Summary Basis for Regulatory Action Template

Date: November 13, 2025

From: Emilia Sippert, Chair of the Review Committee

BLA/STN#: 125848/0, 125849/0, 125850/0, 125851/0, 125852/0, 125853/0, 125854/0, 125855/0

Applicant Name: The American National Red Cross

Date of Submission: January 24, 2025

MDUFA Goal Date: November 24, 2025

Proprietary Name:
125848/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-C (Monoclonal)
125849/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-E (Monoclonal)
125850/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-c (Monoclonal)
125851/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-k (Monoclonal)(IgG)
125852/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-Jk^a (Monoclonal)
125853/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-Jk^b (Monoclonal)
125854/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-S (Monoclonal)
125855/0 American Red Cross (Red Cross) Blood Grouping Reagent Anti-s (Monoclonal)

Established Name (common or usual name):
125848/0 Blood Grouping Reagent, Anti-C (Monoclonal)
125849/0 Blood Grouping Reagent, Anti-E (Monoclonal)
125850/0 Blood Grouping Reagent, Anti-c (Monoclonal)
125851/0 Blood Grouping Reagent, Anti-k (Monoclonal) (IgG)
125852/0 Blood Grouping Reagent, Anti-Jk^a (Monoclonal)
125853/0 Blood Grouping Reagent, Anti-Jk^b (Monoclonal)
125854/0 Blood Grouping Reagent, Anti-S (Monoclonal)
125855/0 Blood Grouping Reagent, Anti-s (Monoclonal)

Device Procode: QHR

Intended Use/Indications for Use:

Anti-C, Anti-E, Anti-c:

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American Red Cross (Red Cross) Anti-C (Monoclonal), Anti-E (Monoclonal), and Anti-$\bar{c}$ (Monoclonal) are used for the in vitro detection of the C (RH2), E (RH3), and $\bar{c}$ (RH4) antigens respectively, on human red blood cells by direct agglutination using the manual tube testing method.

Anti-k:
American Red Cross (Red Cross) Anti-$\bar{k}$ (Monoclonal) (IgG) is used for the in vitro detection of the $\bar{k}$ (KEL2) antigen on human red blood cells by the Indirect Antiglobulin Test (IAT).

Anti-Jk^a, Anti-Jk^b:
American Red Cross (Red Cross) Anti-Jk^a (Monoclonal) and Anti-Jk^b (Monoclonal) are used for the in vitro detection of the Jk^a (JK1) and Jk^b (JK2) antigens respectively, on human red blood cells by direct agglutination using the manual tube test.

Anti-S, Anti-s:
American Red Cross (Red Cross) Anti-S (Monoclonal) and Anti-$\bar{s}$ (Monoclonal) are used for the in vitro detection of the S (MNS3) and $\bar{s}$ (MNS4) antigens respectively, on human red blood cells by direct agglutination using the manual tube testing method.

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

Review Office Signatory Authority: Anne Eder, M.D. Ph.D., Director, Office of Blood Research and Review

X 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.**

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Document Title	Reviewer Name
Product Review(s) (product office) • *Clinical* • *Non-Clinical*	Emilia Sippert, CBER/OBRR/DBCD/DRB Kimberly Bigler, CBER/OBRR/DBCD/DRB
Statistical Review(s) • *Clinical* • *Non-Clinical*	Linye Song, CBER/OBPV/DB/DNCE
CMC Review • *CMC (Product Office)* • *Facilities Review (OCBQ/DMPQ)* • *Bioburden* (OCBQ/DBSQC)	Emilia Sippert, CBER/OBRR/DBCD/DRB Kimberly Bigler, CBER/OBRR/DBCD/DRB Philip Thai, CBER/OCBQ/DMPQ/MRB1 Yen Phan, CBER/OCBQ/DBSQC
Labeling Review(s) • *Product Office* • *APLB (OCBQ/APLB)*	Emilia Sippert, CBER/OBRR/DBCD/DRB Kimberly Bigler, CBER/OBRR/DBCD/DRB Sadhna Khatri, CBER/OCBQ/DCM/APLB
Lot Release Protocols/Testing Plans	George Kastanis, CBER/OCBQ/DBSQC
Bioresearch Monitoring Review	Not applicable for this submission
Establishment Inspection Report	Not applicable for this submission, inspection waived

1. Introduction

(b) (4)   The American Red Cross (ARC) located in (b) (4)   (U.S. License # 190), submitted a bundled original Biologics License Application (BLA) requesting approval to manufacture and distribute the eight Blood Grouping Reagents (BGRs), listed in Table 1.

Table 1. STNs, BGRs Proper Name and Proprietary Name

STN	Proper Name	Proprietary Name (Trade name)
BL 125848/0	Blood Grouping Reagent, Anti-C (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-C (Monoclonal)

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BL 125849/0	Blood Grouping Reagent, Anti-E (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-E (Monoclonal)
BL 125850/0	Blood Grouping Reagent, Anti-c (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-c (Monoclonal)
BL 125851/0	Blood Grouping Reagent, Anti-k (Human/Murine Monoclonal) (IgG)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-k (Monoclonal) (IgG)
BL 125852/0	Blood Grouping Reagent, Anti-Jk^a (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-Jk^a (Monoclonal)
BL 125853/0	Blood Grouping Reagent, Anti-Jk^b (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-Jk^b (Monoclonal)
BL 125854/0	Blood Grouping Reagent, Anti-S (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-S (Monoclonal)
BL 125855/0	Blood Grouping Reagent, Anti-s (Human/Murine Monoclonal)	American Red Cross (Red Cross) Blood Grouping Reagent Anti-s (Monoclonal)

The products will hereafter be referred to as Anti-C, Anti-E, Anti-c, Anti-k, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s. The design and manufacture of these BGRs is performed at (b) (4)   .

