



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 125615/0	Blood Grouping Reagent, Anti-A (Murine Monoclonal)	9113D10	This reagent is designed to determine the presence of ABO system blood group antigen A on the surface of human red blood cells by manual method.
BL 125619/0	Blood Grouping Reagent, Anti-B (Murine Monoclonal)	9621A8	This reagent is designed to determine the presence of ABO system blood group antigen B on the surface of human red blood cells by manual method.
BL 125620/0	Blood Grouping Reagent, Anti-D (Human/Murine Monoclonal)	P3X61	These reagents are designed to determine the presence of the blood Rhesus antigen D (RH1) on the surface of human red blood cells by manual method.
BL 125621/0	Blood Grouping Reagent, Anti-D (Human/Murine Monoclonal Blend)	P3X61	
		P3X21223B10	
		P3X290	
BL 125622/0		P3X25513G8	

	Blood Grouping Reagent, Anti-C (Human/Murine Monoclonal)	MS24*	This reagent is designed to determine the presence of the blood group antigen C (Rh2) on the surface of human red blood cells by manual method.
BL 125623/0	Blood Grouping Reagent, Anti-E (Human/Murine Monoclonal)	906	This reagent is designed to determine the presence of the blood group antigen E (Rh3) on the surface of human red blood cells by manual method.
BL 125624/0	Blood Grouping Reagent, Anti-c (Human/Murine Monoclonal)	951	This reagent is designed to determine the presence of the blood group antigen c (Rh4) on the surface of human red blood cells by manual method.
BL 125625/0	Blood Grouping Reagent, Anti-e (Human/Murine Monoclonal)	P3GD512 MS63*	This reagent is designed to determine the presence of the blood group antigen e (Rh5) on the surface of human red blood cells by manual method.
BL 125626/0	Blood Grouping Reagent, Anti-K (Human/Murine Monoclonal)	MS56*	This reagent is designed to determine the presence of the blood group antigen K on the surface of human red blood cells by manual method.

*Clone supplier is Merck-Millipore located in Livingston, UK, US License #1761.

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 <i>January 26, 2017</i> <i>May 22, 2017</i> Darcel Bigelow, OBRR/DBCD/DRB <i>December 14, 2017</i> <i>January 29, 2018</i>
Non-Clinical Review	Ricardo Espinola, OBRR/DBCD/DRB <i>January 26, 2017</i> <i>May 22, 2017</i> Darcel Bigelow, OBRR/DBCD/DRB <i>December 14, 2017</i> <i>January 29, 2018</i>
Statistical Review	Paul Hshieh, OBE/DB/TEB <i>January 30, 2017</i> <i>April 22, 2017</i>
CMC Product Review	Ricardo Espinola, OBRR/DBCD/DRB <i>January 26, 2017</i> <i>May 22, 2017</i> Darcel Bigelow, OBRR/DBCD/DRB <i>December 14, 2017</i> <i>January 29, 2018</i> Simleen Kaur, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden <i>April 4, 2017</i> <i>September 26, 2017</i>
CMC Facilities Review	Priscilla Pastrana, OCBQ/ DMPQ/BII <i>December 14, 2016</i> <i>April 3, 2017</i> <i>December 21, 2017</i>
Labeling Review	Ricardo Espinola, OBRR/DBCD/DRB <i>January 26, 2017</i> <i>May 22, 2017</i> Darcel Bigelow, OBRR/DBCD/ DRB <i>December 14, 2017</i> <i>January 29, 2018</i>

	Dana Jones, OCBQ/DCM/APLB <i>March 14, 2017</i>
Lot Release	Varsha Garnepudi, OCBQ/ DBSQC/QAB <i>April 4, 2017</i> <i>December 19, 2017</i>

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 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 the subsequent amendments to the protocol.

Description of the Device:

The BGRs are human and/or murine monoclonal antibodies derived from in vitro culture of related cell lines listed in table 1. The formulations contain 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 A, B, D, C, E, c, e, K on the surface of human red blood cells by a manual tube technique.

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 produces 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

In vitro Substance (IVS)

The IVSs produced by DIAGAST to manufacture the products listed in Table 1 are identical to the IVSs used to manufacture their already licensed *in vitro* products. The *in vitro* substances produced by DIAGAST are listed below:

Table 3: In Vitro Substances Produced By DIAGAST

BGR <i>In vitro</i> Substance Concentrate Specificity	Monoclonal Antibody Clone ID	<i>In vitro</i> Substance DIAGAST Code	DIAGAST <i>In vitro</i> Product License #
Anti-A ABO1)	9113D10	(b) (4)	BL125169
Anti-A ABO2)	9621A8		BL125169
Anti-D (RH1)	P3X61		BL125172
Anti-D (RH1) (b) (4) **	P3X61		BL125173
	P3X21223B10		
	P3X290		
	P3X35		
Anti-C (RH2)	P3X25513G8		BL125175
	MS24*		
Anti-E (RH3)	906		BL125174
Anti-c (RH4)	951		BL125177
Anti-e (RH5)	P3GD512		BL125176
	MS63*		
Anti-K	MS56*		BL125186

*Clone supplier is Merck-Millipore located in Livingston, UK, US License #1761.
** (b) (4) is Blood Grouping Reagent, Anti-D (Human/Murine Monoclonal Blend).

