

Summary Basis for Regulatory Action Template

From: Annette Ragosta, Chair of the Review Committee

BLA STN#: 125599, 125600, 125601

Applicant Name: Alba Bioscience Limited (Alba)

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

MDUFA Goal Date: February 16, 2018

Proprietary Names/ Established Names:

- ALBAclone® Anti-C (Human/Murine Monoclonal) Blood Grouping Reagent
- ALBAclone® Anti-e (Human/Murine Monoclonal) Blood Grouping Reagent
- ALBAclone® Anti-C^w (Human/Murine Monoclonal) Blood Grouping Reagent

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

- **Anti-C:**
This Anti-C reagent is for the *in vitro* detection and identification of the human C blood group antigen by direct agglutination.
- **Anti-e:**
This Anti-e reagent is for the *in vitro* detection and identification of the human e blood group antigen by direct agglutination.
- **Anti-C^w:**
This Anti-C^w reagent is for the *in vitro* detection and identification of the human C^w blood group antigen by direct agglutination.

Recommended Action:

The Review Committee recommends approval.

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 December 12, 2017
Non-Clinical Review	Annette Ragosta, OBRR/DBCD/DRB December 12, 2017
Statistical Review	Lin Huo, OBE/DB/TEB January 9, 2018
CMC Product Review	<ul style="list-style-type: none"> • Annette Ragosta, OBRR/DBCD/DRB May 18, 2017 • Simleen Kaur, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden September 20, 2016
CMC Facility Review	Jeremy Wally OCBQ/DMPQ/BII January 31, 2018
Labeling Review	Annette Ragosta, OBRR/DBCD/DRB December 12, 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 three Biologics License Applications (BLAs), requesting approval to manufacture and distribute the following Blood Grouping Reagents (BGRs) (see Table 2).

Table 2 STNs, Product and Proprietary Names

STN	Product Name	Proprietary Name
125599/0	Blood Grouping Reagent, Anti-C (Human/Murine Monoclonal)	ALBAclone® Anti-C (Human/Murine Monoclonal)
125600/0	Blood Grouping Reagent, Anti-e (Human/Murine Monoclonal)	ALBAclone® Anti-e (Human/Murine Monoclonal)
125601/0	Blood Grouping Reagent, Anti-C ^w (Human/Murine Monoclonal)	ALBAclone® Anti-C ^w (Human/Murine Monoclonal)

The products will hereafter be referred to as Anti-C, Anti-e, and Anti-C^w.

The manufacture and assembly of these products is performed at Alba Bioscience Limited, 21 Ellen's Glen Road, Liberton, Edinburgh, EH17 7QT, Scotland, United Kingdom.

The in vitro substances (IVS) (also known as For Further Manufacturing Use (FFMU) products), used in the manufacture of the BGRs listed above, are manufactured by (b) (4) under shared manufacturing arrangements (see Table 3). Review of the quality agreements between Alba and (b) (4) and Alba and (b) (4) determined them to be adequate.

Table 3 FFMU Suppliers

SUPPLIER	STN	ANTIBODY (CELL LINE)
(b) (4)		Anti-C (MS-24)
		Anti-C ^w (MS-110)
		Anti-e (MS-63)
		Anti-e (P3GD512)

The Rh blood group system (including the Rh factor) 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 Rh antigens are highly immunogenic, and most of the Rh antibodies should be considered as potential causes of hemolytic transfusion reactions and hemolytic disease of the newborn. For the general population, the prevalence of the C antigen is 70%, the e antigen is 98%, and the C^w antigen is 2%.

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 reagents

Device Description:

Anti-C

The main component of this blood grouping reagent is an IgM antibody derived from the in vitro culture of the IgM secreting human/mouse heterohybridoma of cell line MS-24. The blood grouping reagent also contains bovine material, potentiators, and 0.1% (w/v) sodium azide.

ALBAclone® Anti-C (Human/Murine Monoclonal) has been validated for use by the tube technique which includes a five to fifteen-minute incubation time at 37 degrees Celsius followed by centrifugation. The Anti-C reagent will react with red blood cells that are positive for the C antigen and will produce macroscopic agglutination of the red blood cells in the test tube.

