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Summary Basis for Regulatory Action

From: Susie Lee, Chair of the Review Committee

BLA/ STN#: See Table 1.

Applicant Name: Alba Bioscience Limited

Date of Submission: March 15, 2018

MDUFA Goal Date: April 21, 2019

Proprietary Name: See Table 1.

Established Name (common or usual name): See Table 1.

TABLE 1

STN	Product Name	Cell Line(s)	Trade Name
125567\3	Blood Grouping Reagent, Anti-Fy^a (Monoclonal)(IgG)	DG-FYA-02	ALBAclone®, Anti-Fy^a Monoclonal IgG
125568\3	Blood Grouping Reagent, Anti-Jk^a (Monoclonal)	P3HT7	ALBAclone®, Anti-Jk^a Monoclonal
125569\3	Blood Grouping Reagent, Anti-Jk^b (Monoclonal)	P3.143	ALBAclone®, Anti-Jk^b Monoclonal
125570\3	Blood Grouping Reagent, Anti-S (Monoclonal)(IgG)	PS13JS123	ALBAclone®, Anti-S Monoclonal IgG
125571\3	Blood Grouping Reagent, Anti-s (Monoclonal)(IgG)	P3YAN3	ALBAclone®, Anti-s Monoclonal IgG
125572\3	Blood Grouping Reagent, Anti-K (Monoclonal)	MS-56	ALBAclone®, Anti-K Monoclonal
125573\3	Blood Grouping Reagent, Anti-P1 (Murine Monoclonal)	650	ALBAclone®, Anti-P1 Murine Monoclonal

Intended Use/Indications for Use: See Table 2.

TABLE 2

Product Name	Intended Use/ Indications for Use
Blood Grouping Reagent, Anti-Fy^a (Monoclonal)(IgG)	This Anti-Fy^a reagent is for the *in vitro* detection and identification of the human Fy^a blood group antigen by Indirect Antiglobulin Test.
Blood Grouping Reagent, Anti-Jk^a (Monoclonal)	This Anti-Jk^a reagent is for the *in vitro* detection and identification of the human Jk^a blood group antigen by direct agglutination.
Blood Grouping Reagent, Anti-Jk^b (Monoclonal)	This Anti-Jk^b reagent is for the *in vitro* detection and identification of the human Jk^b blood group antigen

	by direct agglutination.
Blood Grouping Reagent, Anti-S (Monoclonal)(IgG)	This Anti-S reagent is for the *in vitro* detection and identification of the human S blood group antigen by Indirect Antiglobulin Test.
Blood Grouping Reagent, Anti-s (Monoclonal)(IgG)	This Anti-s reagent is for the *in vitro* detection and identification of the human s blood group antigen by Indirect Antiglobulin Test.
Blood Grouping Reagent, Anti-K (Monoclonal)	This Anti-K reagent is for the *in vitro* detection and identification of the human K blood group antigen by direct agglutination
Blood Grouping Reagent, Anti-P1 (Murine Monoclonal)	This Anti-P1 reagent is for the *in vitro* detection and identification of human P1 positive red blood cells by direct agglutination.

Recommended Action: The Review Committee recommends approval of these products.

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

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

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

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

Table 3 indicates the material reviewed when developing the SBRA.

TABLE 3

Document Title	Reviewer Name and Document Date
Clinical Review (product office)	Susie Lee, OBRR/DBCD/DRB • March 27, 2019 Kimberly Bigler, OBRR/DBCD/DRB • March 13, 2019
Statistical Review	Paul Hshieh, OBE/DB/TEB • March 12, 2019
CMC Product Review	Susie Lee, OBRR/DBCD/DRB • March 27, 2019 Kimberly Bigler, OBRR/DBCD/DRB • March 13, 2019
CMC Facilities Review	Priscilla Pastrana, OCBQ/DMPQ/MRBII • November 16, 2018
Labeling Review	Susie Lee, OBRR/DBCD/DRB • March 27, 2019 Kimberly Bigler, OBRR/DBCD/DRB • March 13, 2019 Dana Jones, OCBQ/DCM/APLB • August 29, 2018
Bioburden and Antimicrobial Effectiveness	Simleen Kaur, OCBQ/DBSQC/LMIVTS • May 8, 2018
Lot Release Protocol Template	Garnepudi, Varsha, OCBQ/DBSQC/QAB • December 14, 2018

1. Introduction

Alba Bioscience Limited, (hereafter known as Alba) located in Edinburgh, United Kingdom, submitted an Efficacy Supplement requesting approval to manufacture and distribute the seven Blood Grouping Reagents listed above. These products are indicated for the *in vitro* detection and identification of blood group antigens Fy^a, Jk^a, Jk^b, S, s, K, P1 by direct agglutination test or Indirect Antiglobulin Test (IAT). These reagents will be distributed in the US by Alba under the trade name ALBAclone®.