These BGRs are human/murine monoclonal antibodies intended for qualitative detection of specific antigens on human red blood cells using the manual tube technique. Using direct agglutination methods, Anti-C, Anti-E, Anti-c, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s reagents will react with red blood cells that express corresponding antigens (C, E, c, Jk^a, Jk^b, S, and s). The Anti-k reagent detects the k antigen on red blood cells using an indirect antiglobulin method.

The in vitro substances (IVS), also known as For Further Manufacturing Use (FFMU) products used in the manufacture of the BGRs listed above, are manufactured by (b) (4) Millipore Corporation (Millipore) under shared manufacturing agreements. Millipore submitted companion BLA supplements (see Table 2) for the FFMU products used by ARC to manufacture the final products. The shared manufacturing agreement includes supply, license, and quality agreements.

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Table 2. FFMU Products - STNs, Names, and Cell Lines.

STN	Name of Biological Product	Cell Line
BL 103859/5124	Blood Grouping Reagent, Anti-E (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-80
BL 103859/5125	Blood Grouping Reagent, Anti-E (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-258
BL 103858/5131	Blood Grouping Reagent, Anti-C (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-24
BL 103860/5123	Blood Grouping Reagent, Anti-c (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-33
BL 103861/5117	Blood Grouping Reagent, Anti-Jk^a (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-15
BL 103862/5119	Blood Grouping Reagent, Anti-Jk^b (Human Monoclonal) (IgM) (For Further Manufacturing Use)	MS-8
BL 125239/59	Blood Grouping Reagent, Anti-S (Monoclonal) (IgM) (For Further Manufacturing Use)	MS-94
BL 125498/32	Blood Grouping Reagent, Anti-s (Monoclonal) (For Further Manufacturing Use)	P3BER
BL 125684/18	Blood Grouping Reagent, Anti-k (Monoclonal) (IgG) (For Further Manufacturing Use)	P3A118OL67

Chronology of Events

***Meetings with FDA*:**
FDA held a pre-submission meeting with ARC (BQ210597) on August 2, 2021. Subsequently, FDA provided two additional written feedback responses under BQ210597/1 on February 3, 2023, and BQ210597/2 on July 5, 2023. The meetings included discussions on the following topics: transport studies, stability studies, bioburden studies and validation of (b) (4) method comparison studies; interference studies; anticoagulant studies; validation for antimicrobial effectiveness; potency requirements; and in-house standards.

CBER received the original bundled BLA submission on January 24, 2025, including monoclonal BGRs for Anti-C, Anti-c, Anti-E, Anti-k, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s. ARC submitted ten amendments received on May 05, 2025, May 15, 2025, June 23, 2025, July 03, 2025, July 18, 2025, July 21, 2025, July 30, 2025 in response to information requests (IRs) from FDA.

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2. Background

The Rhesus (Rh) blood group system is one of the most complex human blood group systems, containing over 56 antigens expressed on red blood cells. The *RHCE* gene encodes the major C/c and E/e antigens, with more than 150 known *RHCE* alleles that can result in altered or weakened antigen expression. Antibodies against C, E, and c antigens are clinically significant as they can cause hemolytic transfusion reactions and hemolytic disease of the fetus and newborn (HDFN).

The Kell blood group system includes more than 36 antigens. The k antigen (KEL2), also known as Cellano, is one of the major antigens in the Kell system alongside K (KEL1), Kp^a (KEL3), Kp^b (KEL4), Js^a (KEL6), and Js^b (KEL7). The k antigen is highly prevalent with a 99.8% frequency in Caucasians. Anti-K and Anti-k antibodies are clinically significant as they can cause hemolytic transfusion reactions and HDFN.

The Kidd blood group system includes the Jk^a and Jk^b antigens. Individuals with the Jk(a-b-) phenotype produce anti-Jk3 antibodies that react with all Jk(a+) or Jk(b+) red blood cells. Anti-Jk^a anti-Jk^b and anti-Jk3 antibodies are clinically significant as they can cause hemolytic transfusion reactions, and HDFN.

The S (MNS3) and s (MNS4) antigens, first described in 1947, are polymorphic antithetical antigens within the highly complex MNS blood group system, which consists of 50 antigens. Anti-S and Anti-s antibodies are clinically significant as they can cause hemolytic transfusion reactions and HDFN.

Therefore, accurate detection of these antigens is essential for safe blood transfusion and the prediction of HDFN.

Product description

Anti-C, Anti-E, and Anti-c
Anti-C, Anti-E, and Anti-c are liquid monoclonal BGRs supplied in a vial with dropper assembly for use in typing human red blood cells for the presence of the C, E, and c antigens. The main component of each BGR is an IgM monoclonal antibody derived from the in vitro culture of the human/mouse heterohybridoma cell lines MS-24 (Anti-C), MS-80/MS-258 (Anti-E), and MS-33 (Anti-c). The BGRs also contain bovine material, potentiators, and 0.1% (w/v) sodium azide.

Each BGR is validated for use with the tube technique which includes a five-minute incubation time at 36ºC to 38ºC followed by centrifugation. The BGRs react with red blood cells that are positive for the corresponding antigen and produce visible agglutination of the red blood cells in the test tube.

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Anti-k

Anti-k is a liquid monoclonal BGR supplied in a vial with dropper assembly for use in typing human red blood cells for the presence of the k antigen. The main component of this BGR is an IgG monoclonal antibody derived from the in vitro culture of the human/mouse heterohybridoma cell line P3A118OL67. The BGR also contains bovine material, potentiators, and 0.1% (w/v) sodium azide.

Anti-k is validated for use in indirect antiglobulin tube testing which includes a fifteen-minute incubation at 36ºC to 38ºC, and the addition of an Anti-Human Globulin after a minimum of three washes with isotonic saline. Agglutination indicates the presence of the k antigen. Lack of agglutination indicates the absence of the k antigen.

