Summary Basis for Regulatory Action

From: Darcel Bigelow, Chair of the Review Committee

***BLA*/STN#:** See the table below

Applicant Name: DIAGAST

Date of Submission: August 17, 2016

MDUFA Goal Date: February 3, 2018

Proprietary Name/ Established Name:

Table 1

Submission Tracking Number	Name of Biological Product	Cell Line(s)	Intended Use
BL 125618/0	Blood Grouping Reagent, Anti-s (Human/Murine Monoclonal), IgG	P3YAN3	This reagent is designed to determine the presence of blood group antigen s on the surface of human red blood cells by manual method.
BL 125627/0	Blood Grouping Reagent, Anti-P1 (Murine Monoclonal)	650	This reagent is designed to determine the presence of blood group antigen P1 on the surface of human red blood cells by manual method.
BL 125628/0	Blood Grouping Reagent, Anti-Fy^a (Human/Murine Monoclonal), IgG	DG-FYA-02	These reagents are designed to determine the presence of the blood group antigen Fy^a on the surface of human red blood cells by manual method.

Intended Use/Indication: (copied from page one of the final draft package inserts)

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

Offices Signatory Authority: Jay Epstein, MD, Director, Office of Blood Research and Review

☐ I concur with the summary review.

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

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

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

Table 2: Material Reviewed

Document title	**Reviewer name, Document date**
Clinical Review	Ricardo Espinola, OBRR/DBCD/DRB *January 30, 2017* *May 22, 2017* Darcel Bigelow, OBRR/DBCD/DRB *December 14, 2017* *January 29, 2018*
Non-Clinical Review	Ricardo Espinola, OBRR/DBCD/DRB *January 30, 2017* *May 22, 2017* Darcel Bigelow, OBRR/DBCD/DRB *December 14, 2017* *January 29, 2018*
Statistical Review	Paul Hshieh, OBE/DB/TEB *January 30, 2017* *April 24, 2017*
CMC Product Review	Ricardo Espinola, OBRR/DBCD/DRB *January 30, 2017* *May 22, 2017* Darcel Bigelow, OBRR/DBCD/DRB *December 14, 2017* *January 29, 2017* Simleen Kaur, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden *December 15, 2016*

CMC Facilities Review	Priscilla Pastrana, OCBQ/ DMPQ/BII *December 14, 2016* *April 3, 2017* *December 21, 2017*
Labeling Review	Ricardo Espinola, OBRR/DBCD/DRB *January 30, 2017* *May 22, 2017* Darcel Bigelow, OBRR/DBCD/ DRB *December 14, 2017* *January 29, 2017* Dana Jones, OCBQ/DCM/APLB *March 14, 2017*
Lot Release	Varsha Garnepudi, OCBQ/ DBSQC *April 4, 2017* *December 18, 2017*

1. Introduction

DIAGAST submitted a bundled original Biologics License Application requesting approval to manufacture the Blood Grouping Reagents listed in Table 1. DIAGAST will manufacture the seven Blood Grouping Reagents (BGRs) at their licensed facility (Establishment Registration Number 3006261638) in Loos, France for Grifols Diagnostic Solutions Inc who will distribute the products.

BGRs are used in blood banks to test blood donors and patients and perform compatibility testing. Clinical laboratories commonly perform blood group determination using hemagglutination methods. The principle of the hemagglutination test dates back to the 1900's when Karl Landsteiner identified the A, B, and O blood groups. The same principle applies to the other blood group systems. When reagent antiserum is added to red blood cells containing the corresponding antigen, agglutination occurs.

Intended Use/Indications for Use:
The Intended Use statements are listed above in Table 1.

Chronology:
CBER received the original submission on August 17, 2016 and received 14 amendments from DIAGAST in response to 11 Information Requests and one Complete Response Letter.

2. Background

Meetings with FDA:
DIAGAST requested a pre-submission meeting (BQ150291) with FDA on July 2, 2015. DIAGAST submitted questions regarding the proposed bundled BLA

submissions, and the proposed clinical protocol and clinical study. On September 14, 2015, FDA submitted the responses to DIAGAST and on September 24, 2015 a pre-submission meeting was held regarding the planned clinical study. Based on the discussion at the meeting, an amended protocol was submitted to FDA on October 5, 2015. FDA provided written responses to subsequent admendments to the protocol.

