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## Summary Basis for Regulatory Action

**From:** Meihong Liu, Chair of the Review Committee

**Applicant Name:** Immucor, Inc.

**Date of Submission:** June 26, 2018

**MDUFA Goal Date:** April 27, 2019

**Table 1. BLA STN#/Proprietary Name/Cell Line and Intended Use:**

<b>Submission Tracking Number</b>	<b>Name of Biological Product</b>	<b>Cell Line(s)</b>	<b>Intended Use</b>
BL125686/0	Blood Grouping Reagent, Anti-Fy <sup>b</sup> ( Monoclonal)	SpA264LBg1	Gamma-clone <sup>®</sup> , Blood Grouping Reagent, Anti-Fy <sup>b</sup> ( Monoclonal) is intended for the detection of the Fy <sup>b</sup> (FY2) antigen on red blood cells by direct agglutination tube test.
BL 125687/0	Blood Grouping Reagent, Anti-C <sup>w</sup> ( Monoclonal)	MS-110	Gamma-clone <sup>®</sup> , Blood Grouping Reagent Anti-C <sup>w</sup> ( Monoclonal) is intended for the detection of the C <sup>w</sup> (RH8) antigen on red blood cells by direct agglutination tube test.
BL 125688/0	Blood Grouping Reagent, Anti-k (Monoclonal) (IgG)	P3A118OL67	Gamma-clone <sup>®</sup> Blood Grouping Reagent Anti-k ( Monoclonal) (IgG) is intended for the detection of the k (KEL2) antigen on red blood cells by indirect agglutination tube test.

**Established Name (Common or usual name): Not Applicable**

**Recommended Action:**

The Review Committee recommends approval of these products.

**Review Offices Signatory Authority: Nicole Verdun, MD, Director, Office of Blood Research and Review (OBRR)**

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below (Table 2) indicates the material reviewed when developing the SBRA

**Table 2. Materials reviewed during SBRA Development**

<b>Document title</b>	<b>Reviewer name, Document date</b>
Product Review(s) ( <i>Product office</i> ) <ul style="list-style-type: none"> <li>• <i>Clinical</i></li> <li>• <i>Non-clinical</i></li> </ul>	Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 6, 2018 Review Memo-August 6, 2018 Approval Memo-March 2019
Statistical Review(s) <ul style="list-style-type: none"> <li>• <i>Clinical data</i></li> <li>• <i>Non-clinical data</i></li> </ul>	Paul Hshieh, OBE/DB/TEB Review memo-December 18, 2018
CMC Review(s) <ul style="list-style-type: none"> <li>• <i>CMC (Product Office)</i></li> </ul>	Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 6, 2018 Review Memo-August 6, 2018 Approval Memo-March 2019

<ul style="list-style-type: none"> <li>• Bioburden (<i>OCBQ/DBSQC</i>)</li> <li>• <i>Facilities review (OCBQ/DMPQ)</i></li> </ul>	<p>Claire H. Wernly, OCBQ/DBSQC/LMIVTS Review Memo (Approval), January 25, 2019</p> <p>Ashley Burn, OCBQ/DMPQ/MRBII Priscilla M. Pastrana, OCBQ/DMPQ/MRBII Review Memo (Approval)- December 4, 2018 Inspection Waiver, September 4, 2018</p>
<p>Labeling Review(s)</p> <ul style="list-style-type: none"> <li>• <i>Product Office</i></li> <li>• <i>APLB (OCBQ/APLB)</i></li> </ul>	<p>Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 6, 2018 Review Memo-August 6, 2018 Approval Memo-March 2019</p> <p>Dana Jones, OCBQ/ DCM/APLB Twanda Scales, OCBQ/DCM/APLB Review Memo, February 8, 2019</p>
<p>Lot Release Protocols/Testing Plans</p> <ul style="list-style-type: none"> <li>• <i>OCBQ/DBSQC</i></li> <li>• <i>Product Office</i></li> </ul>	<p>Varsha Garnepudi, OCBQ/DBSQC Review Memo, January 2, 2019</p> <p>Meihong Liu, OBRR/DBCD/DRB Kimberly Bigler, OBRR/DBCD/DRB Elias Paz Alonzo, OBRR/DBCD/DRB Review Memo- December 6, 2018 Review Memo-August 6, 2018 Approval Memo-April 2, 2019</p>