Blood group antigens Fy^a, Jk^a, Jk^b, S, s, K, P1 are clinically significant. These antigens are immunogenic and antibodies to these antigens are potential causes of hemolytic transfusion reactions and hemolytic disease of the fetus and newborn. Clinical

laboratories commonly perform blood group determination using hemagglutination methods. 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 these products.

Chronology Summary of Submission:

CBER received this original submission on March 15, 2018. The submission was filed on May 9, 2018. CBER received four amendments dated September 26, 2018, November 14, 2018, November 28, 2018 and February 19, 2019 in response to three information requests and a Complete Response letter.

Marketing History:

Alba has manufactured and distributed these seven Blood Grouping Reagents as licensed finished products under the trade name ORTHO™ Serum since 2017, as well as under the trade name ALBAclone® for sale in the rest of the world.

Description of the Device:

The main components of the subject Blood Grouping Reagents (BGRs) are human or human/murine monoclonal antibodies specific to the human red blood cell antigens. The formulation ingredients include the purchased antibody concentrate, (b) (4) bovine serum albumin (BSA) and preservative (sodium azide). The subject BGRs are filled into 5 mL or 10 mL (b) (4) glass vials with dropper assembly. These reagents are for *In Vitro* Diagnostic Use.

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".

Alba performs all manufacturing and QC testing at their licensed facility at 21 Ellen's Glen Road, Edinburgh, UK, except that the (b) (4) testing of (b) (4) water and (b) (4) water is contracted out to a sub-contractor, (b) (4) and the mycoplasma testing of the Master Cell Banks (MCB) and Working Cell Banks (WCB) is performed by (b) (4).

a) Manufacturing Summary

Manufacturing of the subject BGRs includes formulation, (b) (4) filling, labeling and packaging, as well as in-process and final release testing. Alba manufactured three conformance lots for each subject BGR, except for Anti-Fy[a] having (b) (4) lots. All substances and products are manufactured or manipulated on a campaign basis to avoid cross contamination, and a full line clearance is performed before beginning production steps. All in-coming materials used for the manufacture of subject BGRs are provided by qualified suppliers and accepted based on the supplier Certificate of Analysis (COA) and qualifying tests. All manufacturing is carried out in a controlled environment.

- **Antibody Concentrates/ *In Vitro* Substances (IVS)**

  The *in vitro* substances (IVS) used in the manufacture of the subject Blood Grouping Reagents (BGRs) are licensed For Further Manufacture Use products (FFMUs), purchased from suppliers, (b) (4) under shared manufacturing arrangements. Table 4 lists the FFMUs, supplier, and release specifications of the IVS prior to being used in the manufacture of the subject BGRs (excerpted from submission).

TABLE 4

(b) (4)

(b) (4)

- ***In Vitro* Products (IVP)**

  The manufacturing processes for the subject BGRs are similar to the processes for the corresponding licensed products, except that (1) the purchased IVS BGRs Anti-Jk[a], Anti-Jk[b], Anti-S and Anti-P1 are filled into the final containers (b) (4) and (2) BGR Anti-K (b) (4), is filled into final contain (b) (4). Table 5 describes the manufacturing steps for subject BGRs (excerpted from submission).