Anti-Jk^a and Anti-Jk^b

Anti-Jk^a and Anti-Jk^b are liquid monoclonal BGRs supplied in a vial with dropper assembly for use in typing human red blood cells for the presence of the Jk^a and Jk^b antigens. The main component of each BGR is an IgM monoclonal antibody derived from the in vitro culture of the human/mouse heterohybridoma cell line MS-15 (Anti-Jk^a), and MS-8 (Anti-Jk^b). The BGRs also contain a (b) (4) buffered (b) (4) solution, bovine serum albumin, macromolecular chemical potentiators, and 0.1% (w/v) sodium azide.

Each BGR is validated for use with the tube technique which includes a fifteen-minute incubation at 18ºC to 28ºC followed by centrifugation. The BGR reacts with red blood cells that are positive for the corresponding antigen and produces visible agglutination of the red blood cells in the test tube.

Anti-S and Anti-s

Anti-S and Anti-s are liquid monoclonal BGRs supplied in a vial with dropper assembly for use in typing human red blood cells for the presence of the S and s antigens. The main component of each BGR is an IgM monoclonal antibody derived from the in vitro culture of the human/mouse heterohybridoma cell line MS-94 (Anti-S) and P3BER (Anti-s). The BGRs also contain a (b) (4) buffered (b) (4) solution, bovine serum albumin, macromolecular chemical potentiators, and 0.1% (w/v) sodium azide.

Each BGR is validated for use with the tube technique which includes a five-minute incubation time at 18 °C to 28 °C followed by centrifugation. The BGR reacts with red blood cells that are positive for the corresponding antigen and produces visible agglutination of the red blood cells in the test tube.

Marketing History

There is no marketing history for the above-mentioned BGRs.

3. Chemistry Manufacturing and Controls (CMC)

a) Manufacturing Summary

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In Vitro Substance (IVS)/ Antibody (b) (4)

The antibody (b) (4) used in the manufacture of the eight subject BGRs (Anti-C, Anti-E, Anti-c, Anti-k, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s) are (b) (4) from the *in vitro* culture of the specific antibody secreting human/mouse heterohybridoma cell lines and are manufactured by Millipore under a shared manufacturing arrangement. Table 2 shows the cell line of each FFMU product. Millipore submitted a bundled Prior Approval Supplement (PAS) and a PAS Efficacy Supplement to distribute the antibody (b) (4) labeled For Further Manufacturing Use (FFMU) to ARC.

ARC acceptance criteria for incoming FFMU includes verification of the Certificate of Analysis (CoA) that accompanies each FFMU lot, and confirmatory (b) (4) testing to ensure the (b) (4) meets the minimum (b) (4) listed on the current lot CoA. CoAs include information on (b) (4)

In Vitro Product (IVP)

All other raw materials besides the FFMU products used for the manufacture of the IVP are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

The IVPs include the following formulation ingredients: the active ingredients antibody (b) (4) , bovine albumin solution (BSA), potentiators (b) (4) , preservative (sodium azide), and (b) (4) buffered (b) (4). Each IVP contains a combination of potentiators.

Manufacturing Process Description

ARC divides the manufacturing process into the following stages: a) Raw material handling, b) (b) (4) production, c) Lot production, d) Filling, e) Release testing, f) Finishing, and g) Release.

Raw material handling

Raw materials are placed in quarantine storage of appropriate temperature. For FFMU products, ARC also verifies the cold chain shipping storage temperature. Inspection and release testing are performed, and in-coming material is stored at temperature-appropriate areas.
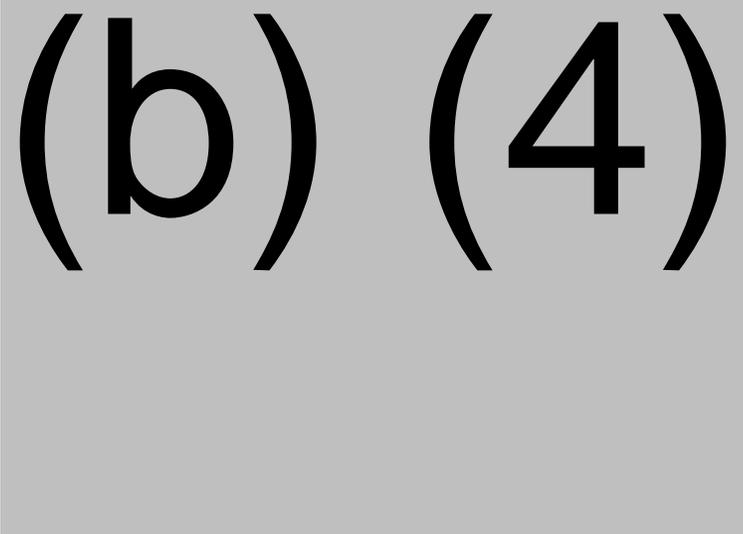
(b) (4) Production

(b) (4)

(b) (4)

Table 3. Minimum and maximum lot volume manufactured for each BGR.
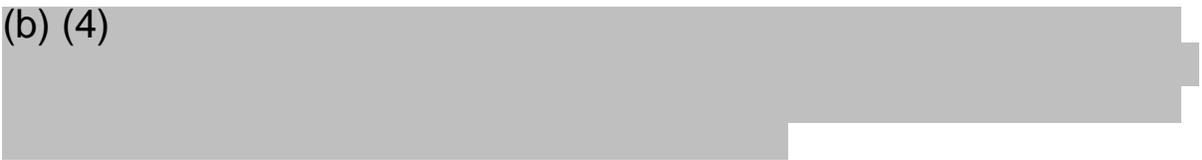
(b) (4)

Lot production

(b) (4)

Filling

(b) (4)

Release Testing

(b) (4)

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Finishing

After label release, the unlabeled vials are transferred to the vial labeling machine for labeling. 100% manual visual inspection is performed for the presence of particulates, defects or damage to container, label, or closure. Labeled vials are placed in the appropriate packaging together with a generic package insert with instructions where to obtain the instructions for use.

Product release

Final inspection is performed (b) (4) selected packages/containers based on ARC's established sampling plan for QC inspections of final products. Final inspection includes (b) (4) confirmation of antibody specificity (identity test). Final containers are kept in labeled (b) (4) at 2-8°C until transferred to distribution room.

