Summary Basis for Regulatory Action Template

From: Annette Ragosta, Chair of the Review Committee

BLA STN#: 125637

Applicant Name: Alba Bioscience Limited (Alba)

Date of Submission: August 31, 2016; application received in CBER on September 8, 2016

MDUFA Goal Date: July 09, 2017

Proprietary Name/ Established Name: ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) Blood Grouping Reagent

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

> The Anti-Fy^b reagent is for the *in vitro* detection and identification of human Fy^b positive red blood cells by direct agglutination.

Recommended Action:
The Review Committee recommends approval of ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) Blood Grouping Reagent.

Review Office(s) Signatory Authority(ies): Jay Epstein, MD, Director, 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, 2017
Non-Clinical Review	Annette Ragosta, OBRR/DBCD/DRB May 18, 2017
Statistical Review	Lin Huo, OBE/DB/TEB April 20, 2017
CMC Product Review	• Annette Ragosta, OBRR/DBCD/DRB May 18, 2017 • Claire Wernly and Simleen Kaur, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden February 1, 2017
CMC Facility Review	Jeremy Wally OCBQ/DMPQ/BII June 23, 2017
Labeling Review(s)	• Annette Ragosta, OBRR/DBCD/DRB May 18, 2017 • Dana Jones, OCBQ/DCM/ALPB March 15, 2017
Lot Release Protocols/Testing Plans	Varsha Garnepudi, OCBQ, DBSQC
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 original Biologics License Application requesting approval to manufacture and distribute Blood Grouping Reagent, Anti-Fy^{b} (Human/Murine Monoclonal). The proprietary name for this product is ALBAclone® Anti-Fy^{b} (Human/Murine Monoclonal). The manufacture and assembly of this product is performed at Alba Bioscience Limited, 21 Ellen's Glen Road, Liberton, Edinburgh, EH17 7QT, Scotland, United Kingdom.

The In Vitro Substance (IVS) is purchased from (b) (4)

under a Shared Manufacturing Arrangement. A companion application has been submitted by (b) (4) .

Anti-Fy^a and anti-Fy^b (Anti-FY1 and Anti-FY2) were described in 1950 and 1951 respectively. Fy^a and Fy^b are a pair of alleles on the long arm of chromosome 1, giving rise to three commonly encountered phenotypes: Fy (a+b-), Fy (a+b+) and Fy (a-b+). These antigens are fully developed at birth. The Fy^a antigen occurs in approximately 66% of Caucasians and 10% of the Black population. The Fy^b antigen occurs in approximately 83% of Caucasians and 23% of the Black population. Antibodies directed against the antigens can cause hemolytic transfusion reactions and hemolytic disease of the newborn.

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:

ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) does not have a foreign marketing history.

Device Description:

The main component of this blood grouping reagent is derived from the *in vitro* culture of the cell line SpA264LBg1, which is a human-mouse heterohybridoma that produces an IgM monoclonal antibody specific for the human red blood cell antigen Fy^b. The cell culture is manufactured and harvested by (b) (4) . The lymphoblastoid B secreting cell lines from an immunized donor were fused with murine myeloma cells. Secreting hybrids were identified using the (b) (4) method ((b) (4)) and Fy^b positive red blood cells. (b) (4) confirmed the specificity on a (b) (4) . (b) (4) manufactures the IVS from this supernatant. The formulation for the Alba blood grouping reagent contains bovine material, potentiators, and 0.1% (w/v) sodium azide.

The final product is filled into a 10 mL glass vial (fill volume of five milliliters) constructed of (b) (4) glass. The closure is a 10 mL dropper assembly that includes a black screw cap and a rubber bulb with a clear glass pipette.

ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) has been validated for use by the tube technique which includes both an immediate spin and five minute incubation time followed by centrifugation. The Anti-Fy^b reagent will react with red blood cells that are positive for the Fy^b antigen and will produce macroscopic agglutination of the red blood cells in the test tube.

Chronology:

CBER received this efficacy supplement on September 8, 2016, and received two amendments from Alba in response to two information requests.

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 Substance (IVS)
The IVS is purchased from (b) (4) under a Shared Manufacturing Agreement. Alba also established a quality agreement with (b) (4) which defines the responsibilities of each party with respect to quality issues.

The raw material used in the (b) (4) IVS is manufactured by (b) (4) . The cell line SpA264LBg1 is a human-mouse heterohybridoma that produces an IgM monoclonal antibody specific for the human red blood cell antigen Fy^b, an antigen of the Duffy blood group system. A Certificate of Analysis (CoA) is obtained from the supplier to show the material has been tested and found to be non–reactive for HBsAg, Anti-HIV1/2, Anti-HCV and Syphilis (21 CFR 610.40).

