Summary Basis for Regulatory Action

From: Annette Ragosta, Chair of the Review Committee

BLA STNs#: 125669 and 125680

Applicant Name: DIAGAST (US License 1744)

Date of Submission: December 22, 2018

Goal Date: August 12, 2019

Proprietary Name/ Established Name:

STNs and Product Names

STN	Product Name	Cell Line
125669/0	Blood Grouping Reagent, Anti-A (Murine Monoclonal) (FFMU)	16243G2
125680/0	Blood Grouping Reagent, Anti-A (Murine Monoclonal) (FFMU)	16247E6

Intended Use: (*Form FDA 356h)*

Intended for further manufacturing of Blood Grouping Reagents

Recommended Action:
The Review Committee recommends approval of this product.

Review Office(s) Signatory Authority(ies): Anne Eder, MD, Acting Deputy 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 (Table 1) indicates the material reviewed when developing the SBRA

TABLE 1

Document title	**Reviewer name, Document date**
Clinical	*Not applicable for this submission*
Statistical Review	*Not applicable for this submission*
CMC Product Review	• Annette Ragosta, OBRR/DBCD/DRB July 2, 2019 • Karla Garcia, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden August 16, 2018
CMC Facility Review	Priscilla Pastrana, OCBQ/DMPQ/BII January 31, 2018
Labeling Review(s)	Annette Ragosta, OBRR/DBCD/DRB August 17, 2018
Lot Release Protocols/Testing Plans	*Not applicable for this submission*
Establishment Inspection Report	*Not applicable for this submission*
Bioresearch Monitoring Review	*Not applicable for this submission*

1. Introduction

DIAGAST (US License # 1744) submitted two Biological License Applications (BLAs) to manufacture and distribute the following Blood Grouping Reagents (BGRs), labeled For Further Manufacturing Use (FFMU); hereafter referred to as Anti-A FFMU:

TABLE 2 - STNs and Product Names

STN	**Product Name**	**Cell Line**
125669/0	Blood Grouping Reagent, Anti-A (Murine Monoclonal) (FFMU)	16243G2
125680/0	Blood Grouping Reagent, Anti-A (Murine Monoclonal) (FFMU)	16247E6

These Anti-A FFMU clones will be utilized by Diagnostic Grifols (SA) (Grifols) in the manufacture of the final product, Blood Grouping Reagent, Anti-A (Murine Monoclonal), under a shared manufacturing arrangement. Grifols submitted a companion BLA application for the in vitro final product under STN 125449/44.

The quality agreement between DIAGAST and Grifols, which defines the responsibilities of each party with respect to quality issues and communication, was reviewed and found to be adequate.

Chronology:

CBER received the original submission for STN 125669 on December 22, 2017. This submission initially included two separate Anti-A FFMU products. Following clarification from FDA that these were considered as separate products and should be submitted as separate BLAs, DIAGAST decided to separate the two FFMU products and submitted a companion submission under STN 125680. This administrative change did not affect the review timelines.

2. Background

Meetings with FDA:

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

Device Description:

The monoclonal antibodies used in the manufacture of the Anti-A FFMU products are derived from the cell culture (b) (4) of immunoglobulin-secreting (b) (4) clones. The specificity, the clone identification numbers (ID), immunoglobulin class (isotype), and (b) (4) of each monoclonal antibody are summarized in Table 3 below.

TABLE 3

Specificity	Clone ID	Isotype	Hybridoma Type
Anti-A	16243G2	IgM	Mouse
Anti-A	16247E6	IgG	Mouse

These murine (b) (4) strains were created by (b) (4) between (b) (4) by (b) (4) . The clones were purchased by DIAGAST in

(b) (4). The human donors from which the red blood cells were collected and used for mouse immunization were tested and found negative for (b) (4). (b) (4) testing was performed on the cell lines and produced negative results.

Initial potency and specificity testing studies were performed to determine the potency and the specificity of the antibodies using (b) (4). Testing was also performed as part of workshops and symposia by several institutions to verify that the monoclonal antibodies were suitable for use as a blood grouping reagent. All studies confirmed the specificity of the two antibodies; however, potency of the antibodies was variable depending on the evaluator and the method used.

DIAGAST prepared Master Cell Banks (MCB) and Working Cell Banks (WCB) of each clone from the vials purchased from (b) (4). The cell banks are characterized for specificity, potency, viability, stability, and the absence of (b) (4) contamination.

The raw materials and components used to produce the Anti-A concentrates and FFMU products are the same as for currently licensed FFMU products. They are accepted by DIAGAST based upon the supplier Certificate of Analysis or Specification Sheet, the DIAGAST Purchasing Technical Specifications, or other material specific qualifying tests. (b) (4) is purchased from sources that certify the (b) (4) are collected in countries free from (b) (4).