At least (b) (4) selected final package or labeled final container is designated as a QC Retention Sample before the lot is released to distribution. Monoclonal BGR retention samples are stored in the QC refrigerator at 2-8°C and retained for at least (b) (4) months after the product expiration.

Date of Manufacture (DOM)

The date of manufacture for Anti-C, Anti-E, Anti-c, Anti-k, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s is defined as the filling date. The expiration date is based on the filling date.

Dating Period

The dating period is 15 months for Anti-c and Anti-k, and 12 months for Anti-C, Anti-E, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s when stored at 2-8 °C.

Specifications and Test Methods

Tables 4, 5, 6, 7, include the required release testing methods and acceptance criteria for Anti-C, Anti-E, Anti-c, Anti-k, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s reagents, respectively.

Table 4. IVP Testing and Acceptance Criteria – Anti-C, Anti-E, and Anti-c

Test	Incubation	Red blood cells for testing	Acceptance criteria
Reactivity (Positive Specificity)	5 minutes 36-38 °C	(b) (4)	
Negative Specificity	5 minutes 36-38 °C		

		(b) (4)	
Potency	5 minutes 36-38 °C		
Microbiology	Minimum of (b) (4)		
pH	N/A		
Total Protein	N/A		

Table 5. IVP Testing and Acceptance Criteria – Anti-k

Test	Incubation	Red blood cells for testing	Acceptance criteria
Reactivity (Positive Specificity)	15 minutes 36-38 °C	(b) (4)	
Negative Specificity	15 minutes 36-38 °C		

Potency	15 minutes 36-38 ˚C	(b) (4)	
Microbiology	Minimum of (b) (4)		
pH	N/A		
Total Protein	N/A		

Table 6. IVP Testing and Acceptance Criteria – Anti-Jk[a] and Anti-Jk[b]

Test	Incubation	Red blood cells for testing	Acceptance criteria
Reactivity (Positive Specificity)	15 minutes 18-28 °C	(b) (4)	
Negative Specificity	15 minutes 18-28 °C		
Potency	15 minutes 18-28 °C	(b) (4)	
Microbiology	Minimum of (b) (4)		
pH	N/A		
Total Protein	N/A		

			(b) (4)	

Table 7. IVP Testing and Acceptance Criteria – Anti-S and Anti-s

Test	Incubation	Red blood cells for testing	Acceptance criteria
Reactivity (Positive Specificity)	5 minutes 18-28 °C	(b) (4)	
Negative Specificity	5 minutes 18-28 °C		
Potency	5 minutes 18-28 °C		
Microbiology	Minimum of (b) (4)		
pH	N/A		
Total Protein	N/A		

Microbiology

BGRs Anti-C, Anti-E, Anti-c, Anti-k, Anti-Jk[a], Anti-Jk[b], Anti-S, and Anti-s are microbiologically controlled products and are considered non-sterile, multiple use devices. The acceptable level of microorganisms that the products may contain is (b) (4) . Microbiological control of the BGRs is assured through the implementation of the following approaches and measures:

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(b) (4)

The analytical methods and their validations and/or qualifications reviewed for the monoclonal blood grouping reagents (BGRs) were found to be adequate for their intended use.

Conformance lots
ARC manufactured a total of (b) (4) conformance lots of each BGR and each lot is reflective of the current container/closure system and product-contact surfaces that are utilized in routine manufacturing. ARC submitted the Device History Records of (b) (4) (b) (4) for each BGR describing the critical manufacturing steps and controls points for Anti-C (b) (4) Anti-E (b) (4) Anti-c (b) (4) Anti-k (b) (4), Anti-Jkª (b) (4) Anti-Jkᵇ (b) (4) Anti-S (b) (4)), and Anti-s (b) (4)
(b) (4)

b) CBER Lot Release

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

c) Facilities review/inspection
Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Blood Grouping Reagents (BGRs) Anti-C (Monoclonal), Anti-E (Monoclonal), Anti-c (Monoclonal), Anti-k (Monoclonal), Anti-Jkª (Monoclonal), Anti-Jkᵇ (Monoclonal), Anti-S (Monoclonal), and Anti-s (Monoclonal) are listed in the table below. The activities performed and inspectional histories are noted in the table.

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Manufacturing Facilities Table for Monoclonal BGRs

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
The American Red Cross (b) (4) *Manufacture (formulation, (b) (4) , fill/finish) of IVD monoclonal blood grouping reagents (DP), labeling/packaging, QC testing, release testing, stability testing*	(b) (4)	(b) (4)	Waiver	OII/OBPO (b) (4) NAI

Acronym key: (include any of the following, as applicable) DP – drug product; IVD – In Vitro Diagnostic; OII – Office of Inspections and Investigations; OBPO – Office of Biological Products Operations; NAI – No Action Indicated; QC – quality control.

(b) (4)
OII/OBPO conducted a surveillance inspection of The American National Red Cross (b) (4) on (b) (4) . No Form FDA 483 was issued, and the inspection is classified as NAI.

d) Environmental Assessment

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 significantly alter the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure

The final container closure system (CCS) for all BGR products consists of a 2 dram glass vial with a dropper assembly. The vial is Type-(b)(4) clear glass, manufactured by (b) (4) . The dropper assembly consists of a polypropylene cap, a black bulb, and Type-(b)(4) clear glass straight point dropper/pipette. The dropper assembly is manufactured and supplied by (b) (4) .

Even though these blood grouping reagents are non-sterile, The American Red Cross (b) (4) performed the container closure integrity testing

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(CCIT) at their (b) (4) facility, employing the (b) (4) methods; all acceptance criteria were met.

4. Software and Instrumentation

Not applicable for this submission.

