Summary Basis for Regulatory Action

Date: January 23, 2019

From: Darcel Bigelow, Chair
Meihong Liu, Scientific Reviewer

BLA/ STN#s: 125664 and 125665

Applicant Name: SIWA Biotech Corp

Date of Submission: September 26, 2017

MDUFA Goal Date: March 26, 2019

Proprietary Name:
Blood Grouping Reagent, Anti-Fy^{a} (Murine Monoclonal) (Recombinant)
Blood Grouping Reagent, Anti-Fy^{b} (Murine Monoclonal) (Recombinant)

Established Name (common or usual name): N/A

Intended Use/Indications for Use: SIWA Biotech's Blood Grouping Reagents, Anti-Fy^{a} and Anti-Fy^{b}, are for the detection of the corresponding red cell antigens when tested by a direct tube agglutination method.

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

Review Office Signatory Authority: Nicole Verdun 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.**

Office of Compliance and Biologics Quality (OCBQ) Signatory Authority: Mary A. Malarkey, Director, OCBQ

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

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

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

The table below indicates the material reviewed when developing the SBRA.

Document Title	**Reviewer Name**
Product Review(s) (*Product office*) • *Clinical* • *Non-Clinical*	Darcel Bigelow, OBRR/DBCD/DRB Meihong Liu, OBRR/DBCD/DRB Review Memo-November 8, 2018 Review Memo-March 12, 2018 Review Memo-June 27, 2018 Approval Memo-February 13, 2019
Statistical Review(s) • *Clinical* • *Non-Clinical*	TieHua Ng, OBE/DB/TEB Review Memo-November 7, 2017 Review Memo-March 8, 2018 Review Memo-June 28, 2018 Review Memo-November 8, 2018

CMC Review • *CMC (Product Office)*	Darcel Bigelow, OBRR/DBCD/DRB Meihong Liu, OBRR/DBCD/DRB Review Memo-November 8, 2018 Review Memo-March 12, 2018 Review Memo-June 27, 2018 Approval Memo-February 13, 2019
• BioBurden *(OCBQ/DBSQC)*	Hyesuk Kong, OCBQ/DBSQC/LMIVTS Review Memo-May 18, 2018
• *Facilities Review (OCBQ/DMPQ)*	Priscilla M. Pastrana, OCBQ/DMPQ/MRBII Review Memo-November 6, 2017 Review Memo-June 27, 2018
• *Establishment Inspection Report(s) (Product Office and OCBQ/DMPQ)*	Darcel Bigelow, OBRR/DBCD/DRB Meihong Liu, OBRR/DBCD/DRB Teresita C. Mercado, OBRR/DBCD/DRB Priscilla M. Pastrana, OCBQ/DMPQ/MRBII Hector Carrero, OCBQ/DMPQ/MRBII Establishment Inspection Report-January 23, 2019
Labeling Review(s) • *Product Office*	Darcel Bigelow, OBRR/DBCD/DRB Meihong Liu, OBRR/DBCD/DRB Review Memo-November 8, 2018 Review Memo-March 12, 2018 Review Memo-June 27, 2018 Approval Memo-February 13, 2019
• *APLB (OCBQ/APLB)*	Dana Jones, OCBQ/DCB/APLB Review Memo-November 13, 2017

Lot Release Protocols/Testing Plans	Marie Anderson, OCBQ/DBSQC/QAB Review Memo- October 30, 2017 Review Memo-March 9, 2018 Lot Release Protocol Review -July 6, 2018

1. Introduction

SIWA Biotech Corporation (SIWA), located in Oklahoma City, Oklahoma submitted two Biologics License Applications (BLAs), requesting approval to manufacture and distribute Blood Grouping Reagents (BGR), Anti-Fy^a (Murine Monoclonal) (Recombinant) and Anti-Fy^b (Murine Monoclonal) (Recombinant). These BGRs are intended for the detection of the corresponding red blood cell antigens when tested by direct agglutination using the tube method.

SIWA manufactures the *In-Vitro Substance* (antibody (b) (4)) at their Oklahoma City, Oklahoma facility (b) (4) , a contract manufacturer located in (b) (4) , manufactures the *In-Vitro Product* (IVP).

2. Background

The most important antigens in the Duffy blood group system are Fy^a and Fy^b. The Fy^a antigen occurs in approximately 66% of Caucasians and approximately 10% of the Black population. The Fy^b antigen occurs in approximately 83% of Caucasians and 23% of the Black population. These antigens are immunogenic and Fya or Fyb antibodies can cause hemolytic transfusion reactions and hemolytic disease of the fetus and newborn.