**1. Introduction**

Immucor, Inc. US (hereafter known as Immucor), located in Norcross, GA submitted a bundled submission for the licensure of three Blood Grouping Reagent (BGRs) listed in Table 1 above. These BGRs are human monoclonal antibodies for use in the direct agglutination test for the qualitative detection of the Fy<sup>b</sup> and C<sup>w</sup> antigens on human red blood cells or for the indirect antiglobulin test (IAT) for the qualitative detection of the k antigen on human red blood cells. The products will hereafter be referred to as Anti-Fy<sup>a</sup>, Anti-C<sup>w</sup>, and Anti-k.

*Chronology:*

CBER received this original submission on June 28, 2018. The submission was filed on July 12, 2018. CBER received eight amendments dated November 8, 2018, January 16, 2019, January 17, 2019, January 30, 2019, February 26, 2019, March 13, 2019, March 21, 2019, and March 28, 2019.

*Meeting with FDA:*

Immucor did not request any pre-submission meetings for these three products.

## **2. Background**

Blood Grouping Reagents, Anti-Fy<sup>b</sup> (Monoclonal), Anti-C<sup>w</sup> (Monoclonal) and Anti-k (Monoclonal) (IgG) are manufactured, labeled, and packaged by Immucor at their licensed Gateway Drive Norcross, GA facility. These BGRs are human monoclonal antibodies for use in the direct agglutination test for the qualitative detection of the Fy<sup>b</sup> and C<sup>w</sup> on human red blood cells or for the indirect antiglobulin test (IAT) for the qualitative detection of the k antigen on human red blood cells.

Fy<sup>a</sup> and Fy<sup>b</sup> are a pair of alleles on the long arm of chromosome 1, giving rise to three commonly encountered phenotypes: Fy (a+b-), Fy (a+b+) and Fy (a-b+). These antigens are fully developed at birth. The Fy<sup>a</sup> antigen occurs in approximately 66% of Caucasians and 10% of the Black population. The Fy<sup>b</sup> antigen occurs in approximately 83% of Caucasians and 23% of the Black population. Antibodies directed against the Duffy antigens can cause hemolytic transfusion reactions and hemolytic disease of the fetus and newborn (HDFN).

The Rh blood group system (including the Rh factor) is the second most important blood group system, after the ABO blood group system. The Rh blood group system consists of 50 defined blood group antigens, among which the five antigens D, C, c, E, and e are the most important. The Rh antigens are highly immunogenic, and most of the Rh antibodies should be considered as potential causes of hemolytic transfusion

reactions and HDFN. The C<sup>W</sup> antigen (RH8) of the Rh blood group system is considered to bear an allelic relationship to C and c, and has a frequency of 2% in the Caucasian population and 1% in individuals of African descent. Anti-C<sup>W</sup> may occur in serum from individuals not known to have been exposed to the C<sup>W</sup> antigen, or may be immune in origin. Anti-C<sup>W</sup> can cause HDFN.

The k (KEL2) antigen is one of the antigens in the Kell blood group system which includes K (KEL1), Kp<sup>a</sup> (KEL3) and Kp<sup>b</sup> (KEL4), Js<sup>a</sup> (KEL6) and Js<sup>b</sup> (KEL7). The k antigen also known as Cellano is highly prevalent and has a 99.8% frequency in Caucasians.

### Device Description:

The main component of the three BGRs is an antibody concentrate derived from the in-vitro culture of the IgM secreting (b) (4) hybridoma cell lines: SpA264LBg1 for the Gamma-clone<sup>®</sup>, Anti-Fy<sup>b</sup> (Monoclonal) and MS-110 for the Gamma-clone<sup>®</sup>, Anti-C<sup>w</sup> (Monoclonal), and IgG secreting (b) (4) hybridoma cell line P3A118OL67 for Gamma-clone<sup>®</sup>, Anti-k (Monoclonal). The three BGRs also contain bovine material and (b) (4) (w/v) sodium azide.