Alba is responsible for shipment of IVS from (b) (4) manufacturing facility in (b) (4) to Alba, located in Edinburgh, UK. Shipping is performed at the recommended IVS storage temperature of (b) (4) by an approved third party company who monitors the shipment temperature. Each batch of IVS is accepted at Alba upon confirmation that the shipment temperature has remained within the recommended IVS storage temperature. The (b) (4) IVS batches used in the manufacturing of the (b) (4) ALBAclone®Anti-Fy^b conformance lots were shipped at (b) (4) temperature and the shipping duration was (b) (4) .

Alba accepts the IVS based upon (b) (4) CoA. Alba also performs the following serological testing prior to release for manufacturing use:

- (b) (4)
- (b) (4)

In Vitro Product (IVP)

Alba manufactures the IVP at their licensed facility, located at 21 Ellen's Glenn Road, Edinburgh, UK. The process includes formulation, filtration, filling, and in-process and final Quality Control (QC) testing. Multiple products are manufactured in the (b) (4) as the Anti-Fy^{b} IVP; Alba provided a comprehensive list of these products in the submission. Cross contamination of the products is controlled by (b) (4) is required before commencing production steps. All raw materials used for the manufacture of the Anti-Fy^{b} IVP are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

Manufacturing Process Description

A trial volume of the IVS is (b) (4); the final (b) (4) factor is determined from the trial (b) (4) test results. A potentiator ((b) (4)) is added and (b) (4) adjustments are performed. The (b) (4) is measured and adjusted to meet the product specification. (b) (4) is performed using a (b) (4), samples are taken for serological QC testing and, if the (b) (4) is approved, filling commences with an initial (b) (4) step.

The IVP is filled into 10 mL (b) (4) glass vials (fill volume of five milliliters) in a (b) (4) validated filling workstation located in a (b) (4) clean room. The filling machine is a semi-automatic filling machine and dropper/caps are applied then tightened using a capping machine. Filled, unlabeled containers are transferred to cold storage. Specificity and potency testing, (b) (4) and bioburden testing are performed on the filled

product. The product progresses to the labeling stage if all required tests meet the pre-determined acceptance criteria. The product is labeled and placed in the appropriate packaging together with the Instructions for Use document. An identity check is performed (confirmation of reactivity) on the labelled vial. The product is stored at 2 to 8 ^{o}C until it is released for distribution by Quality Assurance.

Specifications and Test Methods

The following table (Table 2) includes the required release tests and acceptance criteria for the Anti-Fy^{b} IVP:

TABLE 2

Test Method	**Acceptance Criteria/Range**
Tube Method, Confirmation of Reactivity: Immediate Spin and 5 minutes room temperature, spin	Minimum of (b) (4) weak antigen positive RBC's including Fy(a+b+) and Fy^{x} if possible Must be reactive with Fy^{b} positive red blood cells
Tube Method, Exclusion of contaminating antibodies: Immediate Spin and 5 minutes room temperature, spin	Minimum of (b) (4) Fy^{b} antigen negative RBC's to confirm the absence of the following antibodies: (b) (4) Must be non-reactive with all RBCs.
Tube Method, Potency testing: 5 minutes room temperature, spin	Minimum of (b) (4) Fy(a+b+) RBCs Minimum titration end point of (b) (4)

Test Method	Acceptance Criteria/Range
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Bioburden	(b) (4)

Microbiology

Anti-Fy^b 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:

- The final product contains the preservative (bacteriostatic agent) Sodium Azide (NaN3) at a concentration of 1 g/L, to inhibit growth of micro-organisms.
- 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.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. The 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 BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of ALBAclone®, Blood Grouping Reagent, Anti-Fy^b (Human Monoclonal) is listed in the table below. The activities performed and inspectional history is noted in the table and is further described in the paragraph that follows.

Manufacturing Facilities Table for ALBAclone®, Blood Grouping Reagent, Anti-Fy^{b} (Human Monoclonal)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
***In Vitro* Product Manufacturing and Release Testing**				
Alba Biosciences Limited 21 Ellen's Glen Road Edinburgh EH17 7QT Scotland, UK	3003580203	719392867	Waived	Team Biologics May 2016 VAI

Team Biologics conducted a surveillance inspection of the Alba Biosciences Limited manufacturing facility in Edinburgh, Scotland from May 12-13 and 16-20, 2016. This inspection was classified as VAI and all inspectional 483 observations were resolved.

d) Environmental assessment

The BLA 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 will 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 a (b) (4) 10 mL clear (b) (4) tubular glass vial manufactured by (b) (4), and a 10 mL dropper assembly (black screw cap and rubber bulb with clear glass pipette) manufactured by (b) (4). Alba conducted the container closure integrity testing for vials filled at the Edinburgh, UK facility, employing torque verification, weight verification and visual inspection for turbidity; all of the acceptance criteria were met.

4. Analytical Studies

Analytical studies included stability, anticoagulant, and precision studies.