5. Analytical Studies

Analytical studies included design verification, stability, anticoagulant, interference substances, and in-house performance studies.

a) Design Verification Studies

ARC used FFMU products nearing expiration date to formulate a (b) (4) verification lot for each BGR to demonstrate that the design output met design input. Each lot was placed on a real-time stability protocol. ARC performed non-clinical prospective studies to establish the serological characteristics and performance of the verification lots. Data provided support the test method and limitations sections of the eight BGRs in the Directions for Use (DFU). The following studies were performed by testing well-characterized red blood cells (RBCs) with the verification lots:

Verification of Testing Procedure

ARC confirmed the test method incubation time and temperature for each BGR by testing at least (b) (4) RBC samples with (b) (4), heterozygous, or weak expression of the corresponding antigen. The verification lots demonstrated expected serological performance and reactivity strength using the test method in the reagents DFU.

Performance Testing with Isotonic Saline (b) (4) of pH 6.5 to 7.5

ARC verified the assay performance of each BGR with isotonic saline (b) (4) of pH 6.50 and 7.50. ARC tested RBC samples with (b) (4) heterozygous, or weak expression of the corresponding antigens. Testing was performed at each saline pH range limit recommended in the DFU, 6.50 and 7.50. ARC used in-house, in-use (b) (4) as a control. The verification lots demonstrated expected serological performance when the RBCs were suspended at a 2-4% concentration in either isotonic saline (b) (4) at each end of the pH range.

Spontaneous Agglutination Study

(b) (4)

(b) (4)

For Spontaneous Agglutination testing of (b) (4)

A Direct Antiglobulin Test (DAT) was performed to demonstrate sensitization. (b) (4)

Prozone Study

The verification lots of each BGR were tested, (b) (4)

The BGRs did not demonstrate prozone effect.

Failure Testing

ARC tested a total of (b) (4) well-characterized RBCs (b) (4) , intentionally deviating from the DFU testing procedure in a controlled setting, at specific impact points, listed below:

(b) (4)

All other steps followed the correct test procedure in each run. A control (correct testing procedure) was run within each group. The test method (control) was the most efficient use of reagent and testing time and produced the strongest reactivity. The results varied

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based on the impact point being tested and the reagents, supporting the statement in the DFU "To maximize success in obtaining valid results, follow the DFU carefully. Deviations from the manufacturer's instructions without appropriate validation and controls may produce erroneous results."

Treated Red Blood Cells Study

- For each BGR, (b) (4) well-characterized EDTA samples (b) (4) negative for the corresponding antigen), were each treated with Chloroquine Diphosphate (CDP), EDTA (b) (4) Treatment of the red blood cells was performed using each associated DFU and/or published (public domain) procedures. The same well-characterized cells were left untreated and run in parallel as a control with each treated cell group. The results of the study matched the expected reactions per the antigen's reactivity with the different red cell treatments (enhanced, destroyed, or consistent). However, there were instances where enzyme treatment resulted in cell buttons that were more difficult to resuspend.

Therefore, ARC included a specific limitation in the DFU for Anti-E, Anti-c, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s to indicate that enzyme treated red blood cells may give incorrect results with these BGRs and use of enzyme treated cells with these reagents is not recommended.

b) Stability Studies

ARC conducted comprehensive stability studies to support the proposed shelf life and evaluate product performance under various storage, transport and in-use conditions. The stability studies included the following testing at each time point: visual inspection for color, appearance, and container closure integrity; potency, and reactivity. Additionally, microbiology testing was performed (b) (4) The red blood cell phenotypes, techniques, and acceptance criteria for potency, reactivity, and microbiology testing described in Tables 4 to 7 also apply to stability study testing.

Real-Time Stability Study

Real-time stability testing was conducted for both the verification and conformance lots to support the proposed shelf life. The stability studies with the verification lots were conducted to demonstrate performance of final product manufactured with FFMU source material that was near end of shelf-life. Vials, for both verification and conformance lots, were (b) (4) at 2-8 °C until testing at the following timepoints: Day 0 (release) and 3, 6, 9, 12, 15, (b) (4) (b) (4) months.

The available real time stability study data for the verification and conformance lots support a shelf life of 15 months at 2-8 °C for Anti-c and Anti-k, and 12 months at 2-8 °C for Anti-C, Anti-E, Anti-Jk^a, Anti-Jk^b, Anti-S, and Anti-s. The stability study is currently in progress and will continue through (b) (4) -months.

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In-Use Stability Study

This study was conducted on the (b) (4) conformance lots of each BGR to evaluate the stability of the products under conditions simulating end-user environment. Product vials were removed from 2-8 °C, (b) (4)   , then stored at 18-28 °C for (b) (4) . Following this exposure, vials were returned to 2-8 °C for (b) (4) . This cycle was repeated for (b) (4) consecutive days. Subsequently, vials were stored (b) (4) at 2-8°C until testing at the following timepoints: 3, 6, 9, 12, 15, (b) (4)   months. Results for potency, reactivity, and visual inspection of container/closure results for the conformance lots met acceptance criteria through the timepoints tested. The available in-use stability study data support the current proposed shelf life. The stability testing is currently in progress and will continue through (b) (4) -months.

Real-Time Transport Study

(b) (4)

(b) (4)

Summary Basis for Regulatory Action

Simulated Transport Study

(b) (4)

(b) (4)

Finished Product Microbial Challenge Study

(b) (4)

(b) (4)

c) Anticoagulant Studies

ARC conducted anticoagulant studies with (b) (4) of each BGR to demonstrate that the eight BGRs perform as expected when tested with clotted samples or samples collected in commonly used anticoagulants and additives (EDTA, CPD, CPDA-1, CPD with AS-1, CP2D with AS-3) throughout the recommended sample storage period. According to DFU, blood drawn into EDTA and NBRT (non-barrier red top) tubes should be tested less than or equal to 10 days from collection. Donor samples drawn into CPD, CPDA-1, CPD with AS-1, CP2D with AS-3, and CPD with AS-5 may be tested up to the expiration date of the donor unit (CPD - (b) (4) days, CPDA-1 - (b) (4) days, CPD with AS-1 and CP2D with AS-3 - (b) (4) days). For each BGR, (b) (4) positive samples and (b) (4) negative samples were tested using the tube testing technique detailed in the product DFU as soon as possible after collection (within (b) (4) days) and

again at or (b) (4) after the proposed age limit for each anticoagulant. ARC evaluated CPD with AS-5 separately as part of the interference study.

