Summary Basis for Regulatory Action

From: Annette Ragosta, Chair of the Review Committee

BLA/ STN#: 125465

Applicant Name: Alba Bioscience Limited

Date of Submission: September 12, 2012

MDUFA Goal Date: November 14, 2017

Proprietary Name: Anti-Human Globulin Anti-IgG, -C3d; Polyspecific (Rabbit/Murine Monoclonal) (Green)

Established Name (common or usual name): Anti-Human Globulin (Rabbit/Murine Monoclonal)

Intended Use/Indications for Use: (*copied from page one of the final draft package insert)*

"Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific is intended for use in the direct antiglobulin test to detect the *in vivo* coating of human red blood cells with IgG and/or C3b and/or C3d components.

Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific is intended for use in the indirect antiglobulin test to detect the *in vitro* coating of human red blood cells with IgG and/or C3b and/or C3d components."

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

Review Office 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.

TABLE 1

Document title	Reviewer name, Document date
Clinical	Annette Ragosta, OBRR/DBCD/DRB September 12, 2017
Non-Clinical Review	Annette Ragosta, OBRR/DBCD/DRB September 12, 2017
Statistical Review	Chunrong Chen, OBE/DB/TEB July 27, 2017
CMC Product Review	• Annette Ragosta, OBRR/DBCD/DRB September 12, 2017 • Simleen Kaur, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden November 13, 2016
CMC Facility Review	Priscilla M. Pastrana OCBQ/DMPQ/BII November 10, 2016
Labeling Review(s)	• Annette Ragosta, OBRR/DBCD/DRB • Dana Jones, OCBQ/DCM/ALPB
Lot Release Protocols/Testing Plans	Varsha Garnepudi, OCBQ, DBSQC
Establishment Inspection Report	Not applicable for these submissions, inspection waived
Bioresearch Monitoring Review	Not applicable for these submissions

1. Introduction

Alba Bioscience Limited (Alba) submitted an original Biologics License Application requesting approval to manufacture and distribute Anti-Human Globulin (Rabbit/Murine Monoclonal); hereafter referred to as AHG. The proprietary name for this product is Anti-Human Globulin Anti-IgG, -C3d; Polyspecific (Rabbit/Murine Monoclonal) (Green); hereafter referred to as Polyspecific AHG. This AHG reagent is designed to detect IgG and/or C3b, and/or C3d components on the surface of human red blood cells.

The above mentioned Polyspecific AHG reagent was submitted in a bundle with two other AHG products: AHG (Murine Monoclonal) reviewed under 125463 (hereafter referred to as Anti-C3d), and Anti-AHG (Rabbit) reviewed under 125464

(hereafter referred to as Anti-IgG). Anti-IgG and Anti-C3d are also used as in-vitro substances in the manufacture of the Polyspecific AHG product. See Table 2 below for a summary of the three bundled original BLA submissions.

Alba performs the manufacturing steps of the two in-vitro substances and the final product at their manufacturing facility located at 21 Ellen's Glen Road, Liberton, Edinburgh, EH17 7QT, Scotland, United Kingdom.

TABLE 2 List of Bundled AHG Submissions

Tracking Number	Name of Biological Product/Trade Name	Antibody Source	Intended Use
125463	Anti-Human Globulin (Murine Monoclonal) ALBAclone® Anti-C3d (Murine Monoclonal)	Monoclonal Cell Line 3G8	Anti-Human Globulin, Anti-C3d (Murine Monoclonal) is intended for use in the direct antiglobulin test to detect the *in vivo* coating of human red blood cells with C3b and/or C3d components. For Tube Technique
125464	Anti-Human Globulin Anti-IgG (Rabbit (b) (4))	Rabbit	Anti-Human Globulin, Anti-IgG (Rabbit (b) (4)), is intended for use in the direct antiglobulin test to detect the *in vivo* coating of human red blood cells with IgG. Anti-Human Globulin, Anti-IgG is intended for use in the indirect antiglobulin test to detect the *in vitro* coating of human red blood cells with IgG. For Tube Technique
125465	Anti-Human Globulin (Rabbit/Murine Monoclonal)	Monoclonal Cell Line 3G8 and Rabbit	Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific (Rabbit/Murine Monoclonal) (Green), is intended for use in the direct antiglobulin test to detect the *in vivo* coating of human red blood cells with IgG