Clinical laboratories commonly perform blood group determination using hemagglutination methods. When reagent antiserum is added to red blood cells containing the corresponding antigen, agglutination occurs.

Traditional blood typing reagents are manufactured from monoclonal or polyclonal antibodies produced either from single or multiple B cell clones. Blood Grouping Reagents (BGR), Anti-Fy^{a} (Murine Monoclonal) (Recombinant) and Anti-Fy^{b} (Murine Monoclonal) (Recombinant) are the first recombinant blood grouping reagents approved in CBER.

Chronology Summary of Submission:

September 28, 2017 - Submission Received by FDA
October 11, 2017 – Acknowledgement Letter issued
November 20, 2017 – Filing of submission
July 27, 2018 – Complete Response Letter issued
September 24, 2018 – Response to the Complete Response Letter received

Meetings with FDA:

Summary of Pre-Submission Meeting:

February 24, 2017 - SIWA Biotech Corp requested a pre-submission meeting BQ170018.
March 8, 2017 – Meeting was confirmed for May 17, 2017, 12-1:00 PM.
April 24, 2017 - FDA responded to SIWA's questions.
May 5, 2017 - SIWA canceled the teleconference since FDA adequately responded to their questions.

Marketing History:

There is no foreign marketing history for the above-mentioned blood grouping reagents

Description of the Device:

These blood grouping reagents are recombinant murine IgM monoclonal antibodies produced from Chinese Hamster Ovary (CHO) cell lines established using molecular techniques. The antibodies are diluted in a buffered solution containing bovine albumin, macromolecular potentiators and Sodium Azide as a preservative. These reagents are for In Vitro Diagnostic Use.

Principle of the Assay:

The presence or absence of the Fy^a or Fy^b antigens is determined by testing red blood cells with Blood Grouping Reagents, Anti-Fy^a or Anti-Fy^b, using the direct agglutination tube method. Following centrifugation of red blood cells and Anti-Fy^a or Anti-Fy^b reagents, the presence of the corresponding antigen is indicated by macroscopic agglutination of the red blood cells in the test tube. Lack of agglutination is interpreted as a negative result and indicates the absence of the corresponding antigen.

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*".

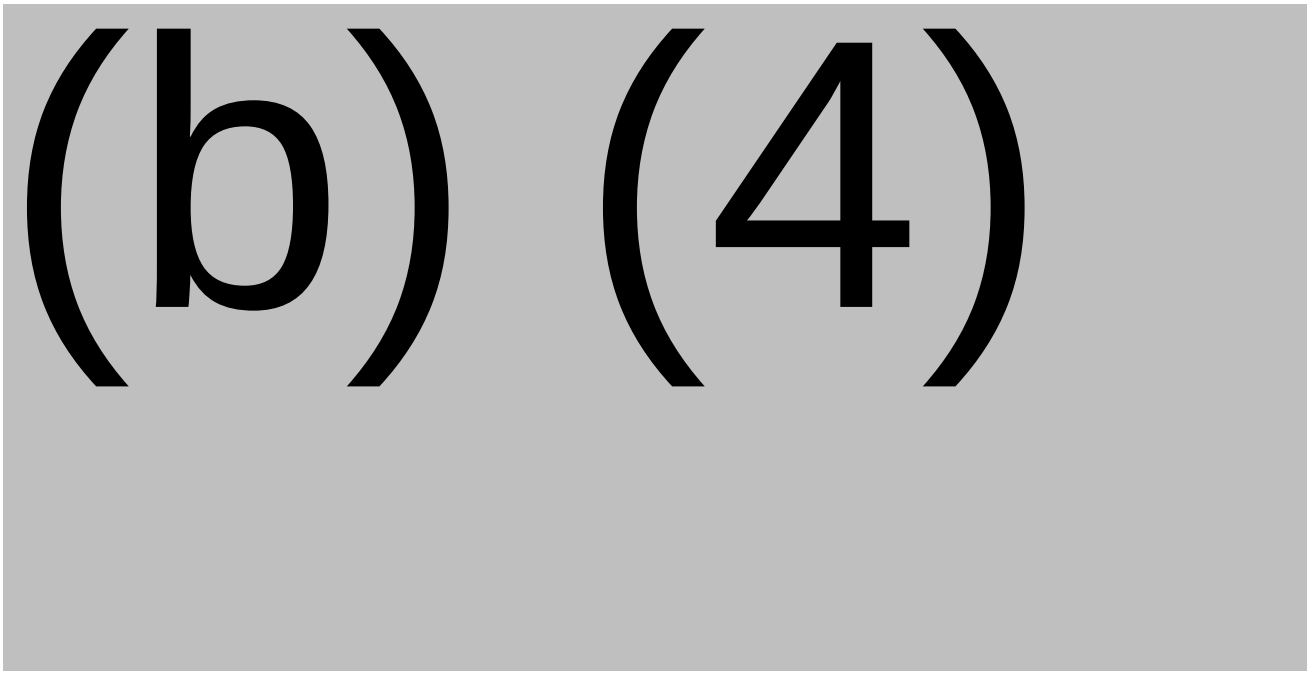
All manufacturing is carried out in a controlled environment.