The results demonstrate 100% agreement with the expected results of well-characterized specimens for all anticoagulants tested. During endpoint testing, some samples collected in NBRT tubes demonstrated hemolysis after the first wash, requiring a second wash as permitted by the test procedure. The DFU for all eight BGRs recommends using washed red cell suspensions.

ARC reported deviations in the anti-E anticoagulant study related to sample availability and sample age. Specifically, no E+ (b) (4) samples were tested in CPD. The testing with samples stored in CPDA-1 included (b) (4) E+ samples instead of (b) (4), with (b) (4) . Additionally, (b) (4) was (b) (4) days old at initial testing rather than (b) (4) days, and (b) (4) withdrawn due to an incorrect endpoint test date. The testing of samples stored in CP2D with AS-3 included (b) (4) heterozygous samples instead of (b) (4), and (b) (4) samples instead of (b) (4), with timing deviations like the samples stored in CPDA-1. Despite these protocol deviations, ARC successfully tested heterozygous (worst case scenario) and negative samples across all anticoagulants, and the results from samples that exceeded the (b) (4) day collection window still met acceptance criteria. In addition, the Anti-E Method Comparison Study, which included samples collected with the above-mentioned anticoagulants, showed expected agreement with the comparator without discrepancies associated with anticoagulant type.

ARC also reported deviations in the anti-k anticoagulant study related to sample availability, as it did not include negative samples stored in CPD, CPDA-1, and CP2D with AS-3. The absence of k- samples was assessed as low risk because these anticoagulants are primarily used in donor units, and false positive results would lead to units being labeled as k+, consequently it would not be used for transfusion to a k-patient. ARC acknowledged this limitation in the DFU, explaining that due to the rarity of the k- phenotype, Red Cross was unable to evaluate the use of Red Cross Anti-k(Monoclonal) (IgG) with CPDA-1, CP2D with AS-3, and CPD with AS-5 samples from k negative individuals.

d) Interference Study

ARC performed the interference studies in-house with (b) (4) of each BGR to evaluate potential impacts on serological performance. The study involved adding interferent substances to well-characterized samples (b) (4)

Additionally, ARC tested reagent performance with samples collected in EDTA tubes and NBR tubes stored (b) (4) to evaluate the impact of tube contents in contact with (b) (4)

Results for each BGR demonstrated the expected reactivity and no adverse impact on the serological performance of the reagents. However, the original study had limitations related to sample availability. No k+ antigen samples collected with AS-5, and k-samples collected in EDTA, NBR or AS-5 were tested. Similarly, the Field Comparison

Summary Basis for Regulatory Action

Study did not include samples collected with AS-5. To address these limitations, ARC provided supplemental study data for Anti-k that included (b) (4) ARC explained that no examples of the K+k- phenotype were obtained due to the very low prevalence of antigen-negative samples in the population. The results from the supplemental study were as expected, with no adverse impact to serological performance detected.

Regarding study limitations related to AS-5, ARC added a note in the DFU stating that due to the rarity of the k- phenotype, they were unable to evaluate the use of anti-k in k- samples collected in CPDA-1, CP2D with AS-3, and CPD with AS-5.

To ensure proper interpretation of test results in the presence of hemolysis, the DFU also includes: "NOTE: Hemolysis, if obtained, should not be interpreted as a positive result since the conditions for complement activation due to a red cell antibody-antigen reaction do not exist."

e) In-House Performance Study

ARC conducted an in-house performance study to evaluate the clinical performance of each BGR by testing (b) (4) against well-characterized red blood cell samples and comparing results to an FDA-licensed reagent. The study design included sample types assessing reagent performance across the full spectrum of antigen expression levels: (b) (4) Well-characterized test cells consisted of either licensed reagent red blood cells (RRBCs) or cells that were phenotyped using at least [(b) (4)] different licensed reagents.

The BGRs demonstrated 100% concordance with the expected antigen phenotypes of the well-characterized samples and the comparator reagent results. All BGRs performed as intended, demonstrating equivalent reactivity, specificity, and sensitivity to the FDA-licensed comparator reagent across all tested red blood cell samples.

6. Clinical Studies

a) Method Comparison Study:

The method comparison clinical study was conducted at nine US external sites, American Red Cross Blood Services, IRLs. These sites were selected to provide geographical diversity and included both donor centers and transfusion services:

- St. Louis – IRL, Donor Center and Transfusion Service
- Johnstown, PA – IRL, Donor Center and Transfusion Service
- Omaha, NE – IRL, Transfusion Service
- Detroit, MI – IRL, Donor Center
- Tucson, AZ – IRL, Donor Center
- Baltimore, MD – IRL, Donor Center
- Great Falls, MT – IRL, Donor Center

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- Birmingham, AL – IRL, Donor Center

- Portland, OR – IRL, Donor Center

Two additional IRLs (located at Pomona, CA and Philadelphia, PA) participated in sample collection and enrollment. Testing for these sites was performed by the Great Falls and Johnstown IRLs, respectively. Therefore, a total of 11 sites participated in the study. A referee laboratory (Boise, ID - IRL) was designated to perform discordant results resolution testing when necessary.

Each participating site tested two lots of each investigational BGR in parallel with a currently licensed US product using de-identified leftover samples. The study design included patient samples collected with EDTA and in NBR tubes, donor unit segments representing various anticoagulants/additives such as CPD w/AS-1, CP2D with AS-3, CPD, and CPDA-1, samples with visible interfering substances such as hemolyzed, icteric, lipemic, and Wharton's jelly (cord blood), and samples from patients with a wide variety of diseases that may interfere with tube testing.

