Summary Basis for Regulatory Action Template

From: Meihong Liu, Devices Review Branch, Chair of Review team

<*BLA/NDA*>/ STN#: See table below.

Applicant Name: Alba Bioscience Limited (Alba)

Date of Submission: July 31, 2014, received in CBER on August 6, 2014

Goal Date: June 20, 2017

Proprietary Name/ Established Name: see the table below

Intended Use: see the table below

STN	Name of Biological Product	Intended Use
BL 125304/35	Blood Grouping Reagent, Anti-D (Monoclonal)(IgM)	ORTHO™ Sera Anti-D (DVI) is for the in vitro detection of human Rh D (DVI) positive red blood cells by the direct agglutination test. Patients and neonates should not be tested with this reagent since it detects partial RhD (DVI).
BL 125314/34	Blood Grouping Reagent, Anti-D (Monoclonal Blend)	ORTHO™ Sera Anti-D (IAT) is for the in vitro detection of human Rh D positive red blood cells by the indirect antiglobulin test.
BL 125310/30	Blood Grouping Reagent, Anti-Lea (Murine Monoclonal)	ORTHO™ Sera Anti-Lea is for the qualitative in vitro detection of human Lea positive red blood cells by the direct agglutination test.
BL125311/29	Blood Grouping Reagent, Anti-Leb (Murine Monoclonal)	ORTHO™ Sera Anti-Leb is for the qualitative in vitro detection of human Leb positive red blood cells by the direct agglutination test.
BL 125309/30	Blood Grouping Reagent, Anti-N (Murine Monoclonal)	ORTHO™ Sera Anti-N is for the qualitative in vitro detection of human N positive red blood cells by the direct agglutination test.

Recommended Action:

The Review Committee recommends approval of this product.

Review Office Signatory Authority: Orieji Illoh, MD, Director, Division of Blood Components and Devices

☐ **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 indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Review(s) • *Clinical (product office)*	Meihong Liu, OBRR/DBCD/DRB • April 24, 2017 Joyce Rockwell, OBRR/DBCD/DRB, • April 30, 2015, March 27, 2015, November 6, 2014
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Chunrong Cheng, OBE/DB/TEB • June 2, 2015, April 8, 2015 , October 3, 2014
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)*	Joyce Rockwell, OBRR/DBCD/DRB • December 4, 2015, April 28, 2015, March 27, 2015, January 24, 2014 Priscilla Pastrana, OCBQ/DMPQ • April 20, 2015, December 5, 2013, February 3, 2014
• Labeling Review(s)	Meihong Liu, OBRR/DBCD/DRB • April 24, 2017 Joyce Rockwell, OBRR/DBCD/DRB • April 24, 2015 Dana Jones, OCBQ/DCM/APLB • April 24, 2015
Other Review(s) • *Bioburden (DBSQC)* • Quality Control, lot release	Hyesuk Kong, OCBQ/DBSQC • April 20, 2015, December 19, 2014, October 3, 2014 Garnepudi, Varsha (OCBQ/DBSQC/QAB) • April 25, 2017, April 28, 2015, February 13, 2015

1. Introduction

Alba Bioscience Limited, (hereafter known as Alba) located in Edinburgh, United Kingdom, submitted an Efficacy Supplement requesting approval of six monoclonal Blood Grouping Reagents (BGRs) for use with the Ortho ID-Micro Typing System™ (MTS)™ Gel Card for Column Agglutination Technology . This supplement is the first of three bundled submissions designated as Rare Antisera for Column Agglutination Technology (RASCAT) Monoclonal Blood Group Reagents. (b) (4)

(b) (4)

All RASCAT reagents are all manufactured, labeled, and packaged by Alba at their licensed Ellen's Glen Road facility where Alba manufactures FDA licensed and 510(k) cleared products as well as blood grouping reagents, red cell products, and controls for the rest of the world. However, the Anti-N vitro substance (IVS) is manufactured by (b) (4) . (b) (4) submitted an original BLA (companion submission) for the Anti-N (Murine Monoclonal)(IgG) (For Further Manufacturing Use), cell line BO3. Alba purchases the Anti-N IVS from (b) (4) labeled as For Further Manufacturing Use (FFMU) to manufacture the final product under a shared manufacturing arrangement. The RASCAT reagents will be distributed by Ortho Clinical Diagnostics (FDA License 1236) under the trade name Ortho™ Sera.