Tracking Number	Name of Biological Product/Trade Name	Antibody Source	Intended Use
	Anti-IgG, -C3d; Polyspecific (Rabbit/Murine Monoclonal)(Green)		and/or C3b and/or C3d components. Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific is intended for use in the indirect antiglobulin test to detect the *in vitro* coating of human red blood cells with IgG and/or C3b and/or C3d components. For Tube Technique

Intended Use/Indications for Use: (*copied from page one of the final draft package insert)*

"Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific is intended for use in the direct antiglobulin test to detect the *in vivo* coating of human red blood cells with IgG and/or C3b and/or C3d components.

Anti-Human Globulin, Anti-IgG,-C3d; Polyspecific is intended for use in the indirect antiglobulin test to detect the *in vitro* coating of human red blood cells with IgG and/or C3b and/or C3d components."

Chronology:

CBER received this original submission on September 12, 2012, and received 22 amendments from Alba in response to three Complete Response letters and 20 information requests.

2. Background

Meetings with FDA:

Alba did not request any pre-submission meetings for this product.

Description of the Device

The main components of this reagent are as follows:

- Rabbit antibody to human IgG, which is produced by immunizing rabbits at (b) (4), located in (b) (4), with an immunogen (purified human IgG) that was manufactured at Alba from (b) (4) human plasma containing IgG blood group antibodies. The harvested rabbit serum containing antibody to human IgG is then shipped to Alba where it is (b) (4).
- Murine monoclonal antibody to C3d (clone number 3G8). The cell line was developed by the (b) (4) in (b) (4) through immunization of a mouse with purified C3d. Both the cell line and the production of the antibody were transferred to Alba in (b) (4) due to the merger of (b) (4) and Alba.

The formulation of the final product contains bovine serum albumin, 0.1% (w/v) sodium azide, Tween 80, and the green colorant tartrazine in addition to the rabbit serum anti-IgG and murine Anti-C3d monoclonal serum. The final product is filled into a 10 milliliter (mL) glass vial (fill volume of ten mL) constructed of (b) (4) glass. The closure is a ten-mL dropper assembly that includes a black screw cap and a rubber bulb with a clear glass pipette.

Principles of the assay

Polyspecific AHG is commonly used in blood banks to perform direct and indirect antiglobulin testing (DAT and IAT). The DAT determines if red blood cells are coated in vivo with immunoglobulin, complement or both. This test is necessary in the investigation of immune-mediated hemolysis. Immune-mediated hemolysis may be observed in hemolytic transfusion reactions, hemolytic disease of the fetus and newborn, autoimmune hemolytic anemia and drug-induced hemolysis. The IAT is used to detect red cell antibodies in patient serum or plasma and is the methodology used for antibody screening, antibody identification, and crossmatch.

Polyspecific AHG has been validated for use by the tube technique. As stated in the intended use statement, this reagent can be used for a DAT to detect red blood cells (RBCs) coated in vivo with IgG, C3b and C3d components or in an IAT to detect RBCs coated in vitro with IgG, C3b and C3d components. For the DAT, one drop of a 2 to 4 percent suspension of RBCs is washed three times, two drops of the Polyspecific AHG reagent are added to the dry red blood cell button, mixed, and centrifuged. For the IAT, serum or plasm is added to one drop of a 2 to 4 percent suspension of RBCs, incubated at 37 ^{o}C for a specified time period, the incubated RBCs are washed three times, two drops of the Polyspecific AHG reagent are added to the dry red blood cell button, mixed, and centrifuged. For both the DAT and IAT, the Polyspecific AHG reagent will cause agglutination of red blood cells coated with IgG and/or C3b and/or C3d components. No agglutination will be observed with uncoated red blood cells

Marketing History:
Alba has manufactured and distributed the Polyspecific AHG reagent for 20 years outside the United States. Specifically, it has been CE marked under Annex II, List B, since February 03, 2004 and distributed under Canadian license number 76757 since April 04, 2008, as well as in 30 other countries.