Testing was performed according to the assay procedures specified in the DFU for investigational and comparator reagents. The comparator reagents are licensed BGRs for the same testing method (manual tube testing) and have the same testing procedure as the investigational reagents.

The acceptance criteria for each reagent are that the lower bound of the one-sided 95% confidence interval for both Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) should exceed 99%. Summary tables of the method comparison test results for all sites combined are presented below.

Table 8. Method comparison study results Red Cross Anti-C, Lot C-2.

N=1533		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-C Lot C-2	Positive	892	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.66%
	Negative	0	641	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.53%

Table 9. Method comparison study results Red Cross Anti-C, Lot C-3.

N=1533		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-C Lot C-3	Positive	892	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.66%
	Negative	0	641	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.53%

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval.

Table 10. Method comparison study results Red Cross Anti-E, Lot E-2.

N=1679		Comparator Reagent				
		Positive	Negative			
Red Cross Anti-E Lot E-2	Positive	467	2	PPA (point estimate)		100.00%
				PPA (95% 1-Sided LCI)		99.36%
	Negative	0	1210	NPA (point estimate)		99.83%*
				NPA (95% 1-Sided LCI)		99.48%

Table 11. Method comparison study results Red Cross Anti-E, Lot E-3.

N=1679		Comparator Reagent				
		Positive	Negative			
Red Cross Anti-E Lot E-3	Positive	467	3	PPA (point estimate)		100.00%
				PPA (95% 1-Sided LCI)		99.36%
	Negative	0	1209	NPA (point estimate)		99.75%*
				NPA (95% 1-Sided LCI)		99.36%

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval. Three discordant results (two at Johnstown IRL and one at Detroit IRL) were reported for investigational reagent Lot E-3 versus the comparator reagent, and two discordant results were reported for investigational reagent Lot E-2 versus the comparator reagent at Johnstown IRL. The investigational reagent lots demonstrated a weak positive result while the comparator had a negative result. During discrepancy investigation by the referee IRL, the testing with the referee reagent yielded negative results in agreement with the comparator reagent. No root cause for the discrepancy was identified.

ARC added the following limitation to the DFU: "Anti-E – Rarely, weak false positive results (≤ 1+) may be seen. Caution should be used when interpreting test results. In this case, testing is recommended with a different licensed Anti-E blood grouping reagent."

Table 12. Method comparison study results Red Cross Anti-c, Lot LC-2.

N=1606		Comparator Reagent				
		Positive	Negative			
Red Cross Anti-c̄ Lot LC-2	Positive	1090	0	PPA (point estimate)		99.91%
				PPA (95% 1-Sided LCI)		99.57%
	Negative	1*	515	NPA (point estimate)		100.00%
				NPA (95% 1-Sided LCI)		99.42%

*Resolved in favor of the investigational reagent. Resolved PPA 100.00% (99.73 95% 1-sided LCI).

Table 13. Method comparison study results Red Cross Anti-c, Lot LC-3.

N=1606	Comparator Reagent	

		Positive	Negative		
Red Cross Anti-c̅ Lot LC-3	Positive	1090	0	PPA (point estimate)	99.91%
				PPA (95% 1-Sided LCI)	99.57%
	Negative	1*	515	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.42%

*Resolved in favor of the investigational reagent. Resolved PPA 100.00% (99.73 95% 1-sided LCI).

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval. One sample showed discordant test results with the investigational reagent lots versus the comparator reagent at Detroit IRL. The investigational reagent lots resulted a negative result and the comparator resulted a weak positive result. During discrepancy investigation by the referee IRL, the investigational, comparator, and referee reagents all yielded negative results.

Table 14. Method comparison study results Red Cross Anti-k, Lot LK-2.

N=1519		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-k Lot LK-2	Positive	1500	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.80%
	Negative	0	19	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	85.41%*

*The PPA met the acceptance criterion. The NPA was at 85.41% due to the low frequency of antigen-negative samples in the population.

Table 15. Method comparison study results Red Cross Anti-k, Lot LK-3.

N=1519		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-k Lot LK-3	Positive	1500	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.80%
	Negative	0	19	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	85.41%*

*The PPA met the acceptance criterion. The NPA was at 85.41% due to the low frequency of antigen-negative samples in the population.

The predetermined acceptance criteria were met for the PPA. However, the NPA was not met at the one-sided lower 95% confidence interval due to the low frequency of k antigen-negative samples in the population.

Summary Basis for Regulatory Action

The low NPA is acceptable because in addition to the Field Comparison Study, ARC performed an in-house accuracy study which included an additional (b) (4) negative samples all resulting 100% agreement.

The study was supplemented with (b) (4) Kp(a+) samples as the presence of the Kp^a antigen may weaken the expression of the k antigen. The investigational reagent and the comparator Anti-k both showed reactivity of (b) (4). As red cells that express the Kp^a antigen may show weaker reactions with Anti-k than those chosen for positive controls, ARC added the following statement to the DFU: "The presence of the Kp^a antigen may result in the diminished expression of k".

Table 16. Method comparison study results Red Cross Anti-Jk^a, Lot JKA-2.

N=1658		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-Jk^a Lot JKA-2	Positive	1211	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.75%
	Negative	0	447	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.33%

Table 17. Method comparison study results Red Cross Anti-Jk^a, Lot JKA-3.

N=1658		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-Jk^a Lot JKA-3	Positive	1211	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.75%
	Negative	0	447	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.33%

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval.

Table 18. Method comparison study results Red Cross Anti-Jk^b, Lot JKB-2.

N=1512*		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-Jk^b Lot JKB-2	Positive	1021	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.71%
	Negative	0	491	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.39%

*Removed 18 samples from initial study results, due to human error when performing testing.

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Table 19. Method comparison study results Red Cross Anti-Jk^b, Lot JKB-3.

N= 1512*		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-Jk^b Lot JKB-3	Positive	1021	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.71%
	Negative	0	491	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.39%

*Removed 18 samples from initial study results, due to human error when performing testing.

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval.