TABLE 5

Manufacturing Step		Anti-K Z132U	Anti-Jk[a] Z162U	Anti-Jk[b] Z166U	Anti-S Z182U	Anti-P1 Z202U	Anti-Fy[a] Z152U	Anti-s Z187U
Process	(b) (4)	(b) (4)						
Formulation								
(b) (4) (b) (4) Filling	Filling							
Labeling and packing	Labeling and Packing							
	Container & Closure	10 mL	5 mL	5 mL	10 mL	10 mL	10 mL	10 mL
	Fill Volume	5 mL	2 mL	2 mL	5 mL	5 mL	5 mL	5 mL

Formulation compositions for the subject BGRs are similar to the compositions for the corresponding licensed products, except that (1) BGR

Anti-s is formulated with (b) (4) and (2) BGRs Anti-s and Anti-Fy[a] are (b) (4). Samples of (b) (4) (b) (4) are taken for in-process QC testing. The Date of Manufacture (DOM) for the subject BGRs is defined as the last date of (b) (4) (b) (4) potency testing.

(b) (4) filling operation is performed in a Class (b) (4) validation (b) (4) located in a Clean room (Class (b) (4) ISO Class (b) (4) The filling equipment and the process is the same as for the licensed products. The subject BGRs are filled into 5- or 10-mL glass vials with dropper assembly. The final containers are labeled and stored at 2-8 °C until being released for distribution. Final QC release testing is performed on labeled vials.

Alba plans to ship the subject BGRs to a (b) (4) storage facility in (b) (4) for product distribution to end users, under a Quality Agreement with (b) (4) Alba authorized agent in the US.

- **Test Methods and Specifications**

  The (b) (4) product release test methods and specifications are the same as for the corresponding licensed products, including potency, specificity, biochemical (b) (4)), and bioburden. Table 6 lists the release specifications of the subject BGRs (IVP) (excerpted from submission).

TABLE 6

IVP	Anti-K	Anti-Jk[a]	Anti-Jk[b]	Anti-S	Anti-P1	Anti-Fy[a]	Anti-s
Product Code	Z132U	Z162U	Z166U	Z182U	Z202U	Z152U	Z187U
Potency	(b) (4)						
Specificity	Positive: (b) (4)						
	Negative: (b) (4)						

(b) (4)	(b) (4)						
Bioburden	(b) (4)						

Potency: Potency testing is performed using (b) (4) (b) (4) The test result is measured as the (b) (4)), defined as the (b) (4)

The potency tests for Anti-K, Anti-S, Anti-P1, Anti-Fy^a and Anti-s were carried out with incubation prior to spin in accordance with the corresponding IFU. For Anti-Jk^a and Anti-Jk^b, the potency tests were carried out with (b) (4) (b) (4) spin. However, the test procedure described in the corresponding IFU is immediate spin (IS) without incubation. During the review cycle, FDA asked Alba to preform potency tests for Anti-Jk^a and Anti-Jk^b in accordance with the test procedure in the IFU. FDA and Alba agreed on a bridging study for Anti-Jk^a and Anti-Jk^b to compare the potency and specificity using both procedures to demonstrate that the IS (b) (4) may be used interchangeably. Alba submitted the study report on February 19, 2019. The study results showed the potency titer is within acceptable range (b) (4) between two methods.

Specificity: Specificity testing is performed to confirm reactivity with antigen positive red blood cells and the absence of contaminating antibodies using red blood cells lacking the corresponding antigen. All specificity testing met the acceptance criteria stated in the Table 6 above.

Biochemical: The acceptable (b) (4) ranges were assigned during validation using the conformance lots, which may be revised following manufacture of additional lots.

Bioburden: BGRs are microbiologically controlled products and are considered non-sterile, multiple use devices. The acceptable level of

microorganisms which the products may contain is (b) (4) . The 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 (b) (4) tested with a validated bioburden method.

- The final products contain the preservative (bacteriostatic agent) sodium azide at a concentration of 0.1% w/v, to inhibit growth of micro-organisms.

b) CBER Lot Release

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

c) Facilities Review/Inspection

Facility information and data provided in the Efficacy Supplement were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the Blood Grouping Reagents Anti-Fy^{a} [(clone DG-FYA-02) (Monoclonal Human) (IgG) Product Code FD151M], Anti-Jk^{a} [(clone P3HT7) (Monoclonal Human) (IgM) Product Code FD162M], Anti-Jk^{b} [(clone P3.143) (Monoclonal Human) (IgM) Product Code FD166M], Anti-S [(clone PS13JS123) (Monoclonal Human) (IgG) Product Code FD182M], Anti-s [(clone P3YAN3) (Monoclonal Human) (IgG) Product Code FD186M], Anti-K [(clone MS-56) (Monoclonal Human) (IgM) Product Code FD132M] and Anti-P1[(clone 650) (Monoclonal Mouse) (IgM) Product Code FD202M] is provided in Table 7.