The Gamma-clone<sup>®</sup> BGRs, Anti-Fy<sup>b</sup> and Anti-C<sup>w</sup> have been validated for use in direct agglutination tube testing that includes a five to fifteen-minute incubation at room temperature (15 °C to 30 °C) followed by centrifugation. The Gamma-clone<sup>®</sup> Anti-k has been validated for use in indirect agglutination tube testing that includes a five to fifteen-minute incubation at 37 °C, and the addition of Gamma-clone<sup>®</sup> Anti-Human Globulin after a minimum of three washes with saline. The three BGRs will specifically react with the corresponding antigens present on red blood cells and give positive results that produce macroscopic agglutination of the red blood cells in the test tube.

### **3. Chemistry Manufacturing and Controls (CMC)**

The applications were submitted in accordance with the recommendations in FDA's Guidance for Industry: "Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for a Biological In-Vitro Diagnostic Product."

All manufacturing of the *in vitro* products (IVPs) including formulation, (b) (4) and filling, microbiology, as well as in-process and final QC testing, are performed by Immucor at their licensed manufacturing facility. All manufacturing is carried out in a controlled environment.

## **a Manufacturing Summary**

### **1) Antibody Concentrate (*In Vitro Substances*)**

The antibody concentrates used in the manufacture of the three BGRs are (b) (4) from the *in vitro* culture of the specific antibody secreting human (b) (4) (b) (4) hybridoma cell lines manufactured by (b) (4) under a shared manufacturing arrangement. (b) (4) submitted two Prior Approval Supplements (PAS) and an original Biologic License Application (BLA) to ship the antibody concentrates labeled For Further Manufacturing Use (FFMU) to Immucor who will further manufacture the antibody concentrates into final container products.

Immucor states they have the option to perform pre-purchase testing on the products to ensure they are within specifications. If pre-purchase testing is not preformed, testing is done on receipt of the antibody concentrate. The specifications of the three antibody concentrates are listed in Table 3 below.

**Table 3. Antibody Concentrate Specifications**

(b) (4)

The reviews of the companion submissions from (b) (4) are documented in separate memos.

**2) *In vitro product (IVP)***

Immucor manipulates critical substances and products used in the 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.

BGRs include the following formulation ingredients: the active ingredients antibody concentrates, bovine serum albumin, preservative (Sodium Azide), in-house prepared solutions (e.g., diluents), and (b) (4). All raw materials used for the manufacture of the three final IVP BGRs are provided by qualified suppliers and accepted based upon the supplier certificate of analysis and qualifying tests, as applicable.

Immucor performs the following manufacturing steps and test methods identical to those for previously approved monoclonal BGRs Anti-Jk<sup>a</sup>, Anti-Jk<sup>b</sup>, Anti-S, Anti-s and Anti-Fy<sup>a</sup> (STN BL 125489/0 et al approved in May 2014).

The manufacturing process after receipt of the three antibody concentrates (FFMU products) from (b) (4) include:

Receipt Testing: Once the FFMU products are received, product from each container is sampled and tested for (b) (4) methods. Incoming material is stored in the (b) (4) until testing is completed; once the FFMU lot is released for use in manufacturing, the containers are stored at (b) (4) in validated (b) (4) rooms.

(b) (4)

(b) (4)



(b) (4)

Filling (Vialing): (b) (4) Filling Machines are used for automatic filling with (b) (4) and capping of glass vials. The vial line is connected to the (b) (4) Labeler. The vialing rooms are environmentally controlled areas for filling operations. One product is filled at a given time and line clearance is performed before each filling operation. Container closure (b) (4) fill volumes are monitored during filling operation. The final product containers are 10 mL glass vials with an attached dropper assembly and the fill volume is 5 mL.

Labelling/Packaging: After filling and capping, unlabeled vials are transferred to the labeling instrument for labeling via a conveyor. A container label is applied to each vial before it is routed to the accumulation area for inspection.

Final release testing, storage/distribution: Labeled products are sent to the Biological Quality Assurance department (BQA Lab (b) (4)) for microbial testing and to the Quality Control Department for final release QC testing. The labeled products are stored in a (b) (4) pending final release to the shipping department for distribution. Released product is stored at 1-10 °C in the shipping department pending distribution to customers.