Marketing History:

The cell culture (b) (4) of Anti-A (cell line16243G2) (Murine Monoclonal) is currently being used in the manufacture of the DIAGAST in-vitro product, Anti-A (Murine Monoclonal) (Formulated for Automated Testing), which was approved in 2008 under STN 125169.

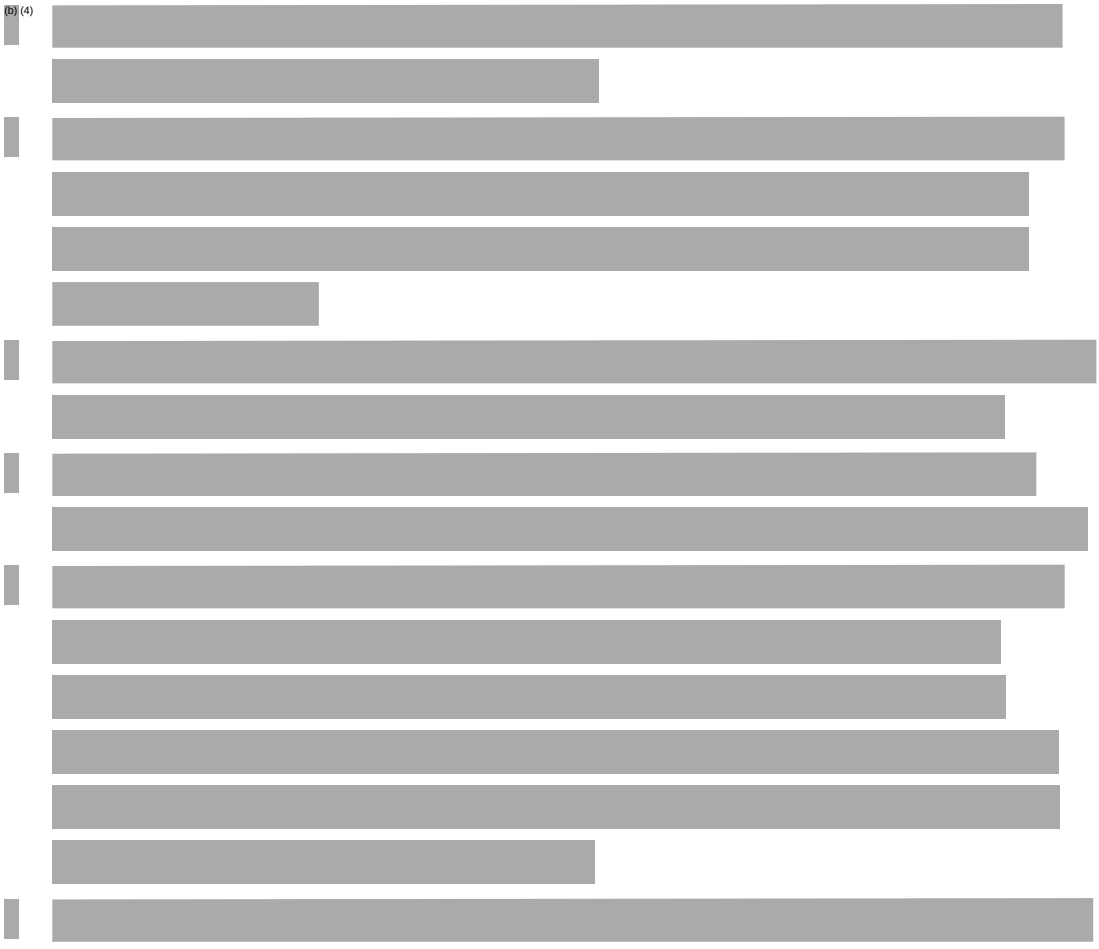
3. Chemistry Manufacturing and Controls (CMC)

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*". All manufacturing is carried out in a controlled environment.