TABLE 7

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
in vitro Products Manufacture (Formulation, (b) (4) Filling, Labeling, Packaging and Storage) and In-Process and Release Testing Alba Biosciences Limited 21 Ellen's Glen Road Edinburgh EH17 7QT Scotland, UK	3003580203	516536641	Waiver	Team Biologics VAI September 10–14, 2018

Team Biologics performed a surveillance inspection September 10-14, 2018. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental Assessment

The Efficacy Supplement 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.

e) Container Closure System

The Blood Grouping Reagents or *in vitro* Products are filled into 5mL or 10mL (b) (4) borosilicate glass vial with 18mm screw neck and rubber 5mL or 10mL glass dropper assembly cap. The dropper is made of (b) (4) borosilicate glass vial. The vial is manufactured by (b) (4). The dropper assembly cap and plastic pipette are manufactured by (b) (4). Alba conducted the container closure integrity testing at the Edinburgh, UK facility,

employing (b) (4) visual inspection for (b) (4) all acceptance criteria were met.

4. Software and Instrumentation

Not Applicable

5. Analytical Studies

a) Stability Study

Alba conducted a real-time stability study to determine shelf-life and open vial stability for the subject BGRs. The study was conducted on three conformance lots of each subject BGR, except Anti-Fy[a] which was on (b) (4) lots. All lots designated for stability testing were opened for (b) (4) at the beginning of the study to demonstrate open vial (in-use) stability and then stored at 2-8 °C until required for testing at the planned time points, day zero, 3, 6, 9, 12, 15, 18, 21, 24, (b) (4) (one year beyond the proposed expiry). At each time point, potency and specificity testing was performed in parallel with a product reference. Bioburden was performed only at day zero, 6, 12, 24 and (b) (4) months.

The real time stability study is currently ongoing. Alba submitted stability results up to (b) (4) months of potency and specificity test results, except for Anti-s which has up to 24 months. Bioburden test results were submitted up to the 24 months timepoint. All testing results met the acceptance criteria for all time points submitted. The results support the shelf life of 24 months for all BGRs. Upon approval, Alba plans (b) (4)

Alba also conducted a simulated transport stability study to determine reagent stability following transportation from Alba to the end user. The study was performed on (b) (4) of each reagent. Vialed reagents were exposed

to extreme temperature (b) (4) then stored at the recommended temperature (2-8 °C). All simulated transport samples met acceptance criteria except for Anti-s at 24-months, whose potency test (b) (4) was more than (b) (4) below the (b) (4) of the reference. As part of the investigation, Alba continued the simulated transport study on Anti-s. Testing was performed at (b) (4) months and both potency and specificity met the acceptance criteria. Alba stated the 24-month timepoint potency result appeared out of trend and was anomalous.

The dating period for the subject BGRs is 24 months when stored at 2-8 °C.

b) Anticoagulant Studies

Alba conducted an anticoagulant study to demonstrate that the subject BGRs will perform as expected when tested with blood samples stored in various anticoagulants over the recommended storage period as stated in the IFU. The clotted samples, or those collected in EDTA, should be tested within fourteen 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. (b) (4) donors were selected and tested for each of the reagents. Specificity testing was performed at each scheduled timepoint. All test results met the acceptance criteria for specificity testing.

c) Precision Study

Alba conducted a precision study to demonstrate reproducibility between lots, runs, days and operators. The study included an internal lot-to-lot study and external precision testing performed at three external sites:(b) (4) The test panel for the precision study was also used for the lot-to-lot study and included the red blood cells listed in Table 8.