Storage conditions: (b) (4) final products are stored in validated cold rooms at 1-10 °C. All cold rooms used for storage are continuously monitored by the (b) (4) system (environmental monitoring system).

(b) (4)

The three conformance lots of Anti-C<sup>w</sup>, Anti-Fy<sup>b</sup> and Anti-k IVP products were (b) (4) these lots were (b) (4) continuing the manufacturing process. Samples from the final filled products of (b) (4) were then placed into real stability studies.



<b>Reactivity</b>	(b) (4)
<b>Non-specific Qualities</b>	(b) (4)
<b>Microbial Assay</b>	No growth at (b) (4) days
(b) (4)	(b) (4)

During the review cycle, FDA recommended that the evaluation of the IVP products for potency should include parallel testing with a reference material or an in-house standard. Immucor explained that there were no established potency reference standards or panels for the initial conformance/validation lots of these IVP products. When the three BLAs are approved, Immucor will use previously approved in-date lots as in-house standards and include parallel testing with in-house standards in the final release testing. Immucor updated their QC release testing protocol and specifications for potency to include titers comparable (b) (4) to the control lot (in-house standard).

**4) Microbiological Control**

BGRs are not considered sterile. Immucor provided microbiological control at the in-process and final release of these products to reduce the risk that introduction of microbial contamination might compromise the quality, safety, purity, potency or performance. Formulation of these IVPs includes addition of sodium azide to a final concentration in final product of (b) (4) and a (b) (4). The (b) (4) sodium azide concentration was used in all validation lots of the three IVP products. The (b) (4) was previously performed in support of Primary STN BL125489/0 (approved May 5, 2014) to demonstrate their proposed sodium azide concentration in preservative solution is effective and adequate in preventing microbial growth using (b) (4).

The proposed sodium azide formulation concentration was

shown to have effective anti-microbial properties in accordance with (b) (4) CBER deemed that the previous (b) (4) can apply to these new products.

In addition, during handling of the final product, Immucor practices in-process control to minimize product contamination. Immucor submitted data demonstrating validation of their (b) (4) bioburden method. CBER reviewed the data and found that the (b) (4) bioburden test method was validated in accordance with guidance provided under (b) (4) and product matrices for Gamma-clone® Anti-Fyb, Anti-Cw and Anti-k BGRs are suitable for the intended test method.

## 5) Conformance lots

A total of three conformance lots of each monoclonal reagent were manufactured and each lot is reflective of the current container/ closure system and product-contact surfaces that are utilized in routine manufacturing. The performance of each product following contact with manufacturing equipment and bulk/final storage containers is represented by the stability data associated with each lot.

### b CBER Lot Release (DMPQ)

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. The firm is not required to submit samples for FDA lot release testing, but the firm provided lot release testing protocols to FDA for review.

### c Facilities review/inspection (DMPQ)

Facility information and data provided in the bundled BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of the Blood Grouping Reagents Anti-Fyb [(Monoclonal) (clone SpA264LBg1) Product Code 0004818], Anti-Cw [(Monoclonal) (clone MS-110), Product Code 0004819] and Anti-k [(Monoclonal) (clone P3A118OL67) Product Code 0004817] are listed in the table 5 below.

**Table 5. Facilities involved in the manufacture of three subject IVP products**

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
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<i>in vitro</i> Product Manufacturing, Release Testing, Labeling, Packaging and Distribution Immucor Inc. 3130 Gateway Dr. Norcross, Georgia	1034569	061446282	Waiver	Team Biologics November 06-17, 2017 VAI
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Team Biologics performed a surveillance inspection of the Immucor Inc. facility from November 06-17, 2017. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

#### **d Environmental Assessment (DMPQ)**

The bundled 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 will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

#### **e Container Closure (PO and DMPQ)**

The container closure system used for the subject *in vitro* products is identical to that used for other currently approved licensed BGRs manufactured by Immucor, Inc. The *in vitro* products are filled into 10mL (b) (4) borosilicate glass vial with 18mm screw neck and natural latex rubber 10mL glass dropper assembly cap or thermoplastic 10mL pipette. The dropper is made of (b) (4) borosilicate glass vial. The plastic pipette is made of (b) (4). The vial is manufactured by (b) (4) (formerly known as (b) (4)). The dropper assembly cap and plastic pipette are manufactured by (b) (4). Immucor conducted the container closure integrity testing at the Norcross, Georgia facility, employing (b) (4) testing method; all acceptance criteria were met.

