	Negative			
Trial Reagent	Positive	2304	0	**PPA**	100.0%	0.99
	Negative	0	786	**NPA**	100.0%	0.99

Acceptance Criteria: ≥ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreements.
Assessment: The performance data met the pre-determined acceptance criteria.

b) Pediatrics

Cord blood and neonate samples were included in the comparator study. Test results demonstrate that these sample types do not affect the results of the reagents' performance.

6. Advisory Committee Meeting

These submissions do not include novel technology; therefore, an advisory committee meeting was not required.

7. Other Relevant Regulatory Issues

There are no relevant regulatory issues for these submissions. The review committee members reviewed their specific sections of the BLAs and resolved any issues through information requests with Alba. The review team sought the expertise of their respective management, when warranted. No internal or external disagreements were communicated to the regulatory project manager or chairperson. All reviewers recommended approval.

8. Labeling

The Advertising and Promotional Labeling Branch (APLB) found the proposed Instructions for Use (IFU), and package and container labeling, acceptable from a promotional and comprehension perspective.

The Product Office reviewed the container labels, IFU documents, and generic packing labels. All labels met the requirements outlined in 21 CFR Part 610.62, 610.64, 660.28 and 21 CFR Part 809.10.

9. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members, representing the necessary review disciplines (DBCD, DMPQ, DB, DCM, and DBSQC) recommend approval. These were independent conclusions based on content of the BLAs, issues satisfactorily resolved during the review cycle, and concurred by their respective management. No internal or external disagreements were brought to the attention of the chairperson.

b) Risk/ Benefit Assessment

The benefits of licensing Anti-D blood grouping reagent include the following:

- Decrease the probability of a product shortage for Anti-D blood grouping reagent. There are few licensed manufacturers of monoclonal blood typing

sera in the United States therefore licensing this product will introduce an additional monoclonal Anti-D blood grouping reagent for use.

- Improve the safety of the blood supply by providing a wide range of monoclonal reagents manufactured with diverse cell lines which can increase the probability of the detection of rare antigen variants.

The evaluation of the validation and clinical studies and the manufacturing process reduces the risks associated with licensing a new blood grouping reagent. In addition, Anti-D blood grouping reagent will be subject to post market surveillance (Medical Device Reporting) which will identify adverse events associated with this product.

c) Recommendation for Post-Marketing Activities

We did not recommend post-marketing activities for these submissions.