



Summary Basis for Regulatory Action

Date:

From: Teresita C. Mercado, Chair of the Review Committee

BLA/NDA>/ STN#: See the table below

Applicant Name: Alba Bioscience, Ltd.

Date of Submission: August 12, 2014

Goal Date: March 21, 2017

Proprietary Name/ Established Name:

Submission Tracking Number	Name of Biological Product	Cell Line(s)	Intended Use
BL 125567/0	Blood Grouping Reagent, Anti-Fy ^a (Monoclonal) (IgG)	DG-FYA-02	ORTHO™ Sera Anti-Fy ^a is for the qualitative in vitro detection of human Fy ^a positive red blood cells by the Indirect Antiglobulin Test.
BL 125568/0	Blood Grouping Reagent, Anti-Jk ^a (Monoclonal)	P3HT7	ORTHO™ Sera Anti-Jk ^a is for the qualitative in vitro detection of human Jk ^a positive red blood cells by the Direct Agglutination Test.
BL 125569/0	Blood Grouping Reagent, Anti-Jk ^b (Monoclonal)	P3.143	ORTHO™ Sera Anti-Jk ^b is for the qualitative in vitro detection of human Jk ^b positive red blood cells by the Direct Agglutination Test.
BL 125570/0	Blood Grouping Reagent, Anti-S (Monoclonal) (IgG)	PS13JS123	ORTHO™ Sera Anti-S is for the qualitative in vitro detection of human S positive red blood cells by the Indirect Antiglobulin Test.
BL 125571/0	Blood Grouping Reagent, Anti-s (Monoclonal) (IgG)	P3YAN3	ORTHO™ Sera Anti-s is for the qualitative in vitro detection of human s positive red blood cells

			by the Indirect Antiglobulin Test.
BL 125572/0	Blood Grouping Reagent, Anti-K (Monoclonal)	MS-56	ORTHO™ Sera Anti-K is for the in vitro detection of human K positive red blood cells by the Direct Agglutination Test.
BL 125573/0	Blood Grouping Reagent, Anti-P1 (MURINE Monoclonal)	650	ORTHO™ Sera Anti-P1 is for the in vitro detection of human P1 positive red blood cells by the Direct Agglutination Test.

Indication:

Recommended Action:

The Review Committee recommends approval of these products.

Offices Signatory Authority: 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 indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
Clinical Review(s) <ul style="list-style-type: none"> • <i>Clinical (product office)</i> 	Joyce Rockwell February 12, 2015 March 20, 2015 May 13, 2015 Oumou Barry May 4, 2016 December 29, 2016
Statistical Review(s) <ul style="list-style-type: none"> • <i>Clinical data</i> • <i>Non-clinical data</i> 	Chunrong Cheng June 2, 2015 December 22, 2016
CMC Review(s) <ul style="list-style-type: none"> • <i>CMC (product office)</i> • <i>Facilities review (OCBQ/DMPQ)</i> 	Joyce Rockwell (Product) February 12, 2015 March 20, 2015 Oumou Barry (Product) May 4, 2017 Priscilla Pastrana (OCBQ/DMPQ) March 12, 2015 May 4, 2015

	March 17, 2016
Labeling Review(s) <ul style="list-style-type: none"> • <i>APLB (OCBQ/APLB)</i> • <i>Product Reviewer</i> 	Dana Jones (OCBQ/ APLB) April 6, 2015 Joyce Rockwell (Product Reviewer) February 12, 2015 April 15, 2015 May 13, 2015 Oumou Barry (Product Reviewer) May 4, 2017
Other Review(s) <ul style="list-style-type: none"> • <i>Bioburden (DBSQC)</i> 	Hyesuk Kong May 26, 2015 October 27, 2016

1. Introduction

Alba Bioscience Limited, (hereafter known as Alba) located in Edinburgh, United Kingdom, submitted a bundled submission for the licensure of the seven Blood Grouping Reagents (BGRs) listed above. These BGRs are designated as Rare Antisera for Column Agglutination Technology (RASCAT) Monoclonal Blood Grouping Reagents (BGRs) and are manufactured for use with the Ortho ID-Micro Typing System™. The RASCAT reagents will be distributed by Ortho Clinical Diagnostics (FDA License 1236) under the trade name Ortho™ Sera.