### **4. Non-Clinical studies**

#### **a Stability**

**Real-time stability study:** Immucor performed real time stability studies on the three BGRs to determine the shelf-life and in-use stability. Three lots of each IVP were stored at 1-10 °C and tested at the initial time point and subsequently every three months including one time point past expiry (at (b) (4) months) for potency, (b) (4) and specificity. For in-use stability testing, (b) (4) from each of the three lots for the three IVPs was opened and (b) (4)

(b) (4) storage at 1-10°C. All three products have an expiration date of 2 years from the date of manufacture when stored at 1-10°C, and in-use stability of (b) (4).

Acceptance criteria: The potency, specificity and reactivity of the lots should be equivalent ((b) (4) throughout the testing intervals. A minimum potency of (b) (4) must be maintained throughout the dating of the lots. Minimum reactivity of (b) (4) is expected with all samples having a (b) (4) Reactivity less than (b) (4) is acceptable with (b) (4) samples. In the response to FDA's November 2, 2018 information request, Immucor explained that bioburden testing is not performed as part of the stability testing protocol since bioburden testing is performed on (b) (4) products in the final container (vial) as part of final release testing. In addition, the products contain preservatives to inhibit the growth of micro-organisms.

Testing results: The results from 9 months after storage were submitted and reviewed. All testing submitted met acceptance criteria except for one heterozygous k antigen positive cell showing 1+ reactivity at the three-month time point. The firm tested (b) (4) additional k+ cells and (b) (4) showed 3+, 3+, 2+ and 3+ reactivity. The stability study is ongoing and will continue for the full (b) (4) months.

## **b Shipping Studies**

Immucor conducted simulated temperature challenge studies to assess the impact of extreme temperature conditions on product stability and performance. For each product, (b) (4)

. All results up to the 9-month testing time point met the acceptance criteria.

Immucor also performed real shipping studies. Immucor packaged each set of reagents and Data Loggers into (b) (4) shipping containers. Immucor shipped (b) (4) to (b) (4) and received it back on (b) (4). The highest temperature during shipment was (b) (4) and a temperature of (b) (4) was maintained for (b) (4). Immucor shipped (b) (4) to (b) (4) and received it back on

(b) (4). The lowest temperature during shipment was 4 °C and a temperature of <10 °C was maintained for (b) (4). The returned vials were observed for leakage and tested for potency, reactivity, and specificity in parallel with unshipped vials stored at 1-10 °C. The testing results met the acceptance criteria including a potency titer of (b) (4), reactivity of at least (b) (4) with all antigen-positive red blood cell samples (b) (4) and negative reaction with a negative control cell.

### **c Anticoagulant Studies**

Immucor conducted an anticoagulant study to demonstrate that the three subject BGRs perform as expected when used with clotted samples or samples in the anticoagulants (EDTA, ACD, CPD, CP2D, CPDA-1) and with RBCs stored with additives AS-1, AS-3 and AS-5 throughout the recommended storage periods. (b) (4) positive samples and (b) (4) negative samples were used in the studies and all samples were tested as soon as possible after collection for the initial testing points and tested again at or after expiration for the anticoagulant used (due to expiration date falling on or near holidays and weekends). Red blood cell suspensions used for testing were prepared from both washed and unwashed samples.

The reactivity of all three validation lots of Anti-Fy<sup>b</sup>, Anti-C<sup>w</sup>, and Anti-k was (b) (4) with samples prepared in the anticoagulants EDTA, ACD, CPD, CP2D, CPDA-1 and RBCs stored with additives AS-1, AS-3 and AS-5 upon initial testing and testing at or after expiration. All clot positive samples when washed showed (b) (4) reactivity and all clot negative samples, washed and unwashed, showed acceptable specificity with no false positive results.