Description of the Device:
These BGRs are human and/or murine monoclonal antibodies derived from in vitro culture of related cell lines listed in table 1. The formulation contains bovine serum albumin, sodium arsenite (0.02%) and sodium azide (<0.1%). The BGRs are manually filled in 14 mL glass vials with a semi-automatic dispenser and dropper capped manually. These BGRs are used to determine the presence of blood grouping antigens s, P1, Fy^a on the surface of human red blood cells by manual method.

Principles of the Assay:
The manual technique employed in a tube utilizes the principle of hemagglutination. Test red blood cells bearing an antigen agglutinate in the presence of the reagent containing the corresponding antibody and produce macroscopic agglutination of the red blood cells in the test tube.

3. Chemistry Manufacturing and Controls (CMC)

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

a) Manufacturing Summary

DIAGAST manufactures the *In-Vitro* Substance (IVS) for Anti-s, P1, Fy^a at their facility, located at Parc Eurasanté, 251, av. Eugéne Avinée, 59120 Loos, France.

In vitro Substance (IVS)

The IVSs produced by DIAGAST are identical to the licensed FFMU products.

Table 3: In-Vitro Substances Produced By DIAGAST

BGR *In vitro* Substance Concentrate Specificity	**Monoclonal Antibody Clone ID**	***In vitro* Substance DIAGAST Code**	**FFMU BGR License #**
Anti-s	P3YAN3	(b) (4)	BL125209
Anti-P1	650		BL125210
Anti-Fy^a	DG-FYA-02		BL125211

(b) (4)

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

(b) (4)

DIAGAST provided representative CoAs or Technical Data Sheets for the raw materials and components from their approved suppliers. Only components that meet incoming raw material requirements are used to produce the BGRs. The raw materials, components, and the IVS are in-process tested according to the CoA or based on in-process testing established at DIAGAST.

In-vitro Product (IVP)

DIAGAST manufactures the IVPs at their licensed facility, located at Loos France.

The manufacturing process includes (b) (4), formulation, filtration, labeling and in-process and final Quality Control testing. Multiple products are manufactured in the same manufacturing areas and share manufacturing equipment. The contamination precautions which include air quality control, cleaning, segregation, line clearance, change over and prevention of cross contamination, gowning requirements, (b) (4) control and contamination prevention are the same as used in the licensed products. All raw materials used for the manufacture of the BGRs are provided by qualified suppliers and accepted based upon the supplier Certificates of Analysis (CoA) and qualifying tests, as applicable.

Manufacturing Process Description

(b) (4)

The BGR IVPs are filled in 14 mL glass vials in a (b) (4). The vials are filled manually with a semi-automatic dispenser and capped manually with dropper caps in a (b) (4). Caps are tightened using the (b) (4) semi-automatic screwing-capping machine. Cap (b) (4) is checked using (b) (4) equipment. The IVPs already filled and capped are stored at 2 °C to 8 °C.

Vial labels are printed. The final product is packed and inspected for proper

labeling to assure that vial and kit labels were properly printed. The final products are stored at 2 °C to 8 °C until release. The final batch release is performed by Quality Assurance.

Date of Manufacture
The date of manufacture (DOM) of the IVPs produced from (b) (4) IVS is the date of (b) (4) . The DOM of the BGR IVPs produced from 2 °C to 8 °C IVS is the date of (b) (4) .

Specification and Test Methods
Specificity, activity, titration, appearance, and volume testing are performed on the (b) (4) filled final product vials, using the standard manual tube agglutination method. All acceptance criteria were met.

Table 5: BGR *In Vitro* Product Acceptance Criteria

BGR *In vitro* Product Stage	Testing Performed	Acceptance Criteria
Final QC Testing (Manual Method)	Appearance	Absence of cloudiness and particles
		Color conforms to Technical Product Specifications
	Specificity	No reaction observed with all RBC tested (from Table 6)
	Activity	Positive reaction with all RBC tested (from Table 6)
	Potency	≥Minimum titer (from Table 6) and within (b) (4) of Reference Standard

Microbiology
The BGRs are microbiologically controlled products considered to be non-sterile, multiple use devices.
Microbiological control of the IVP is accomplished as follows:

- Environmental and in-process controls are in place to limit the presence of micro-organisms, and therefore limit potential contamination of the product through environmental control and aseptic technique.
- The filling process is performed under Class (b) (4) conditions with a Class (b) (4) background environment.
- The final product is (b) (4) to remove microorganisms and tested with a validated bioburden method.
- The final product contains the preservative, (b) (4) sodium azide and 0.02% arsenite, to inhibit growth of micro-organisms.

b) CBER Lot Release

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

c) Facilities review/inspection

Facility information and data provided in this BLA bundle was reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the products listed in the BLA bundle is listed in the table below. The activities performed and inspectional history is noted in the table.