2. Background

All five BGRs were approved in 2009 for use with the standard tube test method.

The Anti-D (Monoclonal) (IgM) produced from (b) (4) cell line was approved for the in vitro detection and identification of human RhD blood group status by direct agglutination. The Anti-D (Monoclonal) (IgM Blend) is a blend of antibodies produced from the cell lines LDM3 and ESD1 and was approved for the in vitro detection and identification of human RhD blood group status in patient samples by direct agglutination, and donor samples by the indirect antiglobulin tests (IAT). Designed for both patient and donor testing, the reagent will detect virtually all weak D (Du) and partial D red cells by direct agglutination, but will only detect DVI by indirect IAT method. The Anti-Le^a (Murine Monoclonal) produced from the cell line LEA(b) (4) was approved for the in vitro detection and identification of human group Le^a red blood cells by direct agglutination. The Anti-Le^b (Murine Monoclonal) produced from the cell line LEB(b) (4), was approved for the in vitro detection and identification of human group Le^b red blood cells by direct agglutination.

All devices have been distributed in the US since their approval dates. This submission does not request any changes to the manufacturing processes or facilities used for the five BGRs or the MTS Gel Cards.

Foreign Marketing History: The blood grouping reagents subject of this application do not have foreign marketing history in their current format as these were developed specifically for ID-MTS™ CAT. However, cell lines used in the manufacture of these blood grouping reagents have been used to manufacture well established CE marked products distributed in Europe and rest of the world.

Chronology: Alba submitted a pre-submission meeting request to FDA (Reference PTS# PS002250) for the RASCAT products on September 5, 2013. The meeting was held on October 24, 2013. FDA had a follow up teleconference with Alba on November 12, 2013. FDA received this efficacy supplement on August 6,

2014. CBER sent multiple Information Request letters and a Complete Response (CR) letter issued on May 22, 2015 for deficiencies that included CMC issues, validation studies, stability studies, performance studies, serological testing, and device history records. FDA issued an Incomplete Response letter on August 25, 2015 for deficiencies not addressed in Alba's July 30, 2015 response to the May 22, 2015 CR Letter. FDA subsequently received 14 amendments from Alba in response to various Information Requests.

3. Chemistry Manufacturing and Controls (CMC)

a) Manufacturing Summary

IVS Manufacturing Process

All manufacturing of In vitro Substances (IVS) including cell culture, fermentation, harvest and concentration, and quality control including microbiological testing are carried out by Alba at their licensed manufacturing facility except for two sub-contracted testing: the (b) (4) testing of (b) (4) water and (b) (4) water is carried out in accordance with (b) (4) standards by the sub-contractor, (b) (4); the mycoplasma testing of Master Cell Banks (MCB) and Working Cell Banks (WCB) is carried out by the sub-contractor, (b) (4).

Alba Bioscience Ltd. does not perform sub-lotting as per 21 CFR 660.51(a)(4) and no reprocessing is carried out during the manufacture of the IVS subject of this submission. The date of manufacture (DOM) for the IVS is defined as the date of delivery to stock.

Raw Materials:

The Hybridoma cell lines of human or murine origin are the raw materials to produce the IVS. All cell lines are 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 due to the consolidation of manufacturing services.

The IVS product descriptions and cell lines are listed in the table below.

Specificity	Anti-D	Anti-D	Anti-D	Anti-Le[a]	Anti-Le[b]
Alba Product code	Y041U	Y051U	Y061U	Y272U	Y282U
Cell line ID	LDM3	ESD1	ESD1M	LEA1	LEB1
Antibody/isotype class	IgM	IgG1	(b) (4) IgM	IgM	IgM

Cell line origin	Human	Human	Human (b) (4)	Murine	Murine

Monoclonal antibodies from the cell lines LDM3, ESD1, and ESD1M are already used by Alba Bioscience Ltd. to manufacture final products: Z041U (a blend of antibodies from the cell lines LDM3 and ESD1, reviewed under STN 125314/0), Z039U (a blend of antibodies from the cell lines LDM1 and ESD1M, reviewed under STN125313) under the U.S. License No. 1807.