a. Manufacturing Summary

Cellular Source

The cell lines that produce Anti-Fy^a and Anti-Fy^b specific recombinant mouse IgM antibodies were developed in (b) (4) stages at SIWA:

(b) (4)



(b) (4)

(b) (4)

Raw Materials and Substances

The raw materials were purchased from qualified suppliers. Cell culture media components were purchased as ready to use, sterile liquids. Each component was received and inspected against the Certificate of Analysis (COA).

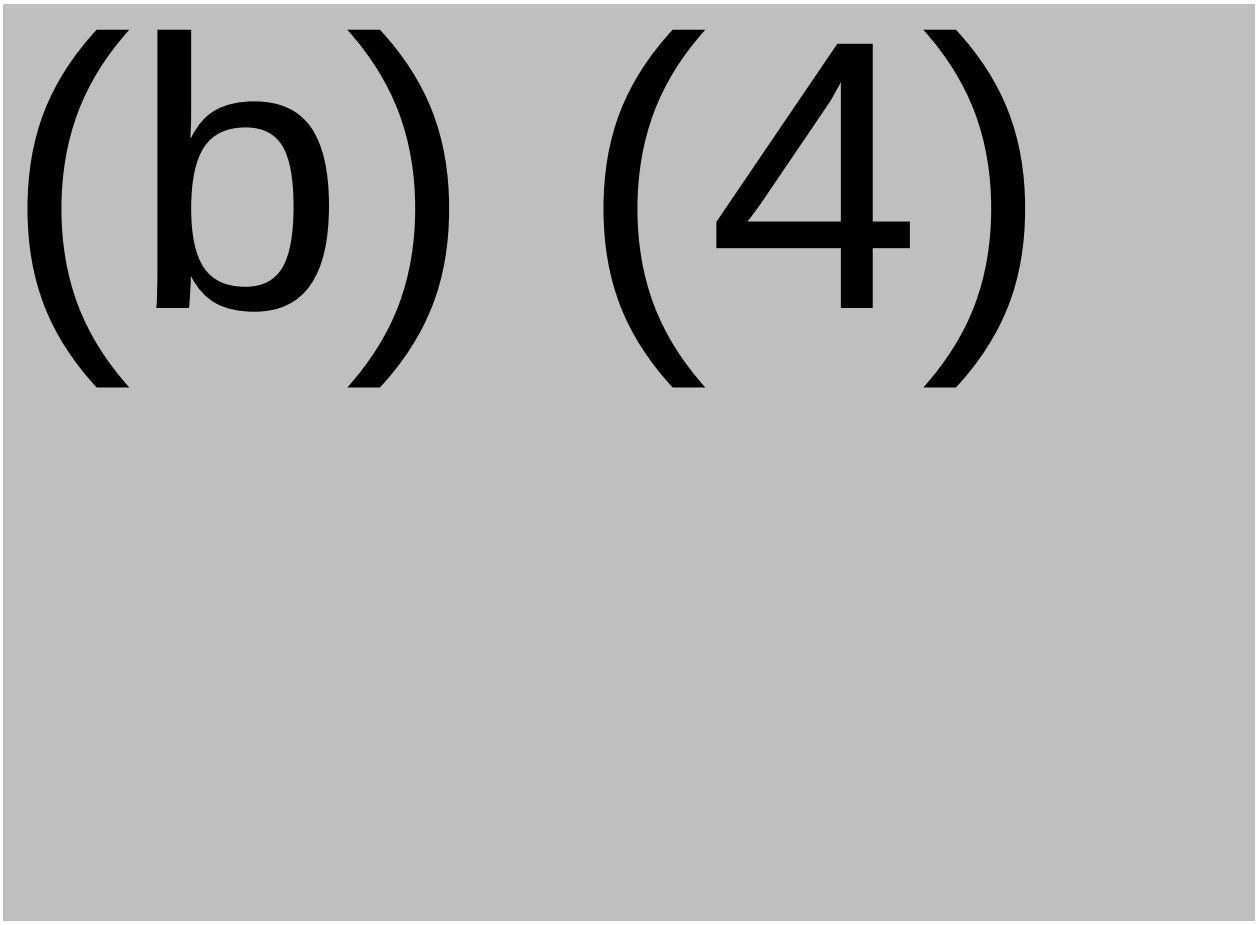
Antibody (b) (4) Manufacturing

The antibody (b) (4) were obtained from the cell culture of clone 310 and clone 401 CHO (b) (4) cells expressing Anti-Fy^a and Anti-Fy^b murine monoclonal IgM antibody. The activity of the antibody (b) (4) in the cell culture media were determined through agglutination assay. The activity of the antibody (b) (4) that have been manufactured to date have demonstrated conformance to the expected results shown in the table below.

Table 1: Activity of Antibody (b) (4)