Anti-C^w

The main component of this blood grouping reagent is an IgM antibody derived from the in vitro culture of the IgM secreting human/mouse heterohybridoma of cell line MS-110. The blood grouping reagent also contains bovine material and 0.1% (w/v) sodium azide.

ALBAclone® Anti-C^w (Human/Murine Monoclonal) has been validated for use by the tube technique which includes a five to fifteen-minute incubation time at 37 degrees Celsius followed by centrifugation. The Anti-C^w reagent will react with red blood cells that are positive for the C^w antigen and will produce macroscopic agglutination of the red blood cells in the test tube.

Anti-e

The main components of this blood grouping reagent are IgM antibodies derived from the in vitro culture of the IgM secreting human/mouse heterohybridomas of cell lines MS-63 and p3GD512. The blood grouping reagent also contains bovine material and 0.1% (w/v) sodium azide.

ALBAclone® Anti-e (Human/Murine Monoclonal) has been validated for use by the tube technique which includes a five to fifteen-minute incubation time at 37 degrees Celsius followed by centrifugation. The Anti-e reagent will react with red blood cells that are positive for the e antigen and will produce macroscopic agglutination of the red blood cells in the test tube.

Chronology:

CBER received the three original BLAs on December 11, 2015, and received ten amendments from Alba in response to one Complete Response letter and seven information requests.

3. Chemistry Manufacturing and Controls (CMC)

The applications were 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 IVS (FFMU) components used in the manufacture of Anti-C, Anti-e, and Anti-C^w are manufactured by (b) (4) under shared manufacturing arrangements.

(b) (4) performed a shipping study to verify adequate temperature control of Anti-e Cell Line P3GD512 during shipment to Alba. The results verify that the packing materials can keep the product within the (b) (4) to (b) (4) temperature range during overnight shipment.

The (b) (4) FFMU products, Anti-C (cell line MS-24), Anti-C^w (cell line MS-10), and Anti-e (cell lines MS-63 and p3GD512), are shipped at ambient temperature.

Alba performs the following tests upon receipt of the FFMUs (Tables 4 to 7):

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

In Vitro Products (IVPs)

Alba manufactures the three IVPs 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 same rooms as the Anti-C, Anti-C^w, and Anti-e IVPs; 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 three IVPs are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

Manufacturing Process Description

Alba provided the following table describing the manufacturing steps for Anti-C^w, Anti-C, and Anti-e reagents (See Table 8 below – *copied from Part 1, CMC Section, II.C, page 6-1*).

Table 8 – Manufacturing steps relevant to each IVP

Manufacturing Step		Product		
Process	(b) (4)	Anti-C	Anti-e	Anti-C ^w
Formulation	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Filtration and Filling	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Labelling and Packing	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Filtration of the three (b) (4) IVP reagents is performed using (b) (4) filters into (b) (4). Both Anti-C and Anti-e are filled into 10 mL (b) (4) borosilicate glass vials with fill volumes of five milliliters and Anti-C^w is filled into a 5mL (b) (4) borosilicate glass volume with a fill volume of two milliliters. The filling process is performed in a Class (b) (4) validated filling workstation located 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 products are labeled and placed in the appropriate packaging together with the Instructions for Use document. Filled, labeled containers are transferred to cold storage. Specificity, potency,

and bioburden testing are performed on the filled products. The products are stored at 2 to 8 °C until they are released for distribution by Quality Assurance.

