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Summary Basis for Regulatory Action - Seraclone Blood Grouping Reagent Anti- Fya (Monoclonal)

Summary Basis for Regulatory Action

MDUFMA Goal Date

From: Teresita C. Mercado, Committee Chair

Subject: Summary Basis of Regulatory Action

BLA #: STN 125212/0

Applicant: Biotest Medical Diagnostics GmbH

Date of Submission: September 22, 2006

Product: Blood Grouping Reagent, Anti-FY^a (Monoclonal)

Proprietary Name: Seraclone®

Potency / Fill volume: ----- / 2 mL

Expiry: 24 months at 2 - 8°C

Proposed Indication: For the detection of the FY^a (FY1) antigen on red blood cells using the tube test method

Recommended Action: Approval

Signatory Authority: Elizabeth Callaghan_____

X I concur with the summary review

□ *I concur with the summary review and include a separate review or addendum to add further analysis*

□ *I do not concur with the summary review and include a separate review or addendum*

Material Reviewed/ Consulted List of specific documentation used in compiling SRBA

CMC Review/ Facilities: George Gentile

CMC Review/Products: Najma Khan, Teresita Mercado, Joanne Pryzbylik,

Statistical Review: Weishi (Vivian) Yuan

Labeling: Najma Khan, Sheryl Kochman, Teresita Mercado, and Joanne Pryzbylik

Product testing & Lot Release: Teresita Mercado and Joanne Pryzbylik

Introduction

Biotest Medical Diagnostics GmbH, located in Dreieich, Germany, U.S. License Number 1798, submitted this original BLA for the manufacture of Seraclone® Blood Grouping Reagent (BGR), Anti-FY^a (Monoclonal), an in vitro diagnostic (IVD) reagent that is intended for typing blood specimens using manual tube agglutination methods. While Anti-FY^a has routinely been manufactured from pooled human plasma, this is the first Anti-FY^a of monoclonal origin to be licensed by FDA. The source material, Blood Grouping Reagent, Anti-FY^a (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] is supplied by Diagast, U.S. License 1744, under a shared manufacturing agreement with Biotest AG.

Background

The Duffy blood group system has five antigenic specificities, i.e., FY^a, Fy^b, By3 and Fy4 and Fy5. The Duffy genes are located on chromosome one at position 1922-23. The Duffy Blood Group System antigens that are most important in routine immunohematology are FY^a (FY1) and Fy^b (FY2). These antigens can be detected on fetal red blood cells early in the gestational age and are well developed at birth. The difference between FY^a and Fy^b is a change in the amino acid at position 43 from aspartic acid (FY^a) to glycine (Fy^b). The Duffy antigen is found on red blood cells, on some epithelial cells, Purkinje cells of the cerebellum, post capillary venules of some organs, endothelial cells of thyroid capillaries and the large lung alveoli. The Duffy antigen on the erythrocytes acts as receptor for the invasion of human malarial

parasites Plasmodium vivax and Plasmodium knowlesi. Individuals who are Duffy negative are resistant to malarial infection. Antibodies to the FY^a antigen may cause hemolytic disease of the fetus and the newborn and has been implicated in hemolytic transfusion reactions. Hemagglutination is the basis of the test for the detection of the FY^a antigen on red blood cells using the Seraclone® Blood Grouping Reagent, (BGR) Anti-FY^a (Monoclonal). The antibody in the reagent binds with the FY^a antigen on the red blood cells, if present. This does not result in a direct (positive) agglutination reaction. The addition of Anti-Human Globulin Reagent causes the antibody-coated red blood cells to be cross-linked together, which is visible as red blood cell agglutination. The absence of agglutination indicates the absence of the FY^a antigen. Determination of the presence or absence of the FY^a antigen on blood donors' red blood cells is critically important when a transfusion recipient is FY^a negative and has made anti-FY^a in response to a previous transfusion or pregnancy. It can also be important in managing pregnancy when the mother lacks the FY^a antigen and the fetus possesses the FY^a antigen by virtue of inheritance from the father.

CBER received the license application for the Seraclone® BRG, Anti-FY^a (Monoclonal) on September 29, 2006. A Complete Response (CR) letter was issued on July 27, 2007. The response to this letter was received in CBER on December 3, 2007. Two other CR letters dated January 31 and May 16, 2008 were issued to Biotest. The January 31, 2008 CR letter includes labeling and lot release protocol template issues whereas the May 16, 2008 letter contains labeling issues only. All the issues identified in the CR letters have been resolved.