Immucor recommends in the package insert for all three products that washed red cell suspensions be used. Donor blood samples collected in the following anticoagulants and additive solutions may be used through the expiration dates: ten days from collection in EDTA, 21 days from collection in ACD, CPD, CP2D, CP2D, 35 days from collection in CPDA-1, 42 days from collection in additives AS-1, AS-3 and AS-5. Clotted samples could be held for 21 days and require (b) (4) preparation of cell suspension if gross hemolysis is observed.

### **d Interfering Substances**

Immucor tested the effect of the following interfering materials on the product performance: triglyceride (b) (4) mg/dL, bilirubin (icteric, lipemic) (b) (4) mg/dL, and hemolysis grades of (b) (4). Immucor tested three lots of each product with (b) (4) samples. Simulated samples were prepared using RBCs of known antigen types and

spiking with different concentrations of interfering materials. The testing results met the acceptance criteria.

## 5. Clinical Studies

### a Clinical comparison studies

Immucor conducted a clinical study at three external United States locations and one internal site. Three lots of Anti-Fy<sup>b</sup> and Anti-k were tested by manual tube method in parallel with the comparator reagents (FDA licensed Immucor Anti-k polyclonal product and Anti-Fy<sup>b</sup> polyclonal product). Immucor stated that there were no commercially available FDA-licensed Anti-C<sup>w</sup> when the clinical studies were performed, therefore, they prepared their own Anti-C<sup>w</sup> from cell clone (b) (4) . During a teleconference with Immucor on October 10, 2018, FDA informed Immucor that the use of an unlicensed reagent as a comparator in the clinical studies was not acceptable. Immucor performed a new study at one internal site and one external site using the recently approved ALBAclone® Anti-C<sup>w</sup> (Monoclonal) as the comparator. The study samples were left-over random de-identified patient and/or donor samples as well as nitrogen frozen recovered red blood cells. The sample numbers and study sites for the three IVP products are listed in the Table 6 below.

**Table 6. Sample numbers tested at the study sites**

Study site	Number of samples Tested		
	Anti-Fy <sup>b</sup>	Anti-k	Anti-C <sup>w</sup>
BloodWorks Northwest, WA (BWN)	450	450	0
LifeShare Blood Center, LA (LS)	498	498	218
Rochester General Hospital, NY (RGH)	239	239	0
Immucor	667	667	194
Total number of samples tested	1854	1854	412

According to Immucor’s responses to the November 6, 2018 FDA Information Request, the following samples representing disease status and age groups as shown in Table 7 were used in the clinical study.

**Table 7. Disease status and age groups represented in the clinical study**



<b>Conditions</b>	<b>Samples</b>
Pregnancy	95
Solid tumor, Leukemia, Lymphoma	25
Hemolytic, Anemia/Sickle, Cell Anemia	1
Multiple Myeloma, Myelodysplastic Syndrome, increased protein	12
Misc. e.g. nonmalignant disease state, routine surgery	414
Cord Blood samples	30
Greater than 65 years of age (including four samples >80 and two samples 79 years old from one testing site)	194

When discordant results were identified by the testing site, repeat testing was performed. In addition, regardless of the results of the re-test, the discordant samples were also evaluated by PreciseType™ HEA Bead Chip analysis and/or DNA (b) (4) .

**The acceptance criteria** are as follows:

The lower bound of the one-sided 95% confidence intervals (CI) for both the positive percent agreements (PPA) and the negative percent agreements (NPA) with the comparator reagent/method should exceed 99%.