Name/Address	FEI number	DUNS number	Results/Justification
in vitro Substance *in vitro Product* *Release Testing* Diagast EuraSante Parc 215 Avenue Eugène Avinée 59374 LOOS, Cedex, France	3006261638	381527001	Team Biologics February 13-21, 2017 VAI

Team Biologics performed a surveillance inspection of the LOOS, Cedex, France facility February 13-21, 2017. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental Assessment

This BLA bundle included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure

The in vitro products from this BLA bundle are filled into 14mL (b) (4) Glass Vial (b) (4) supplied by (b) (4) and 14 mL glass dropper assembly cap supplied by (b) (4) . Diagast conducted the container closure integrity testing at the LOOS, Cedex, France facility, employing (b) (4) verification and (b) (4) test; all acceptance criteria were met.

4. Analytical Studies

Analytical studies included stability, anticoagulant, and precision studies.

Stability Studies

Three lots of each BGR IVP produced were tested to support the shelf life of up to 24(b) (4) months stored at 2 °C to 8 °C in a 14 mL glass vial. DIAGAST used the

standard manual tube agglutination methods for BGR for testing potency and specificity of the stability samples.

Anti-s, Anti-P1 and Anti-Fy[a] BGR IVPs products were tested at 6, 9, 12, 15, 18, 21 and (b) (4) months for validation of current shelf life for the target shelf life of 24 months.

Table 6 shows details of the red blood cells used for specificity, activity, and titration testing and the corresponding acceptable minimum titer for each antibody.

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

Table 6: RBC's Used for Specificity, Activity and Titration Testing

***In vitro* Product**	**Negative Specificity RBC Used (1)**	**Positive Specificity RBC Used (2)**	**Potency Titration**		
			RBC Used	**Minimum Titer**	**Neat**
Anti-s (MNS4)	(b) (4)				
Anti-P1					
Anti-Fy[a] (FY1)					

(b) (4)

Microbiology testing included (b) (4)

In addition to the real-time stability study on the IVP, DIAGAST also performed a simulated transport stability study. This study was performed between DIAGAST (Loos, France) and Grifols Diagnostic Solutions Inc. (GDS) warehouse provider in the US ((b) (4)) from (b) (4) . Each shipment included samples of three conformance lots of each BGR IVP

kit, (b) (4) packed in a corrugated carton filled with packing paper. A (b) (4) temperature recorder was packed in the carton along with the product. DIAGAST tested the BGR IVP kits for appearance, specificity, and potency (b) (4) .

At GDS (b) (4) the shipment was checked for integrity and stored unopened at 2 °C to 8 °C until it was shipped back to DIAGAST. Once back at DIAGAST, the shipment was checked for integrity and the data recorder was read and analyzed. The product was removed and stored at 2 °C to 8 °C until the performance of stability testing. Specificity, potency and acceptance criteria are the same as for the real-time stability testing as previously described in this review memo. The testing results met the acceptance criteria for the time period included in the stability reports.

Based on the results of the Stress Testing, DIAGAST determined that the recorded temperatures during shipment from DIAGAST to Grifols must remain below (b) (4) with (b) (4) and must take no more than (b) (4) for the shipping method to be acceptable.

Anticoagulant Studies
Two anticoagulant studies were performed at (b) (4) . In the first study, whole blood donor samples (EDTA vs Sodium Citrate and EDTA vs Lithium Heparin) were used. Samples were provided by the (b) (4) , which were tested at 1-3 days and (b) (4) days of collection using these blood grouping reagents for blood typing. There were no differences between the results obtained at the beginning of the study and at the end of the study.

In the second study, (b) (4) whole blood donations were collected in different anticoagulants (CPD, CP2D, CPDA-1 and ACD) and then (b) (4) of these donations were used to manufacture red blood cells (RBCs). For these (b) (4) products, storage solutions were added ((b) (4) , AS-1, and AS-3).

All results for all the samples tested with the DIAGAST BGR throughout the study obtained 100% agreement with the positive or negative results initially obtained with the FDA licensed reagents and the initial EDTA samples tested with the DIAGAST BGR. No discrepancies were observed and no large differences in positive results (greater than 2) from the initial results or DIAGAST results were obtained.

Precision Studies (Reproducibility and Repeatability)

The Reproducibility and Repeatability Study was performed to demonstrate that the test reagent generates reproducible and accurate results using a panel of well-characterized samples across different sites, using different operators, and on different days. The acceptance criterion stated there should be 100% agreement between the test outcomes and the expected results.