For creation of the LEA1 and LEB1 hybridoma cell lines, mice were immunized using the immunogens ((b) (4)). B-cells were then isolated from the spleen of the mouse and fused to murine myeloma cells using a fusogen ((b) (4)), thus obtaining an immortalized cell line (hybridoma).

Alba received all cell lines through a quarantine procedure, checking the accompanying documentations, recording all test results and growth characteristics that are required for the cell lines including the cell line source/origin and culture history of the cell line, and confirming mycoplasma negative results. The initial vials were stored in a dedicated (b) (4) .

Master Cell Bank (MCB): The MCB is prepared from a (b) (4) vial of the optimized original cell lines recovered from (b) (4) and then expanded through growing the cells in culture. Each vial of MCB stocks is assigned with a unique identifier and then held in quarantine until approved.

The Working Cell Bank (WCB): The WCB is prepared by recovery of a (b) (4) vial of the MCB and then expanded through growing the cells in culture. Each vial of MCB stocks is assigned with a unique identifier and then held in quarantine until approved.

In-process tests during cell banking processes include (b) (4) .

The Fetal Bovine Serum (FBS) is the only raw material derived from animal source used in the manufacture of IVS. FBS is sourced from US Department of Agriculture (USDA) approved facilities. Procurement process is performed according to the acceptance criteria.

Other raw materials used for the manufacture of the IVS are provided by qualified suppliers, and are accepted based upon the supplier Certificate of Analysis (CoA), and/or incoming qualifying tests, as applicable, according to the acceptance criteria stated in the relevant Alba Bioscience Ltd. Starting Material Specifications or Final Product Specifications, as appropriate.

No materials of human source are used in the manufacture of IVS.

Cell Culture and Fermentation:

(b) (4)

Harvest and Concentrate:

(b) (4)

In process QC testing:

The IVS in the (b) (4) monoclonal (b) (4) are required to meet defined serological, biochemical and microbiological specifications. The following tests on the IVS subject of this application were performed prior to release for manufacturing the final products, using the established methods by Alba Bioscience Ltd. to determine (b) (4) biochemical and microbiological specifications.

(b) (4)

Biochemical specifications:

(b) (4) measurement is performed using manual assays or using an automated clinical chemistry analyzer. The biochemical specifications for the IVS material subject to this submission are provided in the table below.

IVS acceptable biochemical specifications

Specificity	Anti-D(IAT)	Anti-D(IAT)	Anti-D (DVI)	Anti-Le[a]	Anti-Le[b]
Product code	Y041U	Y051U	Y061U	Y272U	Y282U
Cell line ID	LDM3	ESD1	ESD1M	LEA1	LEB1
(b) (4) acceptable range ((b) (4))	(b) (4)				
(b) (4) acceptable range					

Microbiology Assessment:

The IVS is not sterile but microbiological controlled. The IVS materials that are considered as intermediate products do not undergo (b) (4) . Post harvested (b) (4) until required for formulation to the IVP.

Microbiology control methods in the IVS manufacture process include microbiological testing, complaint file analysis, trend analysis, (b) (4) studies, process control data, environmental monitoring, equipment sanitation validation, employee techniques and clothing requirements . Furthermore, at the time of (b) (4) , Sodium Azide (0.1% g/L) is added to individual production lots to minimize the potential for bacterial growth.

Stability:

The hold times for the IVS are controlled through the assignment of an appropriate expiry date on (b) (4) , a process manufacturing system. The five IVS materials are stored at (b) (4) until required to manufacture final products. A real time stability testing was performed to evaluate their shelf life, and the first (b) (4) lots of IVS were tested at (b) (4) intervals up to expiration and (b) (4) thereafter. Real time study is ongoing. Alpa submitted the data completed from up to (b) (4) . These data, in conjunction with the manufacturing hold time data available provide assurance that the IVS materials are stable for (b) (4) .