Chemistry, Manufacturing and Controls (CMC) and Facilities

The intermediate product/source material, Blood Grouping Reagent, Anti-FY^a (Monoclonal) (For Further Manufacturing Use) [FFMU], manufactured from the cell line DG-FYA-02, is supplied by Diagast, located in Loos, France, U.S. License number 1744, under a shared manufacturing agreement with Biotest. The optimal dilution of the FFMU is determined by pilot testing. The antibody is diluted in a buffered solution; sodium azide and sodium arsenite are used as preservatives. Once the bulk is formulated, it is ----- and sublotted. The date of manufacture (DOM) of the product is the date the bulk container is ----- . The sublotted ----- bulk is automatically filled into 2 ml vials. The product is tested for potency and specificity to assure that all in-process and final product release specifications are met. An in-house reference standard is used during release testing to assure that the test results are reliable and that the product consistently meets established specifications.

BGR Manufacturing Process Flow

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assurance, and production of diagnostic products. Production is conducted in Building No. ---. Some Quality Control testing, product storage and distribution are conducted in Building --, the Quality System/R&D building. Final products are stored in Building --.

The most recent biennial inspection occurred on September 19 – 28, 2006 and was classified as VAI. There were several FDA 483 items which included sublotting bioburden, and documentation issues. The pre-approval inspection for the Seraclone® Anti-FY^a (Monoclonal) was waived since the Biotest facilities were already inspected by Team Biologics ----- . In addition, manufacture of this new product uses some of the same or similar facilities, equipment, and processes as were observed during the 2006 inspection.

There are no ongoing or pending investigations or compliance actions with respect to the Biotest Medical Diagnostics GmbH facilities or their products; therefore the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

Clinical/ Statistical

Field trials were conducted at five (5) sites that included University of Virginia in Charlottesville, VA, Heartland Blood Center in Aurora, IL, University of Colorado Medical Center in Denver CO, Wake Forest Baptist Medical Center in Winston-Salem, NC and Olympus America, Inc. (OAI) Laboratory in Irving TX. Samples were collected from both normal blood donors and patients at the test sites except for the OAI testing facility where samples were obtained from normal donors from the Gulf Coast Blood Center. Testing of FY^a positive and FY^a negative samples was performed using both the Seraclone® (BGR) Anti-FY^a (Monoclonal) and a licensed reference method. The results of the comparison studies are tabulated below.

	Seraclone® Anti-FY^a (Monoclonal) Reagent		
	FY^a Positive	FY^a Negative	Totals
Reference Results FY^a Positive	133	0	133
FY^a Negative	0	104	104
Totals	133	104	237

Seraclone® Anti-FY^a and Reference Reagent	Number in Agreement	Number of tests	% Total Agreement	Lower 95% Confidence Limit
	237	237	100%	98.5%

The positive rate of agreement between the Seraclone® Anti-FY^a (Monoclonal) Reagent and the reference method is 97.3% (LCL).

The negative rate of agreement between the Seraclone® Anti-FY^a (Monoclonal) Reagent and the reference method is 96.5% (LCL).

Biotest performed additional testing of Anti-FY^a at FDA's request. The additional testing was performed at the Biotest Diagnostic Corporation facility in the U.S. and at the Biotest Medical Diagnostics GmbH facility in Germany. Immucor reagents were used as the reference reagent for the Biotest Anti-FY^a. The combined rate of agreement from the original and the 2007 field trials are shown in the following table.

Combined Rate of Agreement (Original Field Trial and 2007 data)

Anti-FY^a DG-FYA-02 and Reference Reagent	Number in Agreement	Number of tests	% Agreement	Lower 95% Confidence Limit
	367	367	100%	99.0%

Labeling

Review of the product labeling was performed by Teresita C. Mercado, Joanne Pryzbylik, Sheryl Kochman and Najma Khan. After several revisions, the product labels were found to be acceptable.

Testing of Conformance Lots

Joanne Pryzbylik and Teresita C. Mercado of the Immunohematology Team tested each conformance lot of the Seraclone® Anti-FY^a (Monoclonal) to verify that each reagent is within the specifications and equivalent to the potency stated in the lot release protocol. The products performed as expected and were deemed suitable for lot release recommendation.

CBER Lot Release

Because the manufacturing facility has limited manufacturing experience for the US market and the cell line from which the product is derived has no track record in the US, this product will be placed on routine lot release. Review of results from selected tests performed by the manufacturer will be the primary mode of regulation of this IVD; however, CBER will perform confirmatory testing of final product in vials according to the lot release test plan.

Environmental Assessment

A categorical exclusion from an environmental assessment under 21 CFR 25.31(c) is justified because the above mentioned product's fall into the category of substances that occur naturally in the environment and action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Recommendations

The review committee unanimously recommends approval of this BLA.

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[Seraclone Blood Grouping Reagent Anti-Fy^a\(Monoclonal\)](#)

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