Clone	Antibody	Fy(a+b-)	Fy(a-b+)	Fy(a+b+)
310	Anti-Fy^a	+	–	+
401	Anti-Fy^b	–	+	+

The following describes the antibody (b) (4) manufacturing process flow



1 page has been determined to be not releasable: (b)(4)

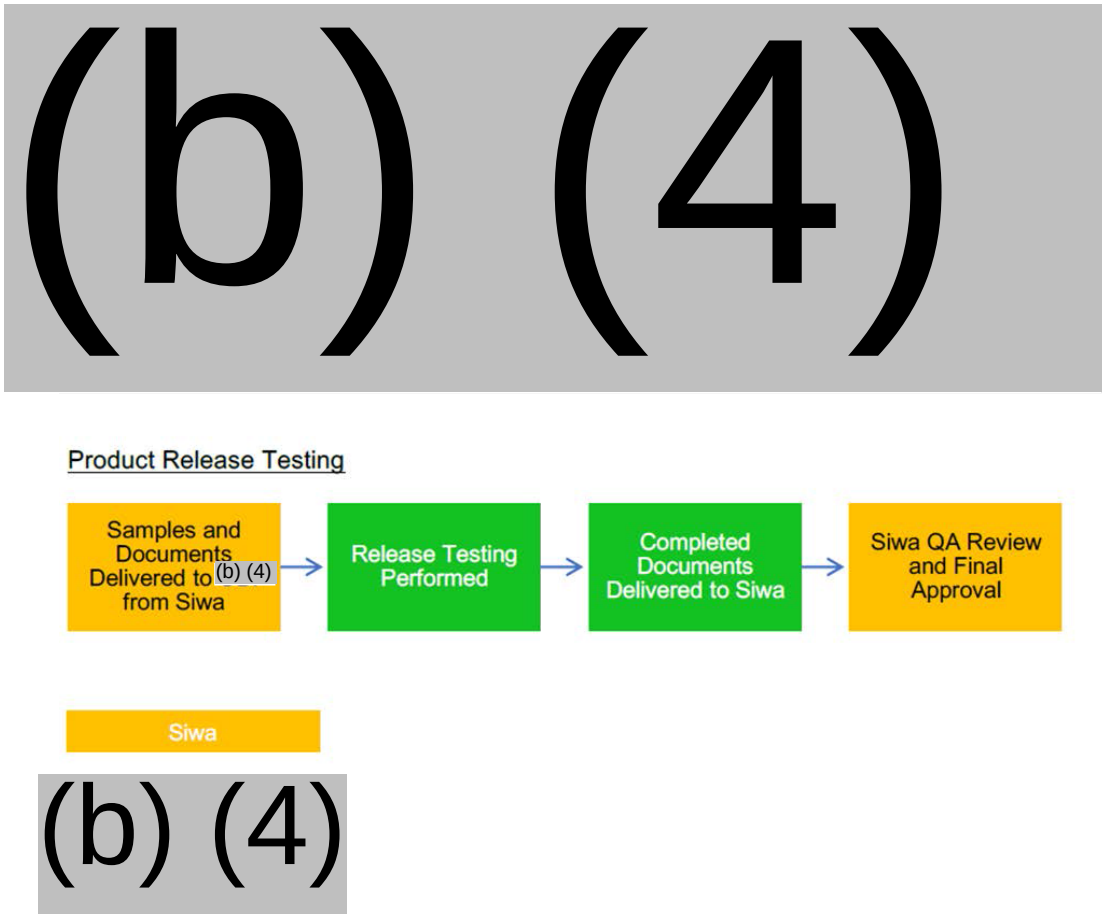
In Vitro Product (IVP) Manufacturing

In Vitro Product (IVP) manufacturing is performed by (b) (4), SIWA (b) (4) located in Oklahoma City, OK. SIWA maintains Quality System Agreements with (b) (4) for the manufacture of the unlabeled in vitro product and with (b) (4) for final testing of the in vitro product. (b) (4) receives the antibody (b) (4) produced by SIWA and performs (b) (4) to (b) (4) the antibody, formulation, (b) (4) and filling of the product into vials with droppers. SIWA determines the antibody activity and provides the (b) (4) instructions to (b) (4) for the formulation of the (b) (4). SIWA performs bulk testing, labeling of final containers, and provides samples of the final containers to (b) (4) for lot release testing.