a) Manufacturing Summary

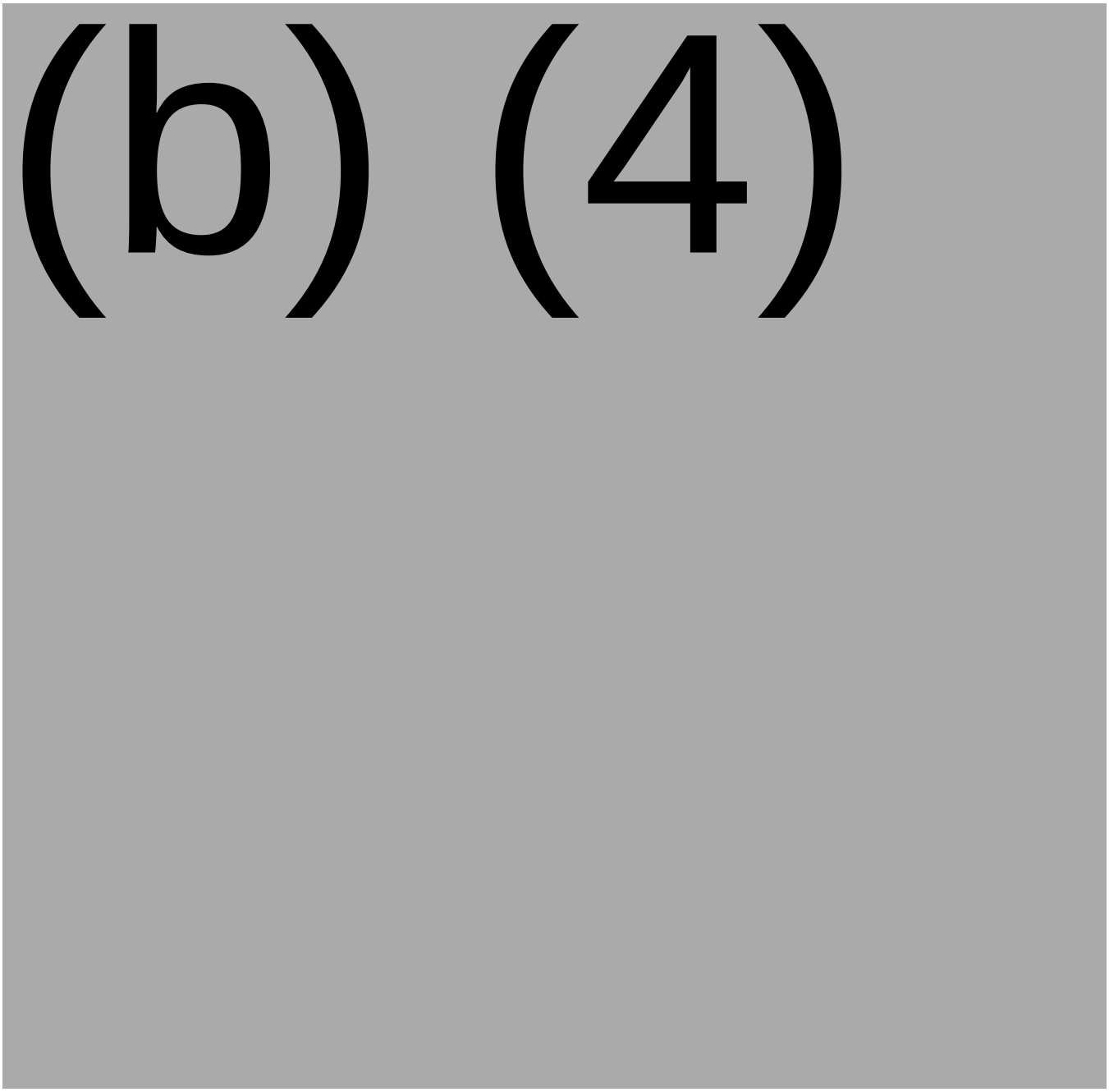
The following is the process flow for the (b) (4) which is the same process for currently licensed BGR FFMU products:

(b) (4)



(b) (4)

The methods used to characterize the two Anti-A FFMU products are (b) (4) , and are summarized in Table 4 below.



b) CBER Lot Release

The Anti-A Blood Grouping Reagents are for further manufacturing use and therefore are not subject to CBER lot release.

c) Facilities Review/Inspection

Facility information and data provided in the Efficacy Application were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the Blood Grouping Reagents Anti-A [(Murine Monoclonal) (Cell line 16243G2)] and Anti-A [(Murine Monoclonal) (Cell line 16247E6)] for Further Manufacturing (FFMU) are listed in the table below. The performed activities and inspectional history are noted in Table 5 below.

TABLE 5

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Results/ Justification
Production of *Blood Grouping Reagent* FFMU In-process and release testing of Blood Grouping Reagent FFMU DIAGAST Parc Eurasante 251 Avenue Eugène Avinée 59374 LOOS, Cedex, France	3006261638	381527001	Waived	Team Biologics VAI February 13-21, 2017 Surveillance

Team Biologics performed a surveillance inspection of the DIAGAST facility in February 2017. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental assessment

These BLAs 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 manufacture of these Blood Grouping Reagents for further manufacturing will not alter significantly the concentration or distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Container/ Closure

The Blood Grouping Reagents FFMU are filled into (b) (4) . DIAGAST verifies the tightness of the container/closure as part of the filling of the Blood Grouping Reagents FFMU at the LOOS, Cedex, France, employing (b) (4) . DIAGAST conducted stability studies to the container/closure of the Blood Grouping Reagents FFMU to demonstrate the effective storage of the Blood Grouping Reagents FFMU at a temperature between (b) (4) for a maximum of (b) (4) , employing (b) (4) ; all acceptance criteria were met.

