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Summary Basis for Regulatory Action

Date: May 17, 2021

From: Kimberly Bigler, Medical Technologist, Review Committee Chair, OBRR/DBCD

BLA/ STN#: 125707/0 and 125708/0

Applicant Name: Diagast

Date of Submission: May 2, 2019

MDUFA Goal Date: June 18, 2022

Proprietary Name:

125707/0: Anti-Human Globulin Anti-C3d FFMU, Murine Monoclonal

125708/0: Anti-Human Globulin Anti-IgG, -C3d FFMU, Rabbit Polyclonal/Murine Monoclonal

Established Name (common or usual name): 125707/0 Anti-Human Globulin (Murine Monoclonal) (For Further Manufacturing Use)

125708/0 Anti-Human Globulin (Rabbit/Murine Monoclonal) (For Further Manufacturing Use)

Device Procode: Not applicable for this submission

Intended Use/Indications for Use: Intended for further manufacturing use in final Anti-Human Globulin reagent

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

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.

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

Document Title	Reviewer Name Document Date
CMC Review <ul style="list-style-type: none"> • CMC (Product Office) • Facilities Review (OCBQ/DMPQ) • QC, Test Methods and Product Quality (OCBQ/DBSQC) 	<ul style="list-style-type: none"> • Kimberly Bigler, DBCD/DRB April 7, 2022 • Priscilla Pastrana, OCBQ/DMPQ January 8, 2020 • Yen Phan, OCBQ/DBSQC January 29, 2020
Labeling Review(s) <ul style="list-style-type: none"> • Product Office 	Kimberly Bigler, DBCD/DRB April 7, 2022

1. Introduction

Diagast (License #1744) submitted two Biological License Applications (BLAs) to manufacture and distribute the following Anti-Human Globulin (AHG) products listed in Table 1, labeled For Further Manufacturing Use (FFMU).

Table 1: STN and Product Name

STN	Product Name	Proprietary Name
125707/0	Anti-Human Globulin (Murine Monoclonal) (For Further Manufacturing Use)	Anti-Human Globulin Anti-C3d FFMU, Murine Monoclonal
125708/0	Anti-Human Globulin (Rabbit/Murine Monoclonal) (For Further Manufacturing Use)	Anti-Human Globulin Anti-IgG, -C3d FFMU, Rabbit Polyclonal/Murine Monoclonal

Diagnostic Grifols intends to use the above mentioned FFMU products to manufacture in vitro final products Anti-C3d and Anti-IgG, -C3d under a Shared Manufacturing Arrangement with Diagast. Diagnostic Grifols submitted a companion BLA application for the in vitro final products Anti-C3d (STN 125705/0) and Anti-IgG, -C3d (STN 125711/0). The quality agreement between Diagast and Diagnostic Grifols S.A., which includes the responsibilities of each party with respect to quality issues and communication, appears adequate.

2. Background

Product Description:

a. Anti-C3d FFMU, Murine Monoclonal

The monoclonal antibody used in the manufacture of the AHG Anti-C3d FFMU reagent is derived from cell culture supernatant of immunoglobulin secreting hybridoma clones. The Anti-C3d murine hybridoma strain, (b) (4)

(b) (4) is used for
Diagast Anti-C3d FFMU production. (b) (4)

The specificity of the monoclonal antibody, clone identification number (ID), immunoglobulin class (isotype), fusion cell partners (hybridoma type), and the original clone producer are summarized in Table 2 below.