Specifications and Test Methods

The following tables include the specifications (Table 9) and required release tests and acceptance criteria (Table 10, 11, and 12) for the Anti-C, Anti-C^w, and Anti-e reagents:

Table 9 IVP Specifications for Anti-C, Anti-C^w, and Anti-e reagents

	Anti-C	Anti-e	Anti-C ^w
Description of Product	Clear Liquid		
Unit Volume	Five mL	Five mL	Two mL
Primary Packaging	10 mL clear glass vials with dropper assemblies and black caps	10 mL clear glass vials with dropper assemblies and black caps	Five mL clear glass vials with dropper assemblies and black caps
Secondary packaging	Single 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 10 IVP Testing and Acceptance Criteria – Anti-C

	Test Method	Acceptance Criteria
Positive Specificity	5 minutes 37°C (b) (4)	(b) (4)

Negative Specificity	15 minutes 37°C (b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
Micro	Bioburden test	(b) (4)
(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)

Table 11 IVP Testing and Acceptance Criteria – Anti-C^w

	Test Method	Acceptance Criteria
Positive Specificity	5 minutes 37°C (b) (4)	(b) (4)
Negative Specificity	15 minutes 37°C (b) (4)	(b) (4)
Potency	5 minutes 37°C (b) (4)	(b) (4)
Micro	Bioburden test	(b) (4)
(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)

Table 12 IVP Testing and Acceptance Criteria – Anti-e

	Test Method	Acceptance Criteria
Positive Specificity	5 minutes 37°C (b) (4) 	(b) (4)
Negative Specificity	15 minutes 37°C (b) (4) 	(b) (4)
Potency	5 minutes 37°C (b) (4)	(b) (4)
Micro	Bioburden test	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Microbiology

Anti-C, Anti-C^w, and Anti-e are microbiologically controlled products and are considered non-sterile, multiple use devices. The acceptable level of micro-organisms which the products may contain is (b) (4) Microbiological control of the final products 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 filtered using a (b) (4) filter 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 templates were submitted to CBER for review and found to be acceptable after revisions. The lot release testing plans were developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the BLAs were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of ALBAclone[®], Blood Grouping Reagent, Anti-C (Human/Murine Monoclonal), ALBAclone[®], Blood Grouping Reagent, Anti-e (Human/Murine Monoclonal), and ALBAclone[®], Blood Grouping Reagent, Anti-C^w (Human/Murine 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-C (Human/Murine Monoclonal), ALBAclone[®], Blood Grouping Reagent, Anti-e (Human/Murine Monoclonal), and ALBAclone[®], Blood Grouping Reagent, Anti-C^w (Human/Murine Monoclonal)

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

VAI = Voluntary Action Indicated

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 BLAs 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 siliconized 5 or 10 mL clear (b) (4) tubular glass vial manufactured by (b) (4) and a 5 or 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 (b) (4) verification, (b) (4) verification and visual inspection for turbidity; all of the acceptance criteria were met.

4. Analytical Studies

Analytical studies included accuracy, stability, anticoagulant, and precision studies.

Accuracy Studies

Alba confirmed the performance of Anti-C, Anti-C^w, and Anti-e blood grouping reagents by testing well-characterized red blood cell samples which were sourced from antibody screen and antibody identification panels from different commercial suppliers. The Anti-C, Anti-C^w, and Anti-e blood grouping reagents demonstrated 100 percent concordance with the expected antigen types of the samples confirming the accuracy of the reagents. A summary of the data for the in-house accuracy studies is presented in Tables 14 to 16 below.

Table 14 – Accuracy Testing – Anti-C

Anti-C	Test Outcome/Antigen characterization	Characterized cell – C antigen			One sided 95% LCL
		Positive	Negative	Total	
Anti-C Z064U	Positive	(b) (4)			
	Negative				
	Total				
Positive Percentage Agreement				100.00	0.99
Negative Percentage Agreement				100.00	0.99

Table 15 – Accuracy Testing - Anti-e

Anti-e	Test Outcome/Antigen characterization	Characterized cell - e antigen			One sided 95% LCL
		Positive	Negative	Total	
Anti-e Z096 U	Positive	(b) (4)			
	Negative				
	Total				
Positive Percentage Agreement				100.00	0.99
Negative Percentage Agreement				100.00	0.98

Table 16 – Accuracy Testing - Anti-C^w

Anti-C ^w	Test Outcome/Antigen characterization	Characterized cell – C ^w antigen			One sided 95% LCL
		Positive	Negative	Total	
Anti-C ^w Z106U	Positive	(b) (4)			
	Negative				
	Total				
Positive Percentage Agreement			(b) (4)	(b) (4)	
Negative Percentage Agreement			100.00	0.99	

The results for positive percent agreement and negative percent agreement of the investigative reagent results compared to the expected results of the well-characterized samples meet the FDA requirement of >99% at the lower bound of the one-sided 95% confidence interval, with the exception of C^w positive and e negative antigens. This was due to the small numbers of C^w positive and e negative samples tested.