Representative Certificates of Analysis or Technical Information for the raw materials and components from their approved suppliers are provided in the submission. Only components that meet incoming raw material requirements are used to produce the BGRs.

The following figure shows the IVP manufacturing process flow. This figure was extracted from the submission.

Figure 1: In Vitro Product Manufacturing Process Flow



IVP Manufacturing Description

(b) (4) receives, inspects, accepts and releases the antibody (b) (4) for further manufacturing. The (b) (4)

(b) (4)

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(b) (4)

The date of manufacturing for the IVP is the date of (b) (4) of the lot.

(b) (4)

are delivered to SIWA and stored at 2-8 °C.

SIWA performs labeling and packaging of filled vials, quality assurance for the final acceptance quality limit inspection and then sends the labeled samples for lot release testing by (b) (4).

Specification and Test Methods

The final product testing protocol includes potency, negative specificity, positive specificity and non-specific reactivity.

Table 2: Specificity Testing for Final Release of Anti-Fy^a

Identity	Clone Identity: 310 Visual Inspection: Colorless to straw color Appearance: Clear
Potency	(b) (4)
Specificity	Non-reactive with red blood cells negative for Fy^a antigen
Reactivity	(b) (4)
Microbial Assay	(b) (4)

Table 3: Specificity Testing for Final Release of Anti Fy^b

Identity	Clone Identity: 401 Visual Inspection: Colorless to straw color Appearance: Clear
Potency	(b) (4)
Specificity	Non-reactive with red blood cells negative for Fy^b antigen
Reactivity	(b) (4)
Microbial Assay	(b) (4)

Microbiology

The manufacture of Anti-Fy^a and Anti-Fy^b BGR is microbiologically controlled and these products are considered as non-sterile, multiple use devices.

To date, SIWA only has bioburden results for the (b) (4) conformance lots. All (b) (4) conformance lots were tested for microbial load and the reported results were less than (b) (4)

Based on the results of these conformance lots, an initial alert limit of (b) (4) will be established. Once more data, including non-zero data, have been obtained in testing of future commercial lots, further assessment will be performed, and limits revised as supported by the results.

The products contain 0.1% sodium azide as a preservative. Preservative effectiveness was performed using the (b) (4) The preservative met criteria for category 2 products. The test method suitability study (b) (4) was performed using (b) (4) of each product. Preservative effectiveness was demonstrated.

- (b) (4)

The Conformance Lots

(b) (4) Anti-Fy^a confirmatory lots, (b) (4) Anti-Fy^a conformance lots, (b) (4) Anti-Fy^b confirmatory lots and (b) (4) Anti-Fy^b conformance lots were manufactured at full scale. SIWA reported that all conformance lots yielded adequate antibody with appropriate specificity to formulate into diluent buffer at a potency of (b) (4)

b. CBER Lot Release

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

c. Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Blood Grouping Reagents Anti- Fya [(Cell Line 310) IgM Murine Monoclonal Recombinant, Product Code (b) (4)] and Anti- Fyb [(Cell Line 401) IgM Murine Monoclonal Recombinant, Product Code (b) (4)] are listed in the table below.

Table 4: Facility Information

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
in vitro Substance (b) (4) *; Labeling and Packaging; In-Process Testing* SIWA Biotech Corp. (b) (4)	3012262296	611724092	Pre-License Inspection	DMPQ April 16-20, 25 and 27, 2018 VAI
(b) (4)	(b) (4)		Pre-License Inspection	DMPQ (b) (4) NAI

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
(b) (4)				
(b) (4)	(b) (4)		Waived	ORA (b) (4) NAI
(b) (4)	(b) (4)		Waived	ORA (b) (4) NAI

DMPQ conducted a pre-license inspection (PLI) at SIWA Biotech Corp. April 16 - 20, 25 and 27, 2018 and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved and the inspection was classified as voluntary action indicated (VAI).

DMPQ conducted a PLI at (b) (4) . from (b) (4) . No Form FDA 483 was issued and the inspection was classified as No Action Indicated (NAI).