DIAGAST manufactures the *in vitro* Substance (IVS) for Anti-A, B, D, D (b) (4), C (P3X22513G8), E, c, e (P3GD512) at their facility, located at Parc Eurasanté, 251, av. Eugène Avinée, 59120 Loos, France.

Merck-Millipore manufactures IVS Anti-C (MS24), e (MS63) and K at their facility, located at 4 Fleming Road, Kirkton Campus, Livingston, EH54 7BN, UK. DIAGAST purchases these IVSs from Merck-Millipore under a Shared Manufacturing Arrangement.

(b) (4)
[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

(b) (4)

[Redacted text block]

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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) 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 <i>In vitro</i> 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 each 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
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<i>in vitro Substance in vitro Product Release Testing</i> Diagast EuraSante Parc 215 Avenue Eugène Avinée 59374 LOOS, Cedex, France	3006261638	381527001	Team Biologics February 13-21, 2017 VAI
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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. DIAGAST used the standard manual tube agglutination methods for BGR for testing potency and specificity of the stability samples.

Anti-A, Anti-B and Anti-D BGR IVPs products were tested at 6, 12, 18 and 24 months for validation of current shelf life and then at (b) (4) months for an extended target shelf life of (b) (4) months.

Anti-C, Anti-E, Anti-c, Anti-e and Anti-K BGR IVPs were tested at 6, 12, 18, 21 and (b) (4) months for an extended target shelf life of 24 months.

Table 6, extracted from the submission, 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. The stability study supports the proposed 24 month dating period.

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

<i>In-Vitro</i> Product	Negative Specificity RBC Used (1)	Positive Specificity RBC Used (2)	Potency (Titration)		
			RBC Used	Minimum Titer	Neat
Anti-A	(b)	(4)	(b)	(4)	(4)
Anti-B					
Anti-D					
Anti-C					
Anti-c					
Anti-E					
Anti-e					
Anti-K					

Microbiology testing included (b) (4)

[Redacted text block]

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 individual BGRs were tested in parallel with currently licensed US products using de-identified leftover clinical (patient or donor) samples. Discordant results were resolved by testing with the Referee Laboratory/resolver method.

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. 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 Sample Data from all Sites

		Number	Lower 95% CI	Acceptance Criteria	Point Estimate
Anti-A	NPA	1811/1811	99.83%	99%	100%
	PPA	1221/1222	99.61%	99%	99.92%
Anti-B	NPA	2544/2544	99.88%	99%	100%
	PPA	489/489	99.39%	99%	100%

Anti-AB	NPA	1447/1447	99.79%	99%	100%
	PPA	1584/1586	99.60%	99%	99.87%
Anti-D IgM	NPA	496/496	99.40%	99%	100%
	PPA	2538/2538	99.88%	99%	100%
Anti-D (b) (4) * (IgM/IgG)	NPA	488/488	99.39%	99%	100%
	PPA	2546/2546	99.88%	99%	100%
Anti-D IgG	NPA	488/488	99.39%	99%	100%
	PPA	2546/2546	99.88%	99%	100%
Anti-C	NPA	799/800	99.41%	99%	99.88%
	PPA	1080/1080	99.72%	99%	100%
Anti-E	NPA	1408/1408	99.79%	99%	100%
	PPA	472/472	99.37%	99%	100%
Anti-c	NPA	327/327	99.09%	99%	100%
	PPA	1553/1553	99.81%	99%	100%
Anti-e	NPA	77/79	92.24%	99%	97.47%
	PPA	1890/1891	99.75%	99%	99.95%
Anti-K	NPA	3314/3314	99.91%	99%	100%
	PPA	306/306	99.03%	99%	100%

BGR Anti-e did not meet the acceptance criteria for NPA. Due to the high antigenic frequency of the e antigen in the United States population, only 79 e-negative samples were seen in 1,970 random and selected samples.

There were three discordant results.

- Two discordant results were due to clerical data entry errors, a NP and PN.
NP: Negative result obtained by the comparative method but positive by the method under test.
PN: Positive result obtained by the comparative method but negative by the method under test.
- One discordant result (positive with test reagent and negative with comparator reagent) gave the same results upon retesting with the test and comparator reagents. Testing with a resolver reagent confirmed that the sample was e-antigen positive confirming the DIAGAST positive result.

All the other BGRs included in this submission met the acceptance criteria. The results of the comparison study will be included in the Instructions for Use of the BGRs, under Specific Performance Characteristics Section, for each product.

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 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.

c) Recommendation for Postmarketing Activities

We did not recommend any postmarketing activities.

Concurrence Page

Application Type and Number: BLA 125615, 125619, 125620, 125621, 125622, 125623, 125624, 12625, 125626

COMMUNICATION TYPE: SBRA-IVD BGR

History:

Created: Darcel Bigelow/November 2, 2017

Revised: Oriji Illoh/November 24, 2017, December 18

Revised: Darcel Bigelow/December 5, 2017, February 1, 2018

Revised: Nicole Verdun/February 1, 2018

Concurrence:

Office/Division	Name/Signature/Date
OBRR/DBCD	Darcel Bigelow
OCBQ/DMPQ	Priscilla Pastrana
OBCQ	Mary Malarkey