2. Background

The seven BGRs will be manufactured, labeled, and packaged by Alba at their licensed Ellen's Glen Road facility. These Blood Grouping Reagents are human and/or murine monoclonal, and are manually added to the microtubes of either the MTS™ Buffered Gel Card or the MTS™ Anti-IgG Card, for direct agglutination or indirect antiglobulin test (IAT) for the qualitative detection of the Fy^a, Jk^a, Jk^b, K, P1, S, and s antigens on human red blood cells.

Jk^a and Jk^b antigens are part of the Kidd blood group system, Fy^a antigen belongs to the Duffy blood group system, K (Kell) antigen is the most important antigen in the Kell system and the S and s antigens belong to the MNS blood group system. Antibodies to these antigens are clinically significant as they can cause hemolytic transfusion reactions and hemolytic disease of the fetus and the newborn (HDFN).

The P1 antigen is present on red blood cells and tissue cells. It is present in about 80% of the population. Antibodies to P1 are occasionally clinically significant and have been implicated in hemolytic transfusion reactions.

The RASCAT reagents were the subject of a pre-submission meeting, reference PTS # PS002250 held on October 24, 2013. The discussion included the proposed clinical studies and the bundling of the submissions. FDA received the application on August 21, 2014 and filed them on October 15, 2014. FDA issued a Complete Response (CR) letter

on June 9, 2015 outlining deficiencies including shipping validation studies, the bioburden test method. FDA issued a second CR letter on May 16, 2016 regarding incomplete performance evaluation reports, lot release and labeling issues. All outstanding issues have been resolved.

3. Chemistry Manufacturing and Controls (CMC)

All manufacturing of the in vitro products (IVPs) to include (formulation, (b) (4) and filling, microbiology, as well as in-process and final QC testing) are performed by Alba Bioscience Ltd, at their licensed manufacturing facility. However, the (b) (4) (b) (4) testing of (b) (4) Water and (b) (4) water are carried out in accordance with the (b) (4) standards by a sub-contractor; (b) (4)

a) Manufacturing Process Description

Manufacturing of the BGRs covers (b) (4) main stages: the in vitro substances (IVS), (b) (4) and filling/packaging of the final product.

In Vitro Substances (IVSs)

The in vitro substances (also known as antibody concentrates) used in the manufacture of these seven Blood Grouping Reagents (BGRs) are manufactured by (b) (4), under a shared manufacturing arrangement. (b) (4) submitted supplements to their Biologic License Applications to ship the antibody concentrates labeled For Further Manufacturing Use (FFMU) to Alba who will further manufacture the antibody concentrates into final container products. The table below lists the FFMUs, supplier, and release specifications of the IVSs prior to being used in the manufacture of the final product.

(b) (4)



(b) (4)

(b) (4)

The IVPs are filled into the final container (5mL) glass tubing vials made of (b) (4) highly resistant (b) (4) glass which meets the compliance criteria of (b) (4). Filled, unlabeled containers are then transferred to the (b) (4) cold store and samples of all specificities (except Anti-Jk^a and Anti-P1) are sent for serological, biochemical and microbiological assessment. The products are stored until satisfactory test results are received to allow progress to the labeling stage. Identity is checked by serological testing and label inspection is performed at the labeled stage to confirm identity. The manufacturing process for BGRs Anti-Jk^a and Anti-P1 differs slightly from the other BGRs in that they are not tested at the unlabeled stage. These two products proceed to labeling and packaging with samples sent for serological testing, biochemical and microbiological assessment.

b) Product Quality

QC release testing is performed on the IVP within the final primary container to confirm reactivity with antigen positive red blood cells using a (b) (4). Testing is also performed to confirm the absence of contaminating antibodies, using (b) (4). Potency of the IVP is confirmed by performing tests involving serial dilutions of the respective reagent and testing using the Column Agglutination Technology (CAT).