Stability Studies

Stability studies were performed to support the proposed shelf life of 24 months at 2-8 °C. All (b) (4) conformance lots of ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) 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)

Microbiology testing was performed at day zero (post-fill), 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 12 months of potency and specification test results for the real time stability study. The data show that the minimum potency titration end point of (b) (4) was met for each of the time points. All Fy^b antigen positive red blood cells tested as positive reactions with a minimum of a (b) (4) reaction grade and the Fy^b antigen negative red blood cells gave clear negative reactions.

In addition to the real time stability study on the IVP, Alba also performed a simulated transport stability study on one conformance lot to determine the impact of extreme temperature conditions which could potentially occur during

transportation of the product between Alba and the end user. Vialled reagent underwent the following simulated worst case conditions:

- (b) (4)
- (b) (4)
- (b) (4)

Alba provided 12 months of potency and specification test results for the simulated transport study. The data show that the minimum potency titration end point of (b) (4) was met for each of the time points. In addition, all Fy^b antigen positive red blood cells returned unequivocal positive reactions with a minimum of a (b) (4) reaction grade and the Fy^b antigen negative red blood cells gave clear negative reactions.

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. Testing was performed in accordance with the test method listed in the package insert and included four homozygote positive cells, two heterozygote positive cells, and four negative cells. The results demonstrate that the designated sample types do not affect the results of the reagent's performance.

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 there should be 100% agreement between the test outcomes and the expected results.

The external study was performed at three sites, using (b) (4) lots of test reagent against a panel of (b) (4) reagent red blood cells. The testing was performed by three operators over (b) (4) non-consecutive days, with (b) (4) testing performed by each operator within each run. (b) (4) lots of blood bank saline were also assessed for its effect on the results. 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 against a panel of (b) (4) reagent red blood cells using (b) (4) lots of the investigative reagent. (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-Fy^b (Human/Murine Monoclonal) was tested in parallel with currently licensed US products using de-identified leftover clinical samples at multiple clinical locations. The acceptance criterion is as follows: $\geq$ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreements. The study was conducted at the following five sites:

- Alba Bioscience Limited (internal site)
- Gulf Coast Regional Blood Center, Houston, TX
- Memorial Blood Center, St. Paul, MN
- Blood Center of Wisconsin, Milwaukee, WI
- Duke University Hospital , Durham, NC

The four US study sites were selected for the diversity of their locations and donor or patient populations. Three lots of the ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) reagent were included in the study. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents. The following table (Table 3) includes a summary of the test results and the statistical analysis of the study.

TABLE 3: Summary of Comparator Testing over all trial sites:

		COMPARATOR REAGENT		
		Positive	Negative	Total
TRIAL REAGENT	Positive	730	3	733
	Negative	1	526	527
	Total	731	529	1260
Positive Percentage Agreement (Concordance)				99.9 %
Positive Percentage Agreement (One-sided 95% lower confidence limit)				99%
Negative Percentage Agreement (Concordance)				99.4%
Negative Percentage Agreement (One-sided 95% lower confidence limit)				99%

There were four discordant results in the study:

- One discordant false negative result by the trial reagent was due to a Direct Antiglobulin Test (DAT) positive sample that caused false positive results with both the comparator and the resolver reagents. The ALBAclone®Anti-Fy^b trial reagent is not affected by DAT positive results.
- One discordant false positive result was due to the detection of Fy^x

antigen by the trial reagent which was confirmed by molecular testing. Both the comparator and resolver reagents do not claim to detect the Fy^x antigen.

- Two discordant false positive results did not have sufficient samples available to perform molecular analysis. Alba stated the discrepancies may be due to differences in the sensitivity of the comparator and resolver reagents

In summary, the study results met the pre-determined acceptance criterion ($\geq$ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreement) and demonstrate that the ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) reagent is comparable to US licensed products with the same intended use.

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 reagent's performance.

6. Advisory Committee Meeting

This supplement does not include novel technology; therefore, an advisory committee meeting was not required.

7. Other Relevant Regulatory Issues

There are no relevant regulatory issues for this submission. The review committee members reviewed their specific sections of the BLA 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 of ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) Blood Grouping Reagent.

8. Labeling

The Product Office and the Advertising and Promotional Labeling Branch reviewed the container labels, the Instructions For Use (IFU) document, 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 BLA, 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 ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) Blood Grouping Reagent include the following:

- Decrease the probability of a product shortage for Anti-Fy^b 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-Fy^b 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, ALBAclone® Anti-Fy^b (Human/Murine Monoclonal) 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 this submission.

Concurrence Page

Application Type and Number: BLA 125637

COMMUNICATION TYPE:

History:	Teresita Mercado	June 06, 2017
	Orieji Illoh, MD	June 08, 2017
	Nicole Verdun, MD	June 29, 2017
	Jeremy Wally	June 30, 2017
	Mary Malarkey	July 3, 2017

Concurrence:

Office/Division	Name/Signature	Date
OBRR/DBCD	Annette Ragosta	
OBRR/DBCD	Teresita Mercado	
OCBQ	Mary Malarkey	
OBRR/DBCD	Orieji Illoh, MD	
OBRR/DBCD	Nicole Verdun, MD	