Table 2: Description of Clones

Specificity	Clone ID	Isotype	Hybridoma	Clone Producer
AHG Anti-C3d	12011D1	IgM	Murine	Lille-RBTC

Diagast prepares Master Cell Banks (MCB) and Working Cell Banks (WCB) of the Anti-C3d clone from the vials purchased. The cell banks are characterized for (b) (4)

Initial potency and specificity testing studies of the monoclonal antibody clone is performed by the (b) (4) technique to determine the activity of the clone and to verify the specificity of antibody using reference panels of known samples.

b. Anti-IgG, -C3d FFMU, Rabbit Polyclonal/Murine Monoclonal

The AHG Anti-IgG, -C3d FFMU product is a blend of murine monoclonal antibody anti-C3d, as described above, and rabbit polyclonal antibody anti-IgG. The Anti-IgG is a polyclonal in vitro substance (IVS) produced from (b) (4) rabbit polyclonal anti-human IgG collected from (b) (4) rabbits that are (b) (4)

All raw materials and components used to produce both FFMU products are accepted from approved suppliers based on their Certification of Analysis or Technical Information for the critical raw materials. The procedures for supplier evaluation and receiving materials are the same as for currently licensed products.

(b) (4)

Chronology:

FDA received the submissions on May 2, 2019. On February 27, 2020, FDA sent Diagast a Complete Response Letter to put these submissions on hold to address problems with the companion submissions submitted by Diagnostic Grifols for the in-

vitro products (BL 125705/0 and BL 125711/0). Diagast responded to the Complete Response on December 17, 2021.

Marketing History:

Diagast manufactures the Anti-C3d in vitro substance and FFMU for their licensed in vitro product AHG Anti-C3d for manual tube technique (BL 125616/0). FDA approved this application on February 1, 2018.

The Anti-IgG component of the Anti-IgG, -C3d FFMU product in this submission is identical to the currently licensed Diagast AHG Anti-IgG FFMU (Rabbit Polyclonal) (BL125439/0) which was approved on July 19, 2013. Diagast supplies this product to Diagnostic Grifols.

3. Chemistry Manufacturing and Controls (CMC)

Diagast submitted the application 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." Diagast manufactures the products in a controlled environment.

a) Manufacturing Summary

(b) (4)

(b) (4)

iii. Manufacture of the Anti-C3d FFMU product

The following is the process flow for the (b) (4)

(b) (4)

- Filling and Labeling:
 - Maximum validation batch is (b) (4)
 - Filled into HDPE (b) (4) bottles with polypropylene plastic screw caps depending on batch size
 - Labels are applied manually
 - Product is stored at 2-8 °C
 - A (b) (4) sample (b) (4) is filled, labeled, and shipped to IVP manufacturer to allow for receipt testing by IVP manufacturer
- Quality Control Testing is performed for appearance, potency, specificity, and bioburden

iv. Manufacture of the Anti-IgG, -C3d FFMU product

The following is the process flow for the (b) (4)

(b) (4)

- Filling and Labeling:
 - Maximum validation batch is (b) (4)
 - Filled into PETG (b) (4) bottles with HDPE plastic screw caps depending on batch size
 - Labels are applied manually
 - Product is stored at 2-8 °C
 - A (b) (4) sample (b) (4) is filled, labeled, and shipped to IVP manufacturer to allow for receipt testing by IVP manufacturer

- Quality Control Testing is performed for appearance, potency, specificity, and bioburden

The date of manufacture of the FFMU is defined as the date of the final filtration before the filling operation. The expiration of the FFMU products is 24 months when stored at 2-8 °C. The methods used to characterize the FFMU products are specificity, potency, absence of contamination antibodies, and biochemistry (pH, protein and osmolarity), and are summarized in Table 4 below.

Table 4: FFMU QC Testing

Test	Test Method	Cells	Acceptance Criteria
Negative Specificity	<div style="font-size: 48px; font-weight: bold;">(b)</div> <div style="font-size: 48px; font-weight: bold;">(4)</div>		
Specificity with (b) (4)			
Potency (Anti-C3d)	<div style="font-size: 48px; font-weight: bold;">(b)</div> <div style="font-size: 48px; font-weight: bold;">(4)</div>		
Potency (Anti-IgG, - C3d)			

Biochemistry (Anti-C3d)	(b) (4)
Biochemistry (Anti-IgG, -C3d)	
Visual Inspection	

b) CBER Lot Release

Routine lot release by CBER is not required for the Anti-Human Globulin (Murine Monoclonal) and Anti-Human Globulin (Rabbit/Murine Monoclonal) Reagents because they are for further manufacturing use.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture and testing of the Anti-Human Globulins (AHGs) Anti-IgG, -C3d (Rabbit Polyclonal/Murine Monoclonal) FFMU and Anti-C3d (IgM Murine Monoclonal) FFMU is listed in the table below.