3. Chemistry Manufacturing and Controls (CMC)

The application was submitted in accordance with the recommendations in FDA's Guidance for Industry: "*Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Biological in-Vitro Diagnostic Product*". All manufacturing is carried out in a controlled environment.

a) Manufacturing Summary

Alba manufactures Anti-IgG and Anti-C3d In-Vitro Substances (IVS) and the

Polyspecific AHG In Vitro Product (IVP) reagent at their licensed facility, located at 21 Ellen's Glenn Road, Edinburgh, UK. The manufacturing processes include (b) (4), formulation, filtration, filling, labelling, and in-process and final Quality Control (QC) testing. Multiple products are manufactured in the same rooms as the two IVS and the IVP reagent; 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 the production steps. All raw materials used for the manufacture of Polyspecific AHG are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

IVS –Anti-C3d

The cell line, 3G8, used in the production of the IVS, is of murine origin and was developed by the (b) (4) in (b) (4) through immunization of a mouse with purified C3d. Both the cell line and the production of the antibody were transferred to Alba in (b) (4) due to the merger of (b) (4) and Alba. The viability and stability of the cell line have been well-documented in the device history records of the manufacturing lots that have been distributed outside the US since 1997.

(b) (4)

IVS – Anti-IgG

Rabbit antibody to human IgG is produced by immunizing rabbits at (b) (4), located in (b) (4), with an immunogen (purified human IgG) that was manufactured at Alba from (b) (4) human plasma containing IgG blood group antibodies. The proposed shelf life for the immunogen is (b) (4). Thus far, the (b) (4) assay acceptance criteria have been met up to (b) (4). (Acceptance criteria: "(b) (4)."") The rabbit serum is received from (b) (4) with animal health certification documents. Following approval for processing by QA the rabbit serum is passed to the formulation department where it is (b) (4).

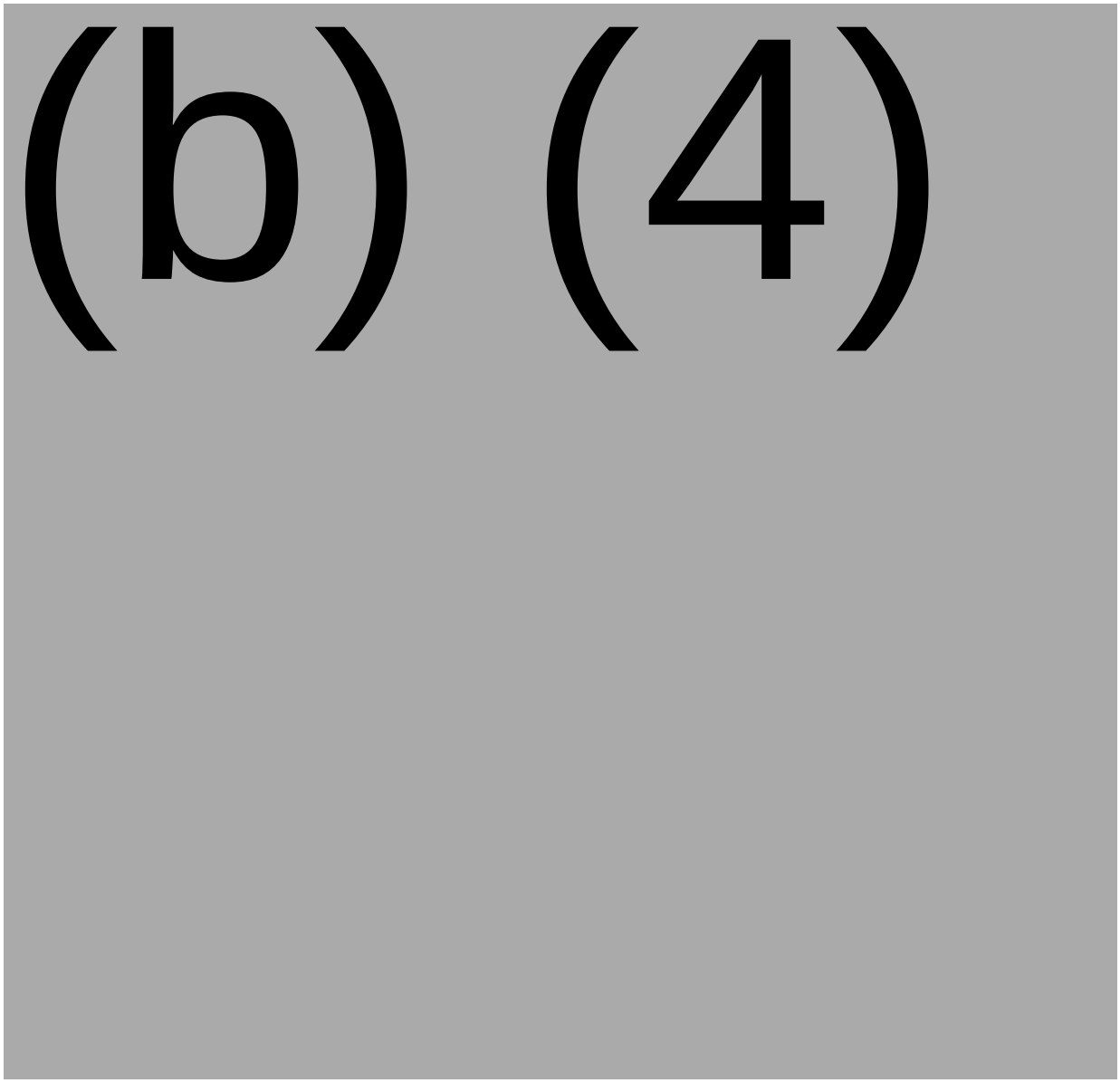
(b) (4)