TABLE 8

Subject BGR	Test Panel Red Blood Cells Phenotypes			
	Cell 1	Cell 2	Cell 3	Cell4

Anti-K (Z132U)	kk[2]	Kk[1]	kk[2]	Kk[1]
Anti-Fy[a] (Z152U)	Fy(a+b-)	Fy(a+b+)[1]	Fy(a-b+)[2]	Fy(a+b-)
Anti-Jk[a] (Z162U)	Jk(a+b-)	Jk(a-b+)[2]	Jk(a+b+)[1]	Jk(a+b-)
Anti-Jk[b] (Z166U)	Jk(a+b-)[2]	Jk(a-b+)	Jk(a+b+)[1]	Jk(a+b-)[2]
Anti-S (Z182U)	Ss[1]	SS	ss[2]	ss[2]
Anti-s (Z187U)	Ss[1]	SS[2]	Ss[1]	Ss[1]
Anti-P1 (Z202U)	P1(-)[2]	P1(+)	P1(-)[2]	P1(+)

Note: 1 = heterozygous cells
2 = negative cells

- **Internal Lot-to-Lot Study:** Three lots of trial reagent were tested against the precision test panel with replicates (separated by a minimum of (b) (4)), by three operators over a minimum of (b) (4) non-consecutive days, considering different days and times, and (b) (4) runs to confirm reproducibility/repeatability of test results. For each trial reagent, the total number of runs was 36 ((b) (runs/day x (b) (4 days x 3 operators) and the total number of data points was 288 ((b) (4) runs x (b) (replicates/run x (b) (cells/panel). The 3 reagent lots were evenly distributed among the 36 runs. All antigen positive and antigen negative samples reacted as expected.

- **External Precision Study:** (b) (4) of each reagent was tested against the precision test panel with replicates by three operators over a minimum of (b) (4) non-consecutive days, similar to the internal lot-to-lot study design. For each trial reagent, the total number of runs was 90 ((b) (4 runs/day x (b) (days x 3 operators x (b) (sites) and the total number of data points was 720 ((b) (4) runs x (b) (4 replicates/run x (b) (cells/panel). All antigen positive and antigen negative samples reacted as expected.

6. Clinical Studies

a) Comparator Study

The comparator study tested each of the subject BGRs (the Trial) in parallel with a corresponding FDA licensed product (the Comparator) to demonstrate the subject BGRs perform as expected in the hands of end user. The study was conducted at the following sites:

- Alba Bioscience Ltd (internal site, non-US site)
- Gulf Coast Regional Blood Center (GCR)
- Memorial Blood Center (MBC)
- Blood Center of Wisconsin (BCW)

The three US study sites were selected to cover representative population distributions. Samples tested were de-identified leftover donor or patient samples. Test samples included elderly and neonate/cord blood samples and available disease states at the trial sites at the time of the study. Also included were lipemic, icteric and hemolyzed samples. A minimum of two lots of each trial reagent were tested against 300 red blood cell samples in parallel with the comparator in each US test site. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents. Table 9 lists the trial reagents (subject BGRs) and the comparators reagents (excerpted from the submission).

TABLE 9

Trial Reagent	Comparator Reagent (Manufacturer)
ALBAclone® Anti-K (Z132U)	ALBAsera® Anti-K (Alba, Z131U)
ALBAclone® Anti-Fy^{a} (Z152U)	ALBAsera® Anti-Fy^{a} (Alba, Z151U)
ALBAclone® Anti-Jk^{a} (Z162U)	Gamma-clone® Anti-Jk^{a} (Immucor)
ALBAclone® Anti-Jk^{b} (Z166U)	Gamma-clone® Anti-Jk^{b} (Immucor)
ALBAclone® Anti-S (Z182U)	Gamma-clone® Anti-S (Immucor)
ALBAclone® Anti-s (Z187U)	ALBAsera® Anti-s (Alba, Z186U)
ALBAclone® Anti-P1 (Z202U)	Gamma-clone® Anti-P1 (Immucor)

The acceptance criteria for each of the trial reagents requires ≥ 99% concordance at the lower bound of the one-sided 95% confidence interval (95% LCL) for both positive and negative percentage agreements (PPA/NPA). Table 10 shows the

PPA and NPA for each reagent. The agreements that did not meet the acceptance criteria have been italicized.