<i>Name/Address</i>	<i>FEI Number</i>	<i>DUNS Number</i>	<i>Inspection/Waiver</i>	<i>Justification/Results</i>
<i>DIAGAST</i> <i>Parc Eurasante</i> <i>251 Avenue</i> <i>Eugène Avinée</i> <i>59120</i> <i>LOOS, Cedex,</i> <i>France</i> <i>Production and</i> <i>testing of the in</i> <i>vitro substance</i>	3006261638	266383577	Waiver	<i>March 2019</i> <i>Surveillance</i> <i>ORA</i> <i>VAI</i>

Team Biologics performed a surveillance inspection of Diagast from March 14 – 21, 2019. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure

Anti-Human Globulins (AHGs) Anti-IgG, -C3d (Rabbit Polyclonal/Murine Monoclonal) FFMU and Anti-C3d (IgM Murine Monoclonal) FFMU are filled into (b) (4) and single-use high density polyethylene (HDPE) bottles and screw caps are made of low-density polyethylene (LDPE), high density polyethylene (HDPE) or a combination of both. Diagast verified the tightness of the container/closure as part of the filling of these AHG FFMU Products at the LOOS, Cedex, France, employing (b) (4) verification; all acceptance criteria were met. Diagast conducted stability studies for the container/closure of the AHG FFMU Products to demonstrate their effective storage at a temperature range between 2°C to 8°C for a maximum of 24 months, employing appearance, potency, and specificity testing; all acceptance criteria were met.

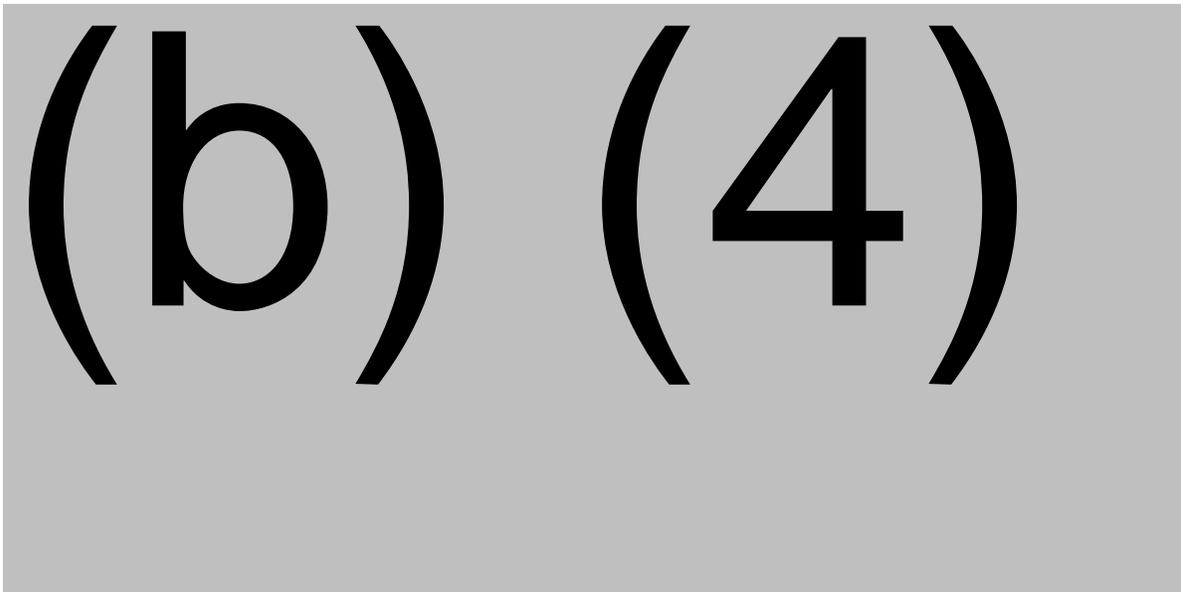
4. Software and Instrumentation

Not applicable for this submission.