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 informed Alba that the potency specifications for the IVP currently state “comparable to the reference.” However comparing the IVP to the reference material may cause the potency release specification to fluctuate. FDA and Alba agreed upon a minimum titer endpoint for each BGR during a teleconference with Alba on April 22, 2015. Alba submitted a potency titer endpoint for each BGR which is included in amendment 12 (CR response) received on August 11, 2015. BGRs Anti-Jk^a, Anti-Jk^b, Anti-K, Anti-P1, and Anti-S should have a minimum potency titer of (b) (4) whereas BGRs Anti-Fy^a and Anti-s should have a minimum potency titer of (b) (4).

BGRs are microbiologically controlled products, therefore, they are not considered sterile. Formulation of these IVPs includes addition of sodium azide as a preservative and (b) (4). In addition, during handling of the final product, in process control is practiced to minimize product contamination. Alba submitted data to demonstrate validation of their (b) (4) bioburden method. CBER reviewed the data and found that the bioburden test method was in accordance with (b) (4) standard and the IVPs are suitable for their intended use. Additionally, the proposed sodium azide concentration ($\leq 0.1\%$) for the various products was shown to have effective antimicrobial properties in accordance with (b) (4).

Alba conducted a real-time stability study to determine shelf-life and in-use stability (after opening) for the BGRs covered by this submission. (b) (4) conformance lots (including open vial) of each product were used in 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 for testing at various time points. Alba also conducted a simulated transport stability study to assess 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.

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

c) CBER Lot Release (only applicable for BLAs)

The lot release protocol templates were submitted to CBER for review and found to be acceptable after revisions. Lot release testing plans were developed by CBER and will be used for routine lot release.

d) Facilities review/inspection

Facility information and data provided in the BLA bundle were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Blood Grouping Reagent Anti-Fy^a (clone DG-FYA-02) (Monoclonal Human) (IgG) Product Code FD151M, Blood Grouping Reagent Anti-Jk^a (clone P3HT7) (Monoclonal Human) (IgM) Product Code FD162M, Blood Grouping Reagent Anti-Jk^b (clone P3.143) (Monoclonal Human) (IgM) Product Code FD166M, Blood Grouping Reagent Anti-S (clone PS13JS123) (Monoclonal Human) (IgG) Product Code FD182M, Blood Grouping Reagent Anti-s (clone P3YAN3) (Monoclonal Human) (IgG) Product Code FD186M, Blood Grouping Reagent Anti-K (clone MS-56) (Monoclonal Human) (IgM) Product Code FD132M and Blood Grouping Reagent Anti-P1 (clone 650) (Monoclonal Mouse) (IgM) Product Code FD202M are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for Blood Grouping Reagent Anti-Fy^a (clone DG-FYA-02) (Monoclonal Human) (IgG) Product Code FD151M, Blood

Grouping Reagent Anti-Jk^a (clone P3HT7) (Monoclonal Human) (IgM) Product Code FD162M, Blood Grouping Reagent Anti-Jk^b (clone P3.143) (Monoclonal Human) (IgM) Product Code FD166M, Blood Grouping Reagent Anti-S (clone PS13JS123) (Monoclonal Human) (IgG) Product Code FD182M, Blood Grouping Reagent Anti-s (clone P3YAN3) (Monoclonal Human) (IgG) Product Code FD186M, Blood Grouping Reagent Anti-K (clone MS-56) (Monoclonal Human) (IgM) Product Code FD132M and Blood Grouping Reagent Anti-P1 (clone 650) (Monoclonal Mouse) (IgM) Product Code Code FD202M