IVS Testing

See Table 3 below for details on the (b) (4) testing for the Anti-IgG and Anti-C3d IVS material.

Table 3 IVS (b) (4) Testing

(b) (4)



(b) (4)

In Vitro Product (IVP)

All raw materials used for the manufacture of the Polyspecific AHG IVP are provided by qualified suppliers and accepted based upon the supplier CoA

and qualifying tests, as applicable.

Manufacturing Process Description

A diluent buffer using (b) (4) Tween 80, sodium azide, and bovine serum albumin is manufactured, tested and released prior to the addition of the (b) (4) Anti-IgG and Anti-C3d IVS materials. The dye (Patent Blue Violet and Tartrazine) is added to the diluent buffer and Anti-IgG/Anti-C3d solution. Filtration of the (b) (4) Polyspecific AHG IVP is performed using a (b) (4) filter into an (b) (4). The maximum validated hold time between formulation and filtration/filling of the (b) (4). The IVP is filled into 10 mL (b) (4) glass vials (fill volume of 10 milliliters) 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 product is 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 product. The product is stored at 2 to 8 °C until it is released for distribution by Quality Assurance.

Date of Manufacture (DOM)

The DOM is the date of performance of the (b) (4).

IVP Specifications and Test Methods

The following tables include the specifications (Table 4) and required release tests and acceptance criteria (Table 5) for the Polyspecific AHG IVP:

Table 4 IVP Specifications

Description of Product	Clear Green Liquid Unit Volume: 10 mL
Primary Packaging	10 mL clear glass vials with dropper assemblies and black caps Secondary packaging: 1, 3, and 10 vial cartons
Storage Conditions	2-8 °C
Transport Requirement	Ambient temperature
Expiry Date/Shelf Life	Two years from the start date of the (b) (4)

Table 5 IVP Testing and Acceptance Criteria

Specificity	(b) (4)
Anti-IgG Potency	

	(b) (4)
Anti-Complement Potency	
Microbiology	

IVP Microbiology Testing

Polyspecific AHG is a microbiologically controlled product and is considered a non-sterile, multiple use device. Microbiological control of the final product is accomplished as follows:

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

c) Facilities review/inspection

Facility information and data provided in this BLA bundle were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of *in vitro Substances* that consist of Monoclonal Antibody Anti-Human Globulin Anti-C3d (ALBAclone) (Murine Monoclonal), and (b) (4) Antibody Anti-Human Globulin Anti-IgG, (Rabbit (b) (4)) in addition to Anti-Human Globulin Anti-IgG, -C3d; Polyspecific (Rabbit (b) (4) and Murine Monoclonal) (*in vitro* Product) is listed in Table 6 below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

TABLE 6

Name/Address	FEI number	DUNS number	Results/Justification
in vitro Substance *in vitro Product* *Release Testing* Alba Biosciences Limited 21 Ellen's Glen Road	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).

d) Environmental Assessment

This BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product 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

The IVS is filled into (b) (4) containers with (b) (4) made of (b) (4) and supplied by (b) (4). Alba Biosciences Limited conducted the container closure integrity testing for these monoclonal antibodies at their Edinburgh location. The testing which consisted of (b) (4) verification met all manufacturer recommended (b) (4) ranges.