5. Analytical Studies

Stability Studies

Diagast performed a real-time stability study on the antibody concentrate. They also performed a real-time stability study, stressed stability study, and a shipping study to determine the effect of temperature, time, transport, and stressed conditions on the FFMU products.



Real Time Stability Study: FFMU products

Diagast validated through real time stability testing that the Anti-C3d FFMU products remain stable when stored in HDPE containers at 2-8 °C for up to 24 months. Testing was performed using the (b) (4) Diagast tested the Anti-IgG, -C3d FFMU products stored in PETG containers at 2-8 °C for up to 24 months.

Diagast performed stability testing by manufacturing three lots of FFMU products obtained from (b) (4). The lots were tested at 3, 6, 9, 12, 18, and (b) (4) months for appearance, specificity, and potency in parallel with the reference standard.

Diagast defined the acceptance criteria as:

- Appearance: (b) (4)
- Negative Specificity: (b) (4)
- Potency and Positive Specificity: (b) (4)
- Titer: (b) (4)

Diagast included the real-time stability summary reports for the three conformance lots in their submission. The results demonstrate their acceptance criteria were met at all timepoints tested and demonstrated the FFMU products are stable when stored at 2-8 °C for up to 24 months.

Diagast plans to test one lot per year of the FFMU products for their on-going stability program. They will perform testing at release, 12 months, and 25 months.

Stressed Stability Study

Diagast performed a transport simulated stressed stability study on (b) (4) (b) (4) and exposed the products to the following conditions:

(b) (4)

They stored the stressed stability product at 2-8 °C until testing at 3, 6, 9, 12, 18 and (b) (4) months. Their acceptance criteria for appearance, negative specificity, positive specificity, and potency were the same as the real-time stability testing. All results met the acceptance criteria.

Shipping Study Validation

Diagast packed the FFMU bottles in plastic boxes for shipment and filled the empty spaces in the box with paper (b) (4) for stability. Diagast shipped the boxes to Diagnostic Grifols in Barcelona Spain by (b) (4) at 2-8 °C controlled temperature.

In addition, Diagast and Diagnostic Grifols performed a shipping study to verify adequate temperature control to Grifols varying climatic conditions. They included (b) (4) vials of FFMU product in each shipment and included a (b) (4) temperature recorder in the carton. When the shipment arrived at Grifols, it was checked for integrity and stored unopened at 2-8 °C until it was shipped back to Diagast. At Diagast, the shipment was checked for integrity and the data recorder was read and analyzed. The product was stored at 2-8 °C until testing at 3, 6, 9, 12,

18 and (b) (4) months. Their acceptance criteria for appearance, negative specificity, positive specificity, and potency were the same as the real-time stability testing. All results met the acceptance criteria.

6. Clinical Studies

Not applicable to this submission.

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, DMPQ, and DBSQC reviewed their specific sections of the two BLAs and resolved any 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 a chairperson. All reviewers recommended approval.

9. Labeling

Diagast submitted a sample final container label for the FFMU. The labels met all applicable requirements in 21 CFR Part 610, Subpart G.

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 the 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 AHG reagents may increase the safety of performing complex antibody identification procedures by providing new cell lines allowing end-users to differentiate if red blood cells are sensitized in vivo by IgG type immunoglobulins or by complement C3d fractions.

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

c) Recommendation for Postmarketing Activities

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