ORA performed a surveillance inspection of the (b) (4) facility from (b) (4) and the (b) (4) facility from (b) (4) . No Forms FDA 483 were issued and the inspections were classified as NAI.

d. Environmental Assessment

The BLAs included a request for a 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 *In-Vitro Product* is filled into 5mL (b) (4) borosilicate glass vial with 18mm screw neck and natural latex rubber 5mL glass dropper assembly cap. The dropper is made of (b) (4) borosilicate glass vial. Both items are manufactured by (b) (4) . SIWA conducted the container closure integrity testing at the Oklahoma City, OK facility, employing (b) (4) (b) (4) method; all acceptance criteria were met.

4. Software and Instrumentation

Not Applicable

5. Analytical Studies

Stability Studies

The proposed expiration date for final container Anti-Fy^a and Anti-Fy^b IVP is 2 years. Real time stability testing was conducted using three conformance lots, testing at every (b) (4) months during two-year storage at 2-8° C plus (b) (4) months past the proposed expiration date. The agglutination test method used for assessing reactivity and potency of both Anti-Fy^a and Anti-Fy^b BGRs was performed according to (b) (4)

The acceptance criteria are listed below:

- Potency: (b) (4) .

- Reactivity: (b) (4) .

SIWA has completed 15 months of stability testing for Fy^a and 21 months for Fy^b for the 24 months shelf life. All acceptance criteria were met. The study is ongoing.

Open vial stability testing was conducted on the three conformance lots over (b) (4) consecutive business days. (b) (4) . The vial was tested for potency and specificity at (b) (4) The acceptance criteria were met.

Temperature excursions was conducted on the three conformance lots with the product vials held at (b) (4) labeled storage temperature (2-8 °C) for the remainder of the expiration dating period. These vials were tested along with untreated vials at the defined time points and (b) (4) past expiration. To date, the temperature excursion stability testing has been performed for 15 months for Anti-Fy^a and 24 months for Anti-Fy^b. All acceptance criteria were met. Stability testing is ongoing.

Post-approval stability testing will be with a minimum of (b) (4) licensed product manufactured per calendar year. The minimum time point testing is at mid-point, expiration and (b) (4) past expiration.

Shipping Study

This study was performed by shipping the product, by (b) (4) shipping, to (b) (4) geographical diverse locations during (b) (4) temperature months. The (b) (4) temperature months were the (b) (4) week of (b) (4) through the (b) (4) of (b) (4) (b) (4) and products were shipped to (b) (4) The (b) (4) temperature months were (b) (4) through (b) (4) (b) (4) and products were shipped to (b) (4)

(b) (4) .

(b) (4) shipments were sent to the locations above on (b) (4) different days of the week in (b) (4) and (b) (4) and (b) (4) and (b) (4) . Each shipment consisted of (b) (4) shipping boxes. (b) (4) . A temperature data log was paced in the center of the box as it was being filled.

Once received, the recipient opened the boxes and inspected the contents for leakage and/or breakage. The inspection results were documented and returned, along with the temperature data logger to SIWA Biotech.

There was a total of (b) (4) packages for each BGR shipped to each location for a total of (b) (4) shipments. The temperature results showed that the (b) (4) temperatures and shipping duration are within the validated temperature range in the temperature excursion study above.

SIWA also performed a study to access the impact of the stability of the product after the packages were shaken. The potency and reactivity results were acceptable.

Sample Aging and Anticoagulant Studies

The study was conducted with blood units (from (b) (4) randomly selected donors with known Duffy phenotypes) containing the following anticoagulants: ACD, CPD, CPDA-1 and CP2D. In addition, an EDTA blood sample was used as a reference to compare the results obtained with the other anticoagulants. The final storage bag with AS-1 and AS-3 additive solutions for (b) (4) donors was also tested. The tests were performed at the end of the expiration date of the blood units plus (b) (4). The acceptance criterion was that all samples demonstrate agreement in its Duffy antigen type with the donor red blood cells in EDTA.

Table 5: Samples from each anticoagulant used in the collection of the donor tested

(b) (4)

All samples demonstrated agreement in its Duffy antigen type with the donor red blood cells in EDTA.

SIWA conducted an additional sample aging and anticoagulant study which consisted of at least (b) (4) antigen positive and (b) (4) antigen negative red blood cells samples stored in the following anticoagulants for (b) (4) days past the sample expiration date: ACD, CPD, CPD with AS-1, CPD with AS-5, CPDA-1, CP2D and CP2D with AS-3. All samples demonstrated agreement between the Duffy antigen type determined at least (b) (4) days after the sample expiration date using Siwa's Anti-Fy^a and Anti-Fy^b BGRs.