Stability Studies

Stability studies were performed on three conformance lots each of Anti-C, Anti-C^w, and Anti-e to support the proposed shelf life of 24 months at 2-8 °C. The RBC types, tests, techniques, and acceptance criteria listed in Tables 10 to 12 above also apply to the real-time stability study. In addition, the change in the difference between the test sample and the reference (b) (4) endpoints at each time point must be (b) (4)

Vials were (b) (4) 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. Microbiology testing is performed at Day zero, 6, 12, 24, (b) (4) months. Alba provided 21 months of potency, specification, and microbiology test results for the real-time stability study for Anti-C and 24 months for Anti-e and Anti-C^w. The acceptance criteria were met for all study time points and support the shelf life of 24 months at 2-8 °C for Anti-C, Anti-C^w, and Anti-e.

In addition to the real-time stability study on the IVPs, Alba also performed a simulated transport stability study on (b) (4) 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)

The RBC types, tests, techniques, and acceptance criteria listed in Tables 10 to 12 above also apply to the simulated transport study. Potency and specificity testing on the temperature cycled reagents met all acceptance criteria and the results show that there is no significant impact on the performance of the reagents after exposure to extreme temperatures that could potentially be encountered during the shipping process.

Anticoagulant Studies

Each of the package inserts for Anti-C, Anti-C^w, and Anti-e include the following test sample limitations:

- Clotted samples and samples collected in EDTA should be tested within 14 days from collection.
- Donor blood collected in ACD, CPD, CPD with AS-1 and AS-5, CPDA-1, CP2D, and CP2D with AS-3, 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. Testing was performed in accordance

with the test method listed in the package insert. The samples were stored at 2 to 8 °C for the duration of the study. (b) (4) donors were selected for each of the three reagents and included a minimum of (b) (4) antigen positive and (b) (4) antigen negative donors. Due to the low frequency of C^w positive (b) (4) and e negative (b) (4) antigens only (b) (4) C^w positive sample and (b) (4) e negative sample were included in the study. Although the positive sample size for the Anti-C^w study and the negative sample size for the anti-e study are not statistically sufficient to demonstrate that the results are not affected by the anticoagulants or sample age, additional samples were included in the comparison study which tested samples with anticoagulants used routinely in hospitals and blood collection facilities in the US. The test results presented in the validation study report were satisfactory and met the acceptance criteria for specificity testing.

Precision Studies

This study was performed at three external sites using (b) (4) each of Anti-C, Anti-C^w, and Anti-e. The test panel for the precision study was also used for the lot-to-lot study and included the following red blood cells:

- Anti-C – (b) (4)
- Anti-C^w – (b) (4)
- Anti-e – (b) (4)

Testing was performed by (b) (4) operators over (b) (4) non-consecutive days at different times, (b) (4) runs per day, in (b) (4). There were no discordant results; all test results gave unequivocal positive and negative reactions as appropriate to the antigen specificity of the reagent red blood cells on the panel. Test results demonstrate that Anti-C, Anti-C^w, and Anti-e blood grouping reagents are reproducible and repeatable.

Lot-to-Lot Study

This study was performed in-house using (b) (4) different lots of Anti-C, Anti-C^w, and Anti-e. The red blood cell panel used in this study was also provided to the

external sites for use in the precision studies. Testing was performed by (b) (4) operators over a (b) (4)-day period, with (b) (4) runs per day in (b) (4). There were no discordant results; all test results gave unequivocal positive and negative reactions as appropriate to the antigen specificity of the reagent red blood cells on the panel. Test results demonstrate lot-to-lot consistency for the Anti-C^w, Anti-C, and Anti-e blood grouping reagents.