The Precision Sample Panel was shipped to the three clinical study sites. . The

testing was performed by (b) (4) operators over (b) (4) non-consecutive days, on one lot of product each with replicate testing performed by each operator within each run.

There were no discrepancies observed among the three sites. Results showed 100% of agreement for all the BGRs. No variability was observed in the strength of reactions among the operators.

5. Clinical Studies

a) Clinical Performance Studies (Comparison Study)

DIAGAST conducted a clinical study to evaluate the performance of the BGRs for their intended use in the hands of end-users in clinical settings. The clinical study was performed at five United States (US) clinical sites which included Blood Center of Wisconsin (BCW), LifeShare Blood Centers (LBC), American Red Cross Blood Center Pacific Northwest (PRC), American Red Cross Blood Center Northeast Pennsylvania (NRC), and Emory University Hospital (EUH).

The studies involved three lots of each of the BGRs. A total of 11,604 de-identified clinical specimen samples were tested in the comparison study, resulting in 45,695 actual tests. Samples were left-over blood samples from patient or donor testing. Overall, 63.2% of the test profiles were conducted on patient samples and 36.8% were donor samples. The testing was performed in a blind manner.

Positive Percentages Agreement (PPA) and Negative Percentages Agreement (NPA) between the DIAGAST and the comparison methods were calculated for each reagent's specificity. The analysis of the results was performed on pooled data from all sites. The acceptance criteria were established to achieve a low confidence bound estimated with 95% confidence for both the PPA and the NPA of at least 99% concordance.

The results of the study are shown in the table below.

Table 7: Statistical Analysis for Comparison Study in Pooled Samples

		Number	Lower 95% CI	Acceptance Criteria	Point Estimate
Anti-s	NPA	131/132	96.46%(1)	99%	99.24%
	PPA	1139/1140	99.58%	99%	99.91%
Anti-P1	NPA	266/271	96.16%(2)	99%	98.15%
	PPA	1000/1000	99.70%	99%	100%
Anti-Fy[a]	NPA	506/507	99.07%	99%	99.80%
	PPA	773/773	99.61%	99%	100%

(1)The NPA for Anti-s was below 99% (96.46%) and did not meet the pre-determined acceptance criteria. The factor contributing to the NPA not meeting the 99% acceptance criteria was the small sample size of 132 due to the low

frequency of s negative phenotype in the U.S. population (11% in Whites and 7% in those of African descent).

(2)The NPA for Anti-P1 was below 99% (96.16%) and did not meet the pre-determined acceptance criteria. The factors contributing to the NPA not meeting the 99% acceptance criteria were the following.

- There were 5 discordant samples. Five negative results were obtained by the comparative method but positive results were obtained by the Diagast reagents. The Referee method confirmed that for 3 of the 5 discrepant results, the DIAGAST results were correct. The other 2 were very weakly reactive with anti-P1 and upon repeat these 2 samples were negative.
- There were not enough P1 negative samples in the study.

b) Other Special Populations

Hospital patients included subjects from all ages including newborns and pediatric patients. A total of 715 tests were done on 143 samples from cord blood or pediatric patients.

6. Advisory Committee Meeting

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

7. Other Relevant Regulatory Issues

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

8. Labeling

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

9. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

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

b) Risk/ Benefit Assessment

The benefits of licensing DIAGAST Anti-A (Murine Monoclonal), Anti-B (Murine Monoclonal), Anti-D (Human/Murine Monoclonal), Anti-D (Human/Murine Monoclonal Blend), Anti-C (Human/Murine Monoclonal), Anti-c (Human/Murine Monoclonal), Anti-E (Human/Murine Monoclonal), Anti-e (Human/Murine Monoclonal) and Anti-K (Human/Murine Monoclonal) are to 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 clinical studies and the manufacturing process reduces the risks associated with licensing a new BGR reagent.

c) Recommendation for Postmarketing Activities

We did not recommend any postmarketing activities.

Concurrence Page

Application Type and Number: BLA 125618, 125627, 125628,

COMMUNICATION TYPE: SBRA-IVD BGR

History:
Created: Darcel Bigelow/November 2, 2017
Revised: Orieji Illoh/November 24, 2017
Revised: Darcel Bigelow/December 5, 2017
Revised: Nicole Verdun/January 31, 2018
Revised: Darcel Bigelow/February 1, 2018

Concurrence:

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