The IVP is filled into a 10mL (b) (4) glass vial with 18mm screw neck and 10 mL glass dropper assembly cap supplied by (b) (4). Alba conducted the container closure integrity testing at the Edinburgh, UK facility, employing (b) (4) verification, (b) (4) verification and visual inspection for turbidity; all acceptance criteria were met.

4. Software and Instrumentation

Not Applicable.

5. Analytical Studies

Analytical studies included stability, anticoagulant, and precision studies.

Stability Studies

Stability studies were performed on three conformance lots (manufactured in 2014) to support the proposed shelf life of 24 months at 2-8 °C. Vials were opened briefly at the start of the study and then stored at 2-8 °C until testing at the following time points: day zero, and 3, 6, 9, 12, 24, (b) (4) months. Potency testing was carried out in parallel with the polyspecific AHG reference stored at (b) (4) °C. The following table (Table 7) includes the sample types, test method, and acceptance criteria for potency and specificity testing.

Table 7 IVP Testing and Acceptance Criteria

Specificity	(b) (4)
Potency	

	(b) (4)
Microbiology	

Alba provided 24 months of potency, specification, and microbiology test results for the real-time stability study. The acceptance criteria were met for all time points for each of the three conformance lots.

In addition to the real-time stability study on the IVP, 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 Table 7 above also apply to the simulated transport study. Potency and specificity testing on the temperature cycled Polyspecific AHG met all acceptance criteria and the results show that there is no significant impact on the performance of the Polyspecific

AHG after exposure to extreme temperatures that could potentially be encountered during the shipping process.

Anticoagulant Studies

The package insert includes the following test sample limitations:

- Clotted samples should be tested prior to refrigeration to avoid *in vitro* sensitization with complement.
- Clotted samples and samples collected in EDTA should be tested within (b) (4) from collection but may be tested at the maximum storage of 14 days.
- Donor blood collected in ACD, CPD, CPDA-1, CP2D, and CP2D with AS-3, may be tested until the expiration date of the donation.

The validation study included all sample 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 following red blood cell samples were included in the study:

- (b) (4)
-
-
-
-

The results demonstrate that the performance of the Polyspecific AHG reagent is not affected by the sample types or the recommended maximum storage times listed in the package insert.

Precision Studies

The Reproducibility and Repeatability Study was performed to demonstrate that the test reagent generates reproducible and accurate results using a panel of well-characterized samples tested on different days at multiple sites, using different lots, and different operators. The acceptance criterion stated there should be (b) (4) agreement between the test outcomes and the expected results.

The external study was performed at three sites, using (b) (4) lot of test reagent. The protocol included (b) (4) precision panels; (b) (4) for the DAT study and (b) (4) for the IAT study. The test panel for the DAT study consisted of (b) (4) . The test panel for the IAT study consisted of (b) (4) . The testing was performed by three operators over (b) (4) non-consecutive days, with (b) (4) testing performed by each operator within each run. (b) (4) lots of (b) (4) were also assessed for its effect on the results. There were no discordant results; all expected positive tests generated unequivocal positive reactions and all expected negative tests generated unequivocal negative reactions.

Alba also conducted an internal lot-to-lot study testing three lots of the reagent against the same test panels used in the external precision study. Three operators performed testing over (b) (4) non-consecutive days. There were no discordant results; all expected positive tests generated unequivocal positive reactions and all expected negative tests generated unequivocal negative reactions.

6. Clinical Studies

a) Clinical Program

The Anti-IgG reagent was tested at a total of seven sites (one internal and six external US sites) in two separate studies (2012 and 2015) in parallel with a licensed US product. The 2015 study was performed to address deficiencies in the 2012 study. The trial sites included different facility sizes and different functions; i.e., blood collection facilities, transfusion services, and clinical laboratories. The study covered all the testing included in the intended use statement; DAT, IAT used in antibody screening and identification, and the crossmatch test. The study also included the use of the following (b) (4)

(b) (4)

The acceptance criterion is as follows: ≥ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreements.