In Vitro Product (IVP) Manufacture Process

Alba manufactures the IVPs at their licensed facility, located at 21 Ellen's Glenn Road, Edinburgh, UK. Alba manipulates all substances and products used in the Alba Bioscience Ltd. manufacturing facility rooms on a campaign basis, that is, "one substance being manipulated at any one time in a defined area" and full line clearance is required before commencing production steps. The final IVP BGRs include the following formulation ingredients: the IVSs which are the active ingredients, bovine serum albumin, preservative, in-house prepared solutions (e.g., diluents), and (b) (4) .

A cross reference of In Vitro Substances (IVS) and IVP subject of this application is provided in the table below:

IVP Description	IVP Product code	Specificity	IVS Item number	IVS Manufacturer
ORTHO™ Sera Anti-D (IAT) Monoclonal IgM/IgG for ID-MTS™ Gel Card	FD041M	Anti-D	Y041U / Y051U	Alba Bioscience Ltd.
ORTHO™ Sera Anti-D (DVI) Monoclonal IgM for ID-MTS™ Gel Card	FD039M	Anti-D	Y061U	Alba Bioscience Ltd.
ORTHO™ Sera Anti-Le^a Monoclonal IgM for ID-MTS™ Gel Card	FD212M	Anti-Le^a	Y272U	Alba Bioscience Ltd.
ORTHO™ Sera Anti-Le^b Monoclonal IgM for ID-MTS™ Gel Card	FD217M	Anti-Le^b	Y282U	Alba Bioscience Ltd.
ORTHO™ Sera Anti-N Monoclonal IgG for ID-MTS™ Gel Card	FD176M	Anti-N	Y235	(b) (4)

All raw materials used for the manufacture of the IVP covered by this application are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

(b) (4) testing of (b) (4) water and (b) (4) water is carried out by a subcontractor.

Alba does not perform sublotting as per 21 CFR 660.51(a)(4) and no reprocessing is carried out during the manufacture of the IVP subject of this submission. The date of manufacture (DOM) for the IVP products is defined as the last date of pre-fill potency testing.

The IVP manufacturing processes include following steps:

- Production of Anti-D (IAT) (monoclonal blend) entails blending of two IVS products.
- The IVS can be concentrated or diluted further if necessary.
- Final formulation (e.g. addition of potentiator) step for Anti-D (DVI) FD039M.
- All five products require the (b) (4) to be measured and adjusted as necessary to meet the product specification. After (b) (4), samples are taken for QC testing to allow the product to be approved for filling.
- The bulk is approved, and filling commences with a (b) (4) step for all five IVPs.
- Filling is carried out by a (b) (4) filling machine. (b) (4) Plastic Caps are applied then tightened using a (b) (4). Filled, unlabeled containers are then transferred to store at 2-8 °C until satisfactory test results are received to allow progress to the labeling stage.
- Labelling and packing: After ensuring that labelling area is clear and verifying that the label information is correct, the labels can be attached to the filled vials. Then, the labelled vials are placed in the appropriate packages labelled with product details.
- The finished IVP is then stored at the +4°C (b) (4) waiting test results and QA release.

Specifications and Test Methods in QC testing:

The QC testing for specificity, potency, biochemical and microbiology is performed on the unlabeled stages for the IVP Anti-D (IAT) (unlabeled product code FDU041), Anti-D (DVI) (unlabeled product code FDU039) and Anti-Le[b] (unlabeled product code FDU217). The Anti-Le[a] and Anti-N IVPs undergo QC testing at the labeled stage. The following specifications should be met.

Specificity, product code	Test Method	Acceptance Criteria/Range		
		Specificity	Potency	(b) (4)

Anti-D (IAT), FD041M	(b) (4)
Anti-D (DVl), FD039M	
Anti-Le[a], FD212M	
Anti-Le[b], FD217M	
Anti-N, FD176M	

During the review cycle, FDA recommended that Alba update their QC release testing specifications for potency to include a minimum titer endpoint for each BGR. FDA and Alba agreed upon a minimum titer endpoint for each BGR during a teleconference with Alba on April 30, 2015. Alba submitted a potency titer endpoint for each BGR which is included in amendment 12 (CR response) received on August 7, 2015. BGRs, Anti-D(IAT), Anti-D(DVI), Anti-Lea, and Anti-Le[b] should have a minimum potency titer of (b) (4) whereas BGRs Anti-N should have a minimum potency titer of (b) (4).