Lot-to-Lot Reproducibility Study

The study was performed using three lots of each BGR and a four-sample Precision Panel with phenotypes $Fy^{(a+b-)}$, $Fy^{(a+b+)}$, $Fy^{(a-b+)}$ and $Fy^{(a-b-)}$. The four samples were tested by (b) (4) technologist in (b) (4) on (b) (4) consecutive days for a total of (b) (4) results.

Results showed that all three lots produced the expected results with antigen positive samples having reactivity scores of (b) (4) Negative results were obtained with antigen negative samples. No discrepancies were observed.

SIWA performed additional lot-to-lot reproducibility studies to provide additional data

points. Each sample was tested over (b) (4) nonconsecutive days in (b) (4) and (b) (4) by (b) (4) operator using 3 lots of reagent for a total of (b) (4) data points per sample.

Results showed that all three lots produced the expected results. All negative results performed as expected. No discrepancies were observed.

Precision Study: Reproducibility and Repeatability Study

The reproducibility and repeatability studies were conducted with one lot of SIWA Anti-Fy^a and one lot of Anti-Fy^b and a four-sample Precision Panel with phenotypes $Fy^{(a+b-)}$, $Fy^{(a+b+)}$, $Fy^{(a-b+)}$ and $Fy^{(a-b-)}$. The reproducibility studies were conducted at three sites: (b) (4) . The testing was performed by (b) (4) technologists at each site using (b) (4) sets of equipment performing (b) (4) runs per day in (b) (4) on (b) (4) non-consecutive days over a (b) (4)-day period. The sponsor requested to perform these studies over a (b) (4)-day period instead of (b) (4)-day period because extended storage may result in degradation of the sample red blood cells or a weakened expression of the Duffy antigens (BQ170018). For each BGR lot, there were a total of (b) (4) (3 sites x (b) (4) operators x 1 lot x (b) (4) runs x (b) (4) replicates x (b) (4) days) results by (b) (4) tube method.

The reproducibility testing for Anti-Fy^a showed positive results for samples with Fy^a antigen and negative results for samples without Fy^a antigen. Similarly, Anti-Fy^b showed positive results for samples with Fy^b antigen and negative results for Anti-Fy^b for samples without Fy^b antigen. There was 100% agreement obtained.

The repeatability study was a subset of the reproducibility study selecting one site (b) (4) and (b) (4) technician before the start of the precision study. There was 100% percent agreement with the expected results.

6. Clinical Studies (Clinical Study – SBC001)

a. Comparison Study

The Comparison Studies were performed at Blood Center of Wisconsin (BCW) in Madison, WI, LifeShare Blood Centers (LS) in Shreveport, LA, and Heartland Blood Center (HBC) in Aurora, IL.

The studies involved three lots of each of the BGRs. A total of 1407 samples were tested in parallel with currently licensed US products. Samples were de-identified, left-over, donor and patient samples that were re-labeled by SIWA. Overall, 51.8% of the testing were conducted on patient samples and 48.2% were donor samples. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents.

The following samples from patients with various diseases and conditions and samples with interfering substances were included in the clinical study.

Table 6: Samples from Patients with Different Conditions and Samples with Interfering Substances

Sample Type	Total
Elderly (>79)	32
Newborn (<1 mo)	26
Myeloma	21
Pregnant Women	50
Lymphoma	22
Leukemia	20
Sickle Cell Anemia	25
Hemolyzed	10
Lipemic	11
Icteric	1
DAT Positive	15

Total	**233**

Positive Percentages Agreement (PPA) and Negative Percentages Agreement (NPA) between SIWA and the comparator methods were calculated for each reagent's specificity. The analysis of the results was performed by pooling the data from all sites. The acceptance criterion for each of the reagents were established to achieve > 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive agreement.

All discordant results were further resolved by the referee laboratory using the (b) (4)

Tables 7 and 8 show a summary of the comparison test results for Anti- Fy^a and Anti Fy^b for all trial sites.

Table 7: Summary of Results for BGR Anti-Fy^a and Comparator Reagents
(b) (4)

	Number	Percent Agreement	Lower 95% CI	Acceptance Criteria
PPA	804/809*	99.4%	98. 7%	99%
NPA	573/574	99.8%	99.2%	99%

The predetermined acceptance criterion was met for the negative percent agreement at the one-sided lower 95% confidence interval. However, the study did not meet the acceptance criterion for the positive percent agreement at the one-sided 95% lower confidence limit: 98.7% versus >99% concordance. Five of the six discordant samples were using the (b) (4) and one discordant sample was not tested due to age.