Name/Address	FEI number	DUNS number	Inspection/waiver	Results/Justification
<i>in vitro</i> Product Manufacturing and Testing Alba Biosciences Limited 21 Ellen's Glen Road Edinburgh EH17 7QT Scotland, UK	3003580203	719392867	Waived	Team Biologics May 2016 VAI

Team Biologics performed a surveillance inspection May 12, 13, 16-20 2016. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

e) Environmental Assessment

The BLA bundle 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.

f) Container Closure

The *in vitro* Products are filled into 5mL (b) (4) glass vial with 18mm screw neck and (b) (4) plastic red cap 8mm/400 with liner, which are provided by (b) (4). Alba conducted the container closure integrity testing at the Edinburgh, UK facility, employing (b) (4) all acceptance criteria were met.

4. Performance Studies

a) Clinical

Alba conducted a clinical study at three external United States locations: New York Blood Center (NYBC), Memorial Blood Center, and Blood Center of Wisconsin. The ORTHO™ Sera BGRs covered in this submission were tested against 300 red blood cell samples internally at the Alba facility. External testing was performed on various samples in parallel with FDA licensed reagents as references or comparators. The study samples were 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.

The performance study samples were tested with the trial (ORTHO™ Sera) BGRs using the column agglutination technique (CAT) and with FDA licensed reagents using the tube method, and the results were compared for concordance. Discrepancy resolution included repeat testing with the trial and comparator reagents, testing using a third resolver test method and performance of DAT. Comparison agreement calculations were performed on: a) samples with known DAT positive status prior to testing and DAT positive samples identified during the discrepancy investigation were removed from the data analysis and b) samples with known DAT positive status prior to testing were removed from the data analysis but DAT positive samples identified during the discrepancy investigation were included in the analysis.

The acceptance criteria for the BGRs is: the lower bound of the one-sided 95% confidence intervals for both the positive and the negative percent agreements with the comparator reagent/method should exceed 0.99-i.e. (95/99). The table below shows the Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA) for each product:

Table 2 Performance data -combined sites results based on the one sided 95% lower confidence limit

Blood Grouping Reagent	Negative Percent Agreement (NPA) DAT Pos Excluded	Negative Percent Agreement /DAT Pos Included	Positive Percent Agreement (PPA) DAT Pos Excluded	Positive Percent Agreement /DAT Pos Included
Ortho™ Sera Anti-Fya	370/374 [97.6]	370/380 [95.6]	738/738 * [99.6]	738/738* [99.6]

Ortho™ Sera Anti-Jk ^a	262/263 * <i>[98.2]</i>	262/263 * <i>[98.2]</i>	868/871* [99.1]	868/871* [99.1]
Ortho™ Sera Anti-Jk ^b	313/314* <i>[98.5]</i>	313/314* <i>[98.5]</i>	819/820* [99.4]	819/820* [99.4]
Ortho™ Sera Anti-K	990/991* [99.5]	990/991* [99.5]	138/138 <i>[97.9]</i>	138/146 <i>[90.3]</i>
Ortho™ Sera Anti-P1	288/294 <i>[96.0]</i>	288/297 <i>[94.8]</i>	848/851* [99.1]	848/851* [99.1]
Ortho™ Sera Anti-S	529/531 <i>[98.8]</i>	529/537 <i>[97.3]</i>	581/581* [99.5]	581/581* [99.5]
Ortho™ Sera Anti-s	128/129 <i>[96.4]</i>	128/130 <i>[95.2]</i>	988/988* [99.7]	988/988* [99.7]

*No DAT samples tested

Note: The agreements that did not meet the acceptance criteria have been italicized [/]
Source: data obtained from the performance reports submitted in amendment 17 (appendices 2.1-2.7) and amendment dated February 28, 2017.