Microbiology:

The acceptable level of microorganisms 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 microorganisms which may be introduced subsequent to the manufacturing process.
- Environmental and in-process controls are in place to limit the presence of microorganisms, and therefore limit potential contamination of the product through environmental control and aseptic technique.

Established Process Hold Times:

Alba conducted a real-time stability study to demonstrate that storage of the BGR products covered by this submission in the primary container under recommended storage conditions (2-8 °C) does not adversely alter the performance characteristics of the product for up to (b) (4) from post fill testing. (b) (4) conformance lots (including open vial) of each product were used in the stability study. Potency, specificity and microbiological testing are performed at defined time points ((b) (4)) during the stability study. The stability sample vials dedicated for serological testing were opened briefly at the start of the study (to demonstrate open vial) and then stored at 2-8 °C until required testing at various time points. The real time stability studies are currently ongoing, interim real time stability results have demonstrated acceptable product performance at all the time points tested to date.

The dating period for these Blood Grouping Reagents is 24 months when stored at 2-8 °C.

Alba also conducted a simulated transport stability study to access the impact of extreme temperature conditions on product stability/performance that may be encountered during shipment of the products. The results of the stability studies are acceptable.

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 DMPQ

Facility information and data provided in the PAS bundle were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Blood Grouping Reagent Anti-N (clone BO3) product code FD176M, Blood Grouping Reagent Anti-Lea (clone LEA1) product code FD212M, Blood Grouping Reagent Anti-Leb (clone LEB1) product code FD217M, Blood Grouping Reagent Anti-D (IAT) (clones LDM3 and ESD1) product code FD041M and Blood Grouping Reagent Anti-D (DVI) (clone ESD1M) product code FD039M are 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	Team Biologics May 2016 VAI

Team Biologics performed a surveillance inspection of the Edinburgh, Scotland, UK facility May 12, 13, 16-20, 2016. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).
No pre-approval inspection was performed as there were no changes to the approved application that would require such an inspection.

d) Environmental Assessment DMPQ

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 DMPQ

The *in vitro* Product is filled into 5mL (b) (4) borosilicate glass vial with 18mm screw neck and (b) (4) plastic red cap 8mm/400 with liner, which are provided by Ortho Clinical Diagnostics (OCD). Alba conducted the container closure integrity testing at the Edinburgh, UK facility, employing torque verification, weight verification and visual inspection for turbidity; all acceptance criteria were met.

4. Performance Studies

a) Clinical Comparison Study

Alba conducted a clinical comparison study internally at the Alba facility, and at three external United States locations: New York Blood Center (NYBC), Memorial Blood Center (MBC), and Blood Center of Wisconsin (BCW). The trial reagents were tested in parallel with FDA licensed reagents as reference (comparator reagent) using 300 samples internally and minimum of 1000 samples at each external site. The study samples included donor samples and de-identified left-over random clinical specimens as well as nitrogen frozen recovered red blood cells. The clinical specimens included the following disease states/conditions/ interfering substances: Multiple Myeloma, Waldenstrom's Macroglobulinemia, pregnancy, lymphoma, leukemia, lipemia, hemolysis, Direct Antiglobulin Test (DAT) positive, weak antigen, sickle cell, elderly, cord blood and warm auto immune hemolytic anemia.

Three lots of each trial reagent were used to test the clinical samples. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents. The one-sided 95% lower confidence limits for positive and negative percentage agreements of the trial reagent test results to the comparator reagent test results were calculated using the Clopper-Pearson exact calculation method. Discrepancy resolution included repeat testing of trial and comparator reagents in duplicate using a fresh red blood cell suspension, testing with a third resolver reagent, and performance of Direct Antiglobulin Test (DAT)

In the original submission, Alba did not specify acceptance criteria for the BGRs covered by this submission. During the review, FDA recommended that Alba amend the performance report to include acceptance criteria for each BGR and ensure the acceptance criteria were met or provide justification if the acceptance criteria were not met. Per the amended report, the Acceptance Criteria were: the lower bound of the one-sided 95% confidence intervals for both the positive and the negative percent agreement with the comparator should exceed 0.99-i.e., (95/99). During the review, the FDA also requested analysis of the results excluding samples with known DAT positive status. The table below shows the Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA) for each product when DAT Positive samples were included and DAT Positive samples excluded:

Blood Grouping Reagent	NPA /DAT Pos Included[a]	NPA /DAT Pos Excluded[b]	PPA /DAT Pos Included[a]	PPA/DAT Pos Excluded[b]
Ortho™ Sera Anti-D (DVI)	921/921 100% (99.68%)	No DAT Pos samples tested	2,692/2,699 99.74% (99.51%)	No DAT Pos samples tested
Ortho™ Sera Anti-D (IAT)	916/919 99.67% (99.16%)	No DAT Pos samples tested	868/871 100% (99.89%)	No DAT Pos samples tested
Ortho™ Sera Anti- Le[a]	887/890 99.66% (99.13%)	No DAT Pos samples tested	234/240 97.50% [*95.13%*]	234/238 98.32% [*96%*]
Ortho™ Sera Anti-Le[b]	315/321 98.13% [*96.34*]	315/320 98.44% [*97%*]	802/803 99.88% (99.41%)	No DAT Pos samples tested
Ortho™ Sera Anti-N*	342/342 100% (99.13%)	No DAT Pos samples tested	791/804 *98.4%* [*97.44%*]	791/799 99.00% [*98%*]

Note: The agreements that did not meet the acceptance criteria are italicized. [ ]

[a] Source: data obtained from the performance reports submitted in amendment 13 (appendices 7.1-7.6) and amendment dated December 19, 2016.

[b] Source: Data obtained from the performance reports submitted in Amendment 14 (Appendix 1.1-1.3) dated May 11, 2017.

Review of the performance data indicates the following studies did not meet the acceptance criteria:

- ORTHO™ Sera Anti-Le[a] did not meet the acceptance criteria for the PPA due to six discrepant results including four obtained at the BCW site. Two discrepancies originated from samples with positive DAT results and therefore resulted in positive reaction with AHG reagent in the comparator method. Four discrepant samples were confirmed for the initial test results on investigation but no rationale can be attributed to the cause of discrepancies. Lea positive red blood cell samples are present significantly less often than Lea negative red blood cell samples, 22% in Caucasians and 23% in Blacks (Reid, Lomas-Francis, and Olsson, 2012).
- ORTHO™ Sera Anti-Le[b] did not meet the acceptance criteria for the NPA due to six discrepant results at the BCW site. Three discrepancies were due to possible test errors because the trial reagent was concordant with the comparator reagent on repeat testing. Two discrepant samples were confirmed for the initial test results on investigation but no rationale can be attributed to the cause of discrepancies. One discrepancy was not noted at the time of testing at the trial site so no additional information was available for further discrepancy investigation.
- ORTHO™ Sera Anti-N did not meet the acceptance criteria for the PPA due to 13 discrepant results including ten discrepant results obtained at the BCW site. In 11 of 13 discrepancies, the resolver gave same results as the trial reagent. Five samples were DAT positive, and eight discrepant samples were confirmed for the initial test results on investigation with freshly prepared red blood cell suspensions. Alba reported that the investigation results showed that temperature influences the performance of this reagent and that erroneous results could result if testing is performed out with the recommended range stated in the IFU. Alba intends to update the IFU specifying that the reagent should be brought to ambient temperature prior to use.

For the Anti-D (DVI) reagent, ten cells previously categorized as Rh DVI were included in Alba site. During discrepancies resolution testing, six categorized DVI cells were recovered from LN2 storage and typed to confirm suitability. It was noted at that time sample 220187-4:2:21 was significantly weaker than the other five category DVI samples tested. All six LN2 recovered category DVI cells were tested on the same day. Five of the cells gave concordant results with the comparator reagent and the discrepant result above returned a 1+ reaction with the comparator by IAT method only.

Alba explained that the high number of discrepancies encountered by the BCW site is consistent with the high proportion of disease state samples tested by BCW in comparison to other trial sites. The study samples included the following disease conditions/interfering substances in testing.

Disease state	Number of samples tested
Multiple Myeloma	10
Waldenstrom's Macroglobulinemia	2
Pregnant	11
Lymphoma	9
Leukemia	11
Lipemic	10
Hemolyzed	10
DAT positive	27

Weak Antigen	10
WAIHA	7
Sickle cell	11
Elderly	11
Cord	10

Source: copied from Section 6.5 of the Performance Evaluation Report.

b) Precision

The precision studies included an internal lot-to-lot study and external study.