4. Software and Instrumentation

Not Applicable

5. Analytical Studies

Stability Studies

DIAGAST performed real-time stability studies, stressed stability studies, and shipping studies to determine the effect of temperature, time, and shipping conditions on the Anti-A FFMU products.

Real-Time Stability Studies

The expiration date of the Anti-A FFMU products stored at (b) (4) is (b) (4) from the date of manufacture of the corresponding lot of (b) (4) . The following is a description of the stability study which validated the expiration date claim.

(b) (4)

Real-time stability summary reports for the (b) (4) FFMU conformance lots for each of the Anti-A FFMU products were included in the submission. The results demonstrate that the Anti-A FFMU products are stable when stored at (b) (4) for (b) (4) .

False positive cross reactions were observed with group B RBCs for clone (b) (4) at high concentration levels (potency titer (b) (4)) and at the (b) (4) time points. This cross reaction with B cells is a known phenomenon for this clone and is considered acceptable within the limit of neat potency of (b) (4) and titer of (b) (4) . Because the antibody concentrate is (b) (4) for the manufacture of blood grouping reagent, false positive reactions with B cells are not observed on the final product. DIAGAST includes this information on the Certificate of Analysis that accompanies the FFMU product.

Stressed Stability Studies

DIAGAST performed stressed stability studies that simulated potential transportation conditions on (b) (4) of the Anti-A FFMU products. Specificity and potency testing and acceptance criteria are the same as those for the real-time stability testing.

The studies included the following conditions:

Both Anti-A FFMU products failed to meet acceptance criteria for (b) (4) at several testing time points. Both Anti-A FFMU products met acceptance criteria for (b) (4); therefore, the shipping conditions will be limited to (b) (4) at (b) (4) and (b) (4) will not be allowed during shipment. The temperature is recorded during shipment and reviewed after receipt for acceptance.

Shipping Validation

A shipping study was performed between DIAGAST and Diagnostic Grifols (Barcelona, Spain). The study was executed to verify adequate temperature control during shipment to Grifols during varying climatic conditions. Each shipment included (b) (4) vials of each Anti-A FFMU product packed in a corrugated carton filled with packing paper. A temperature recorder was packed in the carton along with the product. At arrival at the Grifols facilities the shipment was checked for integrity and stored unopened at (b) (4) 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. Specificity and potency testing and acceptance criteria are the same as for the real-time stability testing. The results demonstrate that the packing materials keep the product within (b) (4) during overnight shipment to Grifols.

Microbiology

The analytical methods and their qualifications reviewed by DBSQC for the Anti-A (Murine Monoclonal) (For Further Manufacturing Use) Reagents were found to be adequate for their intended use.

6. Clinical Studies

Not applicable for this submission.

7. Advisory Committee Meeting

Not applicable for this submission.

8. Other Relevant Regulatory Issues

There are no 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.

9. Labeling

DIAGAST submitted a sample final container label for the IVS; the label was reviewed and determined to be acceptable.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members, representing the necessary review disciplines (DBCD, DMPQ, and DBSQC) recommend approval. These were independent conclusions based on content of the two BLAs, 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

Licensing these two Anti-A FFMU products may increase the safety of the blood supply by providing new cell lines which can increase the probability of the detection of rare antigen variants.

The evaluation of the validation studies and the manufacturing process reduces the risks associate with licensing these new FFMU products. In addition, the final product, Anti-A (Murine Monoclonal), manufactured by Diagnostic Grifols, S.A., will be subject to post market surveillance (medical device reporting) which will identify adverse events associated with this product.

c) Recommendation for Post-marketing Activities

We did not recommend post-marketing activities for this submission.

Concurrence Page

Application Type and Number: BLA 125669 and BLA 125680

COMMUNICATION TYPE:

History:
Drafted by Annette Ragosta July 25, 2019
Reviewed: Teresita Mercado July 25, 2019
Reviewed: Orieji Illoh, MD July 30, 2019
Reviewed: Mary Malarkey July 25, 2019
Reviewed: Anne Eder, MD for Nicole Verdun MD August 8, 2019

Concurrence:

Office/Division	Name/Signature	Date
OBRR/DBCD	Annette Ragosta	
OBRR/DBCD	Teresita Mercado	
OCBQ	Mary Malarkey	
OBRR/DBCD	Orieji Illoh, MD	
OBRR/DBCD	Anne Eder, MD for Nicole Verdun, MD	