TABLE 10

Subject GBR	N	Comp + Trial +	Comp + Trial –	PPA (95% LCL)	Comp – Trial –	Comp – Trial +	NPA (95% LCL)
Anti-Fy^a	1106	662	0	100% (99.55%)	443	1	*99.77% [98.94%]*
Anti-Jk^a	1121	883	0	100% (99.64%)	286	0	*100% [98.97%]*
Anti-Jk^b	1106	757	0	100% (99.61%)	351	0	100% (99.15%)
Anti-S	1104	568	0	100% (99.47%)	536	0	100% (99.44%)
Anti-s	1178	866	0	100% (99.65%)	312	0	100% (99.04%)
Anti-K	1201	308	2	*99.35% [97.98%]*	891	0	100% (99.66%)
Anti-P1	1115	819	1	99.88% (99.42%)	292	3	*98.98% [97.39%]*

Note: Comp + Trial +: both the comparator and the trial reagents were positive, similar for other column names.
N: combined test samples

The trial reagents that did not meet the acceptance criteria for PPA and NPA are listed below.

(1) BGR, Anti-Fy^a did not meet the NPA due to 1 discrepant result at the GCR site. Repeat test and resolution confirmed positive with the trial reagent (2+). Testing with the comparator reagent was initially negative but turned to positive (2+) with repeat testing. The resolver reagent (Gamma-clone® Anti-Fy^a, Immucor) tested positive (+2) as well. GCR suggested that the discrepancy was due to a transcription error in the original test.

(2) BGR, Anti-Jk^a did not meet the NPA because of the low number of Jk^a negative test samples; nevertheless, the point estimate is 100%.

(3) BGR, Anti-K did not meet the PPA due to 2 discrepant results. In one case, the test site (MBC) suggested that the discrepancy was due to a transcription error in the original test. The discrepancy was recorded but not noted at the time of testing; therefore, repeat testing was not performed. The investigation confirmed positive with the comparator reagent (+3). Testing with the trial reagent was initially negative but turned positive (+3) during investigation. The resolver (Gamma-clone® Anti-K, Immucor) tested positive (+3) as well. In

the other case at the BCW site, repeat test and resolution (resolver BioClone® Anti-K, Ortho Clinical Diagnostics) confirmed the original test outcome. The investigation determined the test sample had a positive DAT. BCW suggested that the discrepancy could be attributed to the test sample itself, because a DAT positive sample would react with the anti-human globulin (AHG) reagent in the comparator method.

(4) BGR Anti-P1 did not meet the NPA due to 3 discrepant results at the BCW site. BCW suggested that three discrepant results could be due to the presence of a weak antigen and differences in reagent sensitivity. In one case, repeat test and resolution confirmed positive (+2) with the trial reagent. Testing with the comparator reagent turned to weak positive from the original negative. Testing with the resolver reagent (BioClone® Anti-P1, Ortho Clinical Diagnostics) confirmed positive (+2) as well. In the second case, repeat testing confirmed weak positive with the trial reagent and negative with the comparator reagent. The resolver reagent tested negative. In the third case it was a cord blood sample where repeat testing confirmed positive with the trial (+1) reagent and negative with the comparator reagent. The resolver reagent tested weak positive as well.

b) Pediatrics

The comparator studies for each of the blood grouping reagents included neonate and cord blood samples. Test results demonstrate that these samples do not affect the performance of the reagents.

c) Other Special Populations

The comparator studies included different patient populations at the trial sites. The study included samples from pregnant women and patients with multiple myeloma, lymphomas, leukemia, and sickle cell anemia.

7. Advisory Committee Meeting

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

8. Other Relevant Regulatory Issues

The review committee members from DBCD, DB, DMPQ, DCM and DBSQC reviewed their specific sections of the BLAs and resolved any issues through information requests and a Complete Response letter 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.

9. Labeling

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

Alba submitted container labels, packing labels, and the Instructions for Use (IFU) documents for review. All labels met the requirements outlined in 21 CFR 660 and 21 CFR 809.10.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members, representing the necessary review disciplines (DBCD, DB, DMPQ, 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 subject BGRs are the same monoclonal antibody products that were approved by the FDA in March of 2017 under the trade name ORTHO™ Serum for the detection of blood group Fy^a, Jk^a, Jk^b, S, s, K and P1 antigens on human red blood cells by Column Agglutination Technology (CAT). The licensing of the subject BGRs for test tube technology will not alter the benefit-risk profile of the product because the same manufacturing controls and processes are in place.

c) Recommendation for Post-marketing Activities

There are no post-marketing activities associated with this submission.