Table 8 includes a summary of the comparator IAT testing for all trial sites. Please note this table includes the number of tests performed and does not include the sample size or a breakdown by the test applications listed in the package insert.

TABLE 8: Summary of Comparator Testing over all trial sites for IAT and DAT (includes both 2012 and 2015 studies)

		COMPARATOR REAGENT		
		Positive	Negative	Total
TRIAL REAGENT	Positive	1894	6	1900
	Negative	3	4598	4601
	Total	1897	4604	6501
Positive Percentage Agreement				99.84%
One-sided 95% lower confidence limit				0.99
Negative Percentage Agreement				99.87%
One-sided 95% lower confidence limit				0.99

Table 9 below includes the sample size for each test application listed in the package insert. Please note that the IAT results for the 2012 study were not broken out by test application and therefore were not included in this table (303 positive IAT samples and 1250 negative samples).

TABLE 9: Breakdown of Comparator Testing by test application

TEST	Positive Samples	% Agree	One sided 95% Lower Confidence Limit	Negative Samples	% Agree	One sided 95% Lower Confidence Limit
DAT	357	99.44	0.98	2666	100	0.99
Cross match	422*	99.92	0.99	774**	100	0.99
Antibody Screen	341	100	0.99	362	99.72	0.99
Antibody Identification	80	100	0.96	409	99.76	0.99

*119 ABO crossmatches, 191 non-ABO crossmatches, and 112 external site crossmatches

**221 ABO crossmatches, 94 non-ABO crossmatches, and 449 external site crossmatches

There were two discordant results in the DAT study, one false positive result and one false negative result:

- Upon repeat testing of the false positive result, the resolver reagent agreed with the trial reagent result.
- Upon repeat of the false negative testing, the trial result was weak positive and the resolver result was positive.

Although the one-sided 95% lower confidence limit for positive percentage agreement was only 0.98 for the DAT study and 0.95 for the Antibody Identification study it should be noted that the results are influenced by the number of available positive samples (266 and 65 respectively). For crossmatch and antibody screen the study results met the pre-determined acceptance criterion of ($\geq$ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreement).

In summary, the performance study results demonstrate that the Anti-IgG reagent is comparable to US licensed products with the same intended use.

b) Pediatrics

Cord blood samples were included in the comparator study. Test results demonstrate that this sample type does not affect the reagent's performance.

c) Other Special Populations

Samples were included in the 2012 and 2015 studies from patients with the following conditions:

- Multiple Myeloma
- Waldenstrom's Macroglobulinemia
- Pregnancy
- Lymphoma
- Leukemia
- Lipemic
- Hemolyzed
- Warm Auto Immune Hemolytic Anemia
- Sickle Cell
- Elderly

Test results demonstrate that these sample types do not affect the reagent's performance.

7. Advisory Committee Meeting

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

8. Other Relevant Regulatory Issues

There are no relevant regulatory issues for this submission. The review committee members reviewed their specific sections of the BLA and resolved any issues through information requests with Alba. The review team sought the expertise of their respective management, when warranted. No internal or external disagreements were communicated to the regulatory project manager or chairperson. All reviewers recommended approval of Polyspecific AHG.

9. Labeling

The Product Office and the Advertising and Promotional Labeling Branch reviewed the container labels, the Instructions For Use (IFU) document, and generic packing labels. All labels met the requirements outlined in 21 CFR Part 610.62, 610.64, 660.28 and 21 CFR Part 809.10.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members, representing the necessary review disciplines (DBCD, DMPQ, DB, DCM, and DBSQC) recommend approval. These were independent conclusions based on content of the BLA, issues satisfactorily resolved during the review cycle, and concurred by their respective management. No internal or external disagreements were brought to the attention of the chairperson.

b) Risk/ Benefit Assessment

The benefits and risks of licensing Anti-Human Globulin Anti-IgG (Rabbit) include the following:

- Decrease the probability of a product shortage and improve the safety of the blood supply by providing an additional Polyspecific AHG reagent for use in the US.
- The evaluation of the validation and clinical studies and the manufacturing process reduces the risks associated with licensing a new AHG reagent. In addition, this Polyspecific AHG reagent will be subject to post market surveillance (Medical Device Reporting) which will identify adverse events associated with this product.

c) Recommendation for Post Marketing Activities

We did not recommend post-marketing activities for this submission.