A summary of the BGRs that did not meet the acceptance criteria for negative or positive percent agreement is listed below:

- Ortho™ Sera Anti-Fy^a did not meet the NPA due to 10 discrepant results; 6 samples were DAT positive, 2 discrepancies were due to possible recent transfusion history (sickle cell disease/malignancy) and 2 discrepant results were due to incorrect performance of the test procedure.
- Ortho™ Sera Anti-Jk^a did not meet the NPA due to four discrepant samples. Three samples were confirmed negative on further investigation but there was no rationale for the cause of the discrepancies. The fourth discrepant sample was confirmed to be Jk^a weak positive by molecular testing.
- Ortho™ Sera Anti-Jk^b did not meet the NPA due to two discrepant samples. In one case, the initial test result changed following an investigation indicating an initial test error; in the other case, a root cause could not be determined for the

discrepancy.

- Ortho™ Sera Anti-K did not meet PPA because of the low number of K positive samples. There were 9 discrepant samples. Eight of the discrepancies originated from samples with positive DAT results and therefore resulted in positive reaction with AHG reagent in the comparator method. One discrepancy was due to possible test error because the trial reagent was concordant with the comparator reagent on repeat testing.
- Ortho™ Sera Anti-P1 did not meet the NPA due to 12 discrepancies. Three discrepancies originated from samples with positive DAT results (not recommended for IAT procedure); in five discrepant cases the initial results changed, giving concordant reaction on repeat testing which may indicate initial test error; three discrepant samples confirmed the initial test results on investigation but no rationale was found for the cause of discrepancies; one discrepancy was noted at the time of testing at the trial site but no investigation was performed on this sample.
- Ortho™ Sera Anti-S did not meet the NPA due eight discrepancies which can be attributed to six DAT positive samples and two samples related to sickle cell disease or patient with malignancy and possible recent transfusion history.
- Ortho™ Sera Anti-s did not meet the NPA due to the low number of s negative samples. There were two discrepancies that can be attributed to a positive DAT sample. In the other sample, the initial test result changed to give a concordant result on repeat testing which may indicate test error with the comparator reagent.

b) Precision

The precision studies included an internal lot-to-lot study to demonstrate reproducibility from lot-to-lot, occasion- to-occasion, and operator-to-operator. Alba also performed an external precision study to demonstrate reproducibility from occasion-to-occasion and operator-to-operator.

The internal lot-to-lot study was performed in-house using three lots of reagent tested against a panel of red cell samples, using multiple operators, days and runs to confirm reproducibility /repeatability of test results. Testing was performed by three operators over a minimum of (b) (4) non-consecutive days taking into account different days and times. All antigen positive and antigen negative samples reacted as expected.

The external precision study was carried out at three sites and encompassed testing of one lot of the reagent tested against a panel of three red blood cells. 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 Studies

Alba conducted an anticoagulant study to demonstrate that the BGRs perform as expected when used with samples stored in various anticoagulants throughout the recommended storage period. Samples stored in EDTA should be tested within seven days from collection. Donor blood collected in ACD, CPD, CP2D, CP2D with AS-3, and CPDA-1 may be tested until the expiration date of the donation. NOTE: ORTHO™ Sera Anti-Fy^a, Anti-K, and Anti-S have not been validated for use with CP2D with AS-3. This will be noted in the Instructions for Use.

6. Advisory Committee Meeting

An advisory committee meeting was not convened for these products since they do not include new technology.

7. Labeling

Alba submitted draft labeling for the instruction for use (IFU), the final container labels and the package labels. The labels for the BGRs comply with the requirements in Title 21 CFR 610.62, 610.64, 660.28 and 809.10 and are acceptable.

8. 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 licensure of these seven Blood Grouping Reagents will make available rare blood typing antisera to immunohematology laboratories and blood establishments that employ column agglutination technology.

c) Recommendation for Postmarketing Activities

There are no postmarketing commitments associated with these BLAs.