**Testing results:** Immucor explained that there were five DAT positive samples excluded from analysis. In addition, 50 samples were excluded from the final analysis as they were tested using an expired Checkcell (antiglobulin control cell) reagent. Therefore, a total of 1799 samples were included in the final analysis for Anti-Fy<sup>b</sup> and Anti-k. Table 8 below shows the Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA) for each product:

**Table 8. Negative Percent Agreement (NPA) and Positive Percent Agreement (PPA)**

Blood Grouping Reagent	PPA (Lower bound, one-sided 95% CI)	NPA (Lower bound, one-sided 95% CI)	Discrepant results
Gamma-clone® Anti-Fy <sup>b</sup>	1258/1258, 100% (99.76%)	535/541, 98.89% ( <b>97.60%</b> )	6
Gamma-clone® Anti-k	1793/1793, 100% (99.83%)	6/6, 100% ( <b>60.70%</b> )	0

Gamma-clone® Anti-C <sup>w</sup>	42/42, 100% <b>(93.12%)</b>	370/370, 100% (99.19%)	0
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A summary of the BGRs that did not meet the acceptance criteria for negative or positive percent agreement is listed below:

- 1) Gamma-clone® Anti-Fy<sup>b</sup> did not meet the NPA due to six discrepant results. The molecular testing in the reference laboratory confirmed that the six samples were weak Fy<sup>b</sup> positive consistent with the Gamma-clone® Anti-Fy<sup>b</sup> positive testing results.
- 2) Gamma-clone® Anti-k did not meet acceptance criteria of the NPA due to small number of k negative samples. The k (also known as Cellano) antigen is high frequency in Caucasians and African Americans.
- 3) Gamma-clone® Anti-C<sup>w</sup> did not meet the PPA. In the United States, the frequency of the C<sup>w</sup> antigen among Caucasians is 2% and 1% in African Americans.

Deviations:

- 1) Rochester General Hospital planned to test 446 samples and completed testing of 239 samples due to resourcing issues.
- 2) LifeShare Blood Center excluded 50 samples (LS291 through LS340) from the final analysis as they were tested using an expired antiglobulin control cell reagent.

### **b Precision**

The three external sites performed precision studies to demonstrate reproducibility from lot-to-lot, occasion- to-occasion, operator-to-operator, and repeatability. The sample panel used in the study was (b) (4) of three unique samples. The expected results of the sample panel are listed in Table 9 below.

**Table 9. Expected results of the sample panel**

Sample ID	Expected results		
	Anti-Fy <sup>b</sup>	Anti-C <sup>w</sup>	Anti-k
Sample 1	Positive	negative	negative
Sample 2	Negative	Negative	Positive
Sample 3	Positive	Positive	Positive

Three lots each of the three subject products were tested using the sample panel by (b) (4) technologists at (b) (4) runs per day for (b) (4) non-consecutive days. A total of 180 test results for reproducibility ((b) (4) operators x (b) (4) days x (b) (4) runs x (b) (4) replicates) per site and for the lot-to-lot reproducibility studies ((b) (4) samples x (b) (4) runs x (b) (4) days x 3 lots) were obtained.

The results met 100% Positive Percent Agreement (PPA) and 100% Negative Percent Agreement (NPA) between the reagent and the expected results for all testing.

## **6. Advisory Committee Meeting**

An advisory committee meeting was not convened for these products since the submission does not include new technology.

## **7. Labeling**

Immucor submitted draft labeling for the Instructions 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.

## **8. Recommendations and Risk/ Benefit Assessment**

### **a Recommended Regulatory Action**

The review committee members, representing the necessary review disciplines 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 of licensing Anti-Fy<sup>b</sup>, Anti-C<sup>w</sup>, and Anti-k blood grouping reagents include the following:

- Decrease the probability of product shortages for these BGRs by making rare blood typing antisera available to immunohematology laboratories and blood establishments. There are few licensed manufacturers of monoclonal blood typing sera in the United States therefore licensing these products will introduce additional monoclonal BGRs for use.

- Improve the safety of the blood supply by providing a wide range of monoclonal reagents manufactured with diverse cell lines which can increase the probability of the detection of rare antigen variants.

The evaluation of the validation and clinical studies, and the manufacturing process reduces the risks associated with licensing new blood grouping reagents. In addition, Anti-Fy<sup>b</sup>, Anti-C<sup>w</sup>, and Anti-k blood grouping reagents will be subject to post market surveillance (Medical Device Reporting) which will identify adverse events associated with this product.

## **9. Recommendation for Postmarketing Activities**

There are no postmarketing commitments associated with these BLAs.