5. Clinical Studies

a) Clinical Program

Anti-C, Anti-C^w, and Anti-e blood grouping reagents were tested in parallel with currently licensed US products using de-identified leftover clinical samples at multiple clinical locations. The acceptance criterion for each of the reagents requires $\geq 99\%$ concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive agreement.

The study was conducted at the following five sites (one internal site and four external sites):

- Alba Bioscience Ltd (ABL)
- New York Blood Center (NYBC)
- Gulf Coast Regional Blood Center (GCR)
- Memorial Blood Center (MBC)
- Blood Center of Wisconsin (BCW)

The four US sites covered representative population distributions in the US. Three lots of each 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 tables (Tables 17 to 19) include a summary of the comparison test results for Anti-C^w, Anti-C, and Anti-e blood grouping reagents for all trial sites.

Table 17: Summary of Comparator Testing for Anti-C

Anti-C		Comparator Reagent		
		Positive	Negative	Total
Trial Reagent	Positive	703	0	703
	Negative	0	336	336
	Total	703	336	1039
Point Estimate				100
Positive Percent Agreement (One sided Lower 95% Confidence Interval)				99.6
Point Estimate				100
Negative Percent Agreement (One sided Lower 95% Confidence Interval)				99.1

The predetermined acceptance criterion was met for both the positive and negative percent agreement at the one-sided lower 95% confidence interval.

Table 18: Summary of Comparator Testing for Anti-C^w

Anti-C ^w		Comparator Reagent		
		Positive	Negative	Total
Trial Reagent	Positive	157	1	158
	Negative	8	894	902
	Total	165	895	1060
Point Estimate				95.2
Positive Percent Agreement (One sided Lower 95% Confidence Interval)				91.4
Point Estimate				99.9
Negative Percent Agreement) (One sided Lower 95% Confidence Interval)				99.5

The predetermined acceptance criterion was met for the negative percent agreement at the one-sided lower 95% confidence interval. However, the study did not meet the acceptance criterion for the positive percent agreement at the one-sided 95% lower confidence limit: 91.4 versus $\geq 99\%$ concordance. Eight discrepant C^w samples reported negative results for the trial reagent and positive results for the comparator. The comparator reagent utilizes an enzyme addition method which may cause false positive results with DAT positive samples. Seven of the eight discrepant samples were shown to be DAT positive; no additional information was available on the remaining discrepant

sample. It should also be noted that the results are negatively impacted by the number of available positive samples (165) which is due to the low prevalence of this antigen in the population (0.02).

Table 19: Summary of Comparator Testing for Anti-e

Anti-e		Comparator Reagent		
		Positive	Negative	Total
Trial Reagent	Positive	867	0	867
	Negative	0	172	172
	Total	867	172	1039
Point Estimate				100
Positive Percent Agreement (One sided Lower 95% Confidence Interval)				99.7
Point Estimate				100
Negative Percent Agreement (One sided Lower 95% Confidence Interval)				98.3

The predetermined acceptance criterion was met for the positive percent agreement at the one-sided lower 95% confidence interval. However, the study did not meet the acceptance criterion for the negative percent agreement at the one-sided 95% lower confidence limit: 98.3 versus $\geq 99\%$ concordance. It should be noted that the results are negatively impacted by the number of available negative samples (172) which is due to the high prevalence of this antigen in the population (0.98).

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 other 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 Product Office and the Advertising and Promotional Labeling Branch reviewed the container labels, the Instructions for Use (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-C, Anti-C^w, and Anti-e blood grouping reagents include the following:

- Decrease the probability of a product shortage for Anti-C and Anti-e blood grouping reagents. There are few licensed manufacturers of monoclonal blood typing sera in the United States therefore licensing these products will introduce additional monoclonal Anti-C and Anti-e blood grouping reagents for use.

- There are currently no U.S. licensed monoclonal Anti-C^w blood grouping reagents for use. Therefore, licensing this product will improve the safety of the blood supply.
- 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-C, Anti-C^w, and Anti-e blood grouping reagents 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.