There were 6 discordant samples out of 1383 samples tested.

- 5 discordant samples tested positive with the comparator BGR, but negative with SIWA BGR.
    - 3 tested $Fy^{(a-)}$ by (b) (4) and thus were concordant with SIWA BGR.
    - 1 tested $Fy^{(a+)}$ by (b) (4) and was discordant with SIWA BGR.
    - 1 was not tested because of the sample age.
- 1 discordant sample tested negative with the comparator BGR but positive with SIWA BGR.
    - This sample tested $Fy^{(a-)}$ by (b) (4) and remained discordant with SIWA BGR.

Although the study did not meet the positive percent agreement acceptance criteria, we are accepting the results of the study because three of the six discordant samples were concordant with SIWA by the molecular method.

Table 8: Summary of Results for BGR Anti-Fy^b and Comparator Reagents

(b) (4)

	Number	Percent Agreement	Lower 95% CI	Acceptance Criteria
PPA	900/905	99.4%	98.8%	99%
NPA	469/481	97.5%	96.0%	99%

The predetermined acceptance criterion was met for positive percent agreement at the one-sided lower 95% confidence interval. However, the study did not meet the acceptance criterion for the negative percent agreement at the one-sided 95% lower confidence limit: 97.5% versus >99% concordance.

There were 17 discordant samples out of 1386 samples tested. Twelve of the 17 discordant results were resolved using the (b) (4). One discordant result was resolved using repeat serology with an FDA-licensed Duffy BGR due to insufficient sample to conduct (b) (4) testing. Four were not

tested due to sample age.

- 5 discordant samples tested positive with the comparator BGR, but negative with SIWA BGR.
    - 1 tested Fy^b (GATA), silencing mutation, by (b) (4) and thus was concordant with SIWA BGR.
    - 1 tested $Fy^{(x)}$ (Fy^b weak) by (b) (4) and was discordant with SIWA BGR.
    - 1 tested $Fy^{(b+)}$ by (b) (4) and was discordant with SIWA BGR.
    - 2 were not tested due to sample aging.
- 12 discordant samples tested negative with the comparator BGR, but positive with SIWA BGR.
    - 6 tested $Fy^{(x)}$ (Fy^b weak) by (b) (4) and was concordant with SIWA BGR.
    - 1 tested $Fy^{(b+)}$ by (b) (4) and was concordant with SIWA BGR.
    - 1 tested $Fy^{(b+)}$ by repeat serology with a FDA-licensed Duffy BGR and was concordant with SIWA BGR.
    - 1 tested $Fy^{(b-)}$ by (b) (4) and remained discordant with SIWA BGR.
    - 1 tested Fy^b (GATA), silencing mutation, by (b) (4) and thus was discordant with SIWA BGR
    - 2 were not tested due to sample aging.

Although the study did not meet the acceptance criterion for the negative percent agreement, we are accepting the results of the study since eight of the discordant results were concordant with SIWA by the molecular method, and one of the discordant results was concordant with SIWA by repeat serological testing.

b. Pediatrics

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

c. Other Special Populations

The study included samples from patients with various diseases and conditions as listed Table 6.

7. Advisory Committee Meeting

BGR, Anti-Fy^{a} and Anti-Fy^{b} exist in the market. The SIWA reagents are manufactured with recombinant and culture technologies. The manufacturing processes and final products are similar to previous BGRs. Therefore, an advisory committee meeting was not required.

8. Other Relevant Regulatory Issues

There are no other relevant regulatory issues for this submission. The review committee members reviewed their specific sections of the BLAs and resolved any issues through information requests with SIWA. 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 recommend approval.

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. The Product Office found that all labels met the requirements outlined in 21 CFR Part 610.62, 610.64, 660.28 and 21 CFR Part 809.10.

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

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 the 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 SIWA Anti-Fy^{a} (Murine Monoclonal) (Recombinant) and Anti-Fy^{b} (Murine Monoclonal) (Recombinant) BGRs are to improve the safety of the blood supply by providing a recombinant monoclonal reagent manufactured that can increase the probability of the detection of rare antigen variants. In addition, the test method for these reagents does not require an indirect antiglobulin phase; this allows for a quicker turnaround time.

The evaluation of the validation and clinical studies and the manufacturing process reduces the risks associated with licensing a new BGR reagent. In addition, these BGRs will be subject to post market surveillance (Medical Device Reporting) which will identify adverse events associated with the product.

11. Recommendation for Postmarketing Activities

We did not recommend any postmarketing commitments.