Results for 18 samples were excluded from the Anti-Jk^b analysis due to protocol deviations caused by human errors:

- ***Deviation 1 (Detroit IRL - 3 samples excluded):*** A technician mislabeled test tubes in a three-sample batch and could not determine which result corresponded to each sample. The technician discarded the mislabeled tubes and repeated testing with properly labeled tubes, which yielded concordant results. This violated the study protocol, which prohibits repeat testing. The referee lab obtained concordant results across all reagent types (investigational lots, comparator, and referee reagents), confirming this was user error rather than a reagent issue.

- ***Deviation 2 (Saint Louis IRL - 15 samples excluded):*** In a 15-sample batch, 14 samples tested negative with investigational reagent Lot JKB-3, while only one tested positive, generating several discrepant results with this lot when compared to the comparator reagent. Investigation revealed that the technician likely failed to add the investigational reagent to the first 14 test tubes but properly added it to the final tube and QC tubes. The technician admitted to not visually verifying the reagent addition to each tube before testing. Due to multiple discrepancies, the entire batch was sent to the referee lab, which obtained concordant results across all reagents tested (investigational lots, comparator, and referee reagents).

Table 20. Method comparison study results Red Cross Anti-S, Lot S-2.

N=1517		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-S Lot S-2	Positive	796	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.62%
	Negative	0	721	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.59%

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Table 21. Method comparison study results Red Cross Anti-S, Lot S-3

N=1517		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-S Lot S-3	Positive	796	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.62%
	Negative	0	721	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.59%

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval.

Table 22. Method comparison study results Red Cross Anti-s, Lot LS-2.

N=1699		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-s̄ Lot LS-2	Positive	1271	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.76%
	Negative	0	428	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.30%

Table 23. Method comparison study results Red Cross Anti-s, Lot LS-3.

N=1699		Comparator Reagent			
		Positive	Negative		
Red Cross Anti-s̄ Lot LS-3	Positive	1271	0	PPA (point estimate)	100.00%
				PPA (95% 1-Sided LCI)	99.76%
	Negative	0	428	NPA (point estimate)	100.00%
				NPA (95% 1-Sided LCI)	99.30%

The predetermined acceptance criteria were met for the NPA and PPA at the one-sided lower 95% confidence interval.

b) Precision Study

The precision study was performed at ARC and two external sites (Houston and Tulsa Immunohematology Laboratories) using (b) (4) of each BGR and a (b) (4) licensed reagent red blood cell precision panel including (b) (4) heterozygous, and negative RBC phenotypes as described below:

- **Anti-C:** (b) (4)
- **Anti-c:** (b) (4)

- **Anti-E:** (b) (4)
- **Anti-k:** (b) (4)
- **Anti-Jka:** (b) (4)
- **Anti-Jkb:** (b) (4)
- **Anti-S:** (b) (4)
- **Anti-s:** (b) (4)

Each sample was tested (b) (4) , by (b) (4) operators at each site, with each operator performing (b) (4) runs per day, separated by at least (b) (4) hours, on five non-consecutive days over a 20-day period.

Results showed 100% positive and negative agreements between the different sources of variation. However, during testing for Anti-Jk^a and Anti-Jk^b one operator from one external site recorded (b) (4) reactions This reaction was weaker than expected. ARC stated that this most often reflects the variability in the manual tube test and too vigorous shaking technique. To address this issue, ARC added the following limitations statement in the DFU for each reagent: "The resuspension of the button in serological reactions in the tube test procedure must be carried out by using gentle agitation. Shaking too strongly may cause the agglutinates to be dispersed."

c) Lot-to-Lot Study

The lot-to-lot study was performed in-house using three conformance lots of each BGR and the same samples as the external precision study. Each sample was tested in (b) (4) , by (b) (4) runs per day, separated by at least (b) (4) hours, on five non-consecutive days, over a 20-day period.

The acceptance criteria were 100% agreement between each conformance lot as well as the different sources of variation. Positive serological reactivity should be (b) (4) with all cells tested and within (b) (4) reaction grade difference between the three conformance lots for each panel cell in each testing event.

Results showed 100% agreement with the expected results and between the different sources of variation and conformance lots. Reactivity strength was greater than (b) (4) in all cells tested and there was no variation of reactivity strength greater than (b) (4) reaction grade (i.e., (b) (4) between the three conformance lots in all cells tested. Test results demonstrate lot-to-lot consistency for the investigational reagents.

d) Pediatrics

Cord blood and neonate samples were included in the comparator study. Test results demonstrate that these sample types do not affect the reagents' performance.

e) Other Special Populations

The Method Comparison Study included samples for patients older than 79 years and the external sites noted samples from patients with hematological diseases that could cause interference with testing. Test results demonstrate testing with these samples do not affect the performance of the trial reagents.

Summary Basis for Regulatory Action

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 BLA and resolved all issues through information requests. 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 the chairperson. All reviewers recommended approval.

9. Labeling

ARC submitted container labels, generic packaging labels, and the DFU documents for review. All labels met the requirements outlined in 21 CFR 660 and 21 CFR 809.10.

The Advertising and Promotional Labeling Branch (APLB) found the proposed DFU, the generic packing and container labeling, acceptable from a promotional and comprehensive perspective.

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 these eight BLAs and issues satisfactorily resolved during the review cycle and were 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 blood grouping reagents include the following:
- Decrease the probability of product shortages for these BGRs by making blood grouping reagents available to immunohematology laboratories and blood establishments. There are few licensed manufacturers of monoclonal blood grouping reagents in the United States; therefore, licensing these products will introduce additional monoclonal BGRs for use in the United States.

- 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 detecting rare antigen variants.

Summary Basis for Regulatory Action

The evaluation of the validation studies, manufacturing processes and method comparison studies reduce the risk associated with licensing these BGRs reagents. In addition, these reagents will be subjected to post market surveillance (medical device reporting and biological deviation reporting) which will identify adverse events associated with these products.

c) **Recommendation for Postmarketing Activities**
   FDA does not recommend post-marketing activities for this submission.