Internal lot-to-lot study: the study was performed in-house to demonstrate reproducibility from lot-to-lot, occasion- to-occasion, and operator-to-operator. Three lots of reagent were tested against a panel of red cells (intended as an antibody screening panel) with replicates, by three operators over a minimum of (b) (4) non-consecutive days taking into account different days and times, and multiple runs to confirm reproducibility /repeatability of test results. The total number of data points was 216 (3 lots, 12 runs, 3 cells, 2 replicates). All antigen positive red cells gave positive reactions and all antigen negative red cells gave negative reactions as expected.

The external precision study was carried out at three sites and encompassed testing of one lot of the reagent against a panel of three red blood cells with replicates. Testing was performed by three operators over a minimum of (b) (4) non-consecutive days taking into account different weeks, days and times. All antigen positive and antigen negative samples reacted as expected.

5. Nonclinical study

Alba conducted an anticoagulant study to demonstrate that the Ortho™ sera BGRs perform as expected when used with blood samples collected in various anticoagulants stored throughout the recommended storage period. The package inserts in the specimen collection section for the BGRs covered by this submission include the following sample limitations:

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

The following is a list of the anticoagulants and corresponding testing dates included in the validation study:

EDTA Potassium ((b) (4))
CPD ((b) (4))
ACD ((b) (4))
CPDA-1 ((b) (4))
CP2D ((b) (4))
CP2D with AS-3 ((b) (4))

Specificity 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 data from the anticoagulant study support the specimen collection claims described in the package insert.

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 and Complete Response letters 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 the five licensed RASCAT products covered by this application for use with the Ortho ID-Micro Typing System™.

8. Labeling

Alba submitted sample final 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.

As stated above, these reagents will be distributed by Ortho under the trade name Ortho™ Sera, therefore, Ortho will be responsible for providing the end user the IFU document. Alba provided the procedure that addresses control of the implementation of a revised electronic IFU document and the Quality Agreement between Ortho and Alba that delineates the labeling responsibilities between the two companies.

9. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members representing the necessary review disciplines recommend that the licensed BGR reagents subject to this application be approved for use with the Ortho MTS ID-Micro Typing System™ Gel Card for Column Agglutination Technology (CAT). These were independent conclusions based on the content of this efficacy supplement submission, 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

A comprehensive range of rare blood group antigen typing reagents for use on ID-Micro Typing System™ Gel Card for CAT will be of benefit for patient and donor use in the North American market. This will complement the existing range of licensed reagents available for ID-MTS™ CAT from OCD, provide more testing options and ultimately improve the safety and efficiency of the delivery of compatible blood to patients.

The clinical benefits from using the licensed Blood Grouping Reagents with the Ortho MTS Anti-IgG Gel Card includes reduction in errors associated with subjective interpretation of the manual tube method testing and the capability to review stored test results, if necessary.

c) Recommendation for Postmarketing Activities

There are no post marketing commitments associated with this submission.

Concurrence Page

Application Type and Number: BLA/NDA STN 125304/35 et al

COMMUNICATION TYPE:

History: Drafted by: Meihong Liu May 11, 2017
Reviewed: Teresita Mercado May 15, 2017, May 18, 2017
Revised: Orieji Illoh. May 30, 2017, May 31, 2017

Concurrence:

Note: *the names of people who concurred via email will be added above the table*
Concurrence required:

- *Review Committee Chair*
- *Review Committee Members who contributed to the SBRA*
- *[Original BLA/NDA] Office Director (or Dep Office Director) of the Office participating in the development of the SBR, other than the signatory authority*
- *[Efficacy Supplement] Division Director (or Dep Div Director), product office responsible for the clinical review*

Office/Division	Name/Signature	Date
OBRR/DBCD	Meihong Liu	
OBRR/DBCD	Teresita Mercado	
OCBQ/DMPQ	Priscilla Pastrana	
OCBQ/DMPQ	Mary Malarkey	
OBRR/DBCD	Orieji Illoh	