

Summary Basis for Regulatory Action

Date: October 21, 2016

From: Oumou K Barry, Chair of the Review Committee, CBER, OBRR, Division of Blood Component and Devices (DBCD), Devices Review Branch (DRB)

BLA/ STN#: See Table 1 below,

Applicant Name: Bio-Rad Medical Diagnostics GmbH, located in Dreieich, Germany

Date of Submission: February 27, 2014 received by CBER on March 7, 2014

MDUFA Goal Date: October 21, 2016

Proprietary Name: IH-Card

Table 1: STN, Established Name (common or usual name), and Clone

| STN | Product Name | Clone |
|------------|---|--|
| 125094/113 | Blood Grouping Reagent, Anti-A (Murine Monoclonal) (Formulated for Automated Testing) | 157 50F7 |
| 125096/58 | Blood Grouping Reagent, Anti-A,B (Murine Monoclonal) (Formulated for Automated Testing) | AB5-63A5A2/X9 |
| 125097/67 | Blood Grouping Reagent Anti-D (Monoclonal)(IgM)(Formulated for Automated Testing) | Anti-D (VI+) BS226/ ESD1-M Ant-D (DVI-) B9A4 |
| 125202/50 | Blood Grouping Reagent, Anti-E (Monoclonal) | DEM-1 |

| | | |
|-----------|---|-------------------|
| | (Formulated for Automated Testing) | |
| 125203/48 | Blood Grouping Reagent, Anti-e (Monoclonal) (Formulated for Automated Testing) | Anti-e MS16/21/63 |
| 125204/46 | Blood Grouping Reagent, Anti-K (Monoclonal) (Formulated for Automated Testing) | Anti-K MS56 |
| 125205/46 | Blood Grouping Reagent, Anti-c (Monoclonal) (Formulated for Automated Testing) | Anti-c MS33 |
| 125206/48 | Blood Grouping Reagent, Anti-C (Monoclonal) (Formulated for Automated Testing) | Anti-C MS24 |

Intended Use:

The Blood Grouping Reagents (BGRs) listed above are intended to be used as components to manufacture the IH gel card products. The final in-vitro products (IH-Cards) are intended to be used on the IH-1000 Analyzer for Blood Grouping and Antigen Typing, using the column agglutination and gel filtration technique. For example, IH-Card ABO/D (DVI-)+Rev AI, B is intended for ABO forward and reverse grouping including D (RH1) antigen typing.

Recommended Action: Approval

Signatory Authorities Action:

Division Signatory Authority: Orijei Illoh, MD, Director, Division of Blood Component and Devices

- 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.

Offices Signatory Authority: Mary Malarkey, Director, Office of Compliance and Biologics Quality

- 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.**

Table 2

| Material Reviewed/ Consulted | Specific documentation used in developing the SBRA |
|-------------------------------------|--|
| Reviewer Name – Document(s) | Date |
| Clinical Review | Oumou K Barry, OBRR/DBCD/DRB Review Memo Date: August 16, 2016 |
| Non-Clinical Review | Oumou K Barry, OBRR/DBCD/DRB Review Memo Date: August 16, 2016 |
| Statistical Review | Zhen Jiang, OBE/DB/TEB Review Memos November 26, 2014 October 30, 2015 |
| CMC Facility Review | Chad Burger OCBQ/DMPQ/BII |
| CMC Product Review | Oumou K Barry, OBRR/DBCD/DRB Review Memo Date: August 16, 2016 Simleen Kaur (Microbiology/Bioburden) Review Memo Date: November 6, 2014 |

| | |
|-------------------------------------|--|
| | Karen Campbell (Lot Release Protocols/Testing Plans) OCBQ/DBSQC/QAB Review Memo Date: November 17, 2015 |
| Labeling | Dana Jones OCBQ/DCM/APLB Review Memo Date: August 26, 2014 |
| Lot Release Protocols/Testing Plans | Karen Campbell OCBQ/DBSQC/QAB Review Memo Date: February 11, 2016 |
| Bioresearch Monitoring Review | Not applicable for these submissions |
| Establishment Inspection Report | Chad Burger OCBQ/DMPQ/BII |
| Advisory Committee Transcript | Not applicable |
| Other (list) | Not applicable |

1. Introduction:

Bio-Rad Medical Diagnostics GmbH (BMD), located in Dreieich, Germany (Establishment Registration Number 9610824) submitted to the FDA, 17 applications to obtain approval for an automated immunohematology test system called the IH-System. The submissions consist of:

- Three Biologics License Applications (BLAs): one Anti-Human Globulin and two Blood Grouping Reagents (BGRs).
- Ten Efficacy Supplements: one Anti-Human Globulin, eight BGRs, and one Reagent Red Blood Cells (RRBCs).
- Four 510(k) premarket notifications for the analyzer, software, control and neutral card.

The following is a list of all submissions associated with the IH-System:

- BMD - BLAs and Efficacy Supplements:

- Anti-Human Globulin (Rabbit/Murine Monoclonal)(Formulated for Automated Testing), STN 125529/0
 - Anti-Human Globulin (Formulated for Automated Testing) STN 125098/88
 - Blood Grouping Reagent, Anti-B (Murine Monoclonal)(IgG)(Formulated for Automated Testing), STN 125532/0
 - Blood Grouping Reagent, Anti-D (Monoclonal Blend)(Formulated for Automated Testing), STN 125533/0
 - Blood Grouping Reagent, Anti-A (Murine Monoclonal)(Formulated for Automated Testing), STN 125094/113
 - Blood Grouping Reagent, Anti-A,B (Murine Monoclonal)(Formulated for Automated Testing), STN 125096/58
 - Blood Grouping Reagent, Anti-D (Monoclonal)(IgM)(Formulated for Automated Testing), STN 125097/67
 - Blood Grouping Reagent, Anti-E (Monoclonal)(Formulated for Automated Testing), STN 125202/50
 - Blood Grouping Reagent, Anti-e (Monoclonal)(Formulated for Automated Testing), STN 125203/48
 - Blood Grouping Reagent, Anti-K (Monoclonal)(Formulated for Automated Testing), STN 125204/46
 - Blood Grouping Reagent, Anti-c (Monoclonal)(Formulated for Automated Testing), STN 125205/46
 - Blood Grouping Reagent, Anti-C (Monoclonal)(Formulated for Automated Testing), STN 125206/48
 - Reagent Red Blood Cells For Use in Automated Systems, STN 125208/70
- BMD - Companion 510(k) submissions:
 - BK140106 IH-1000 Analyzer System
 - BK140107 IH-COM (data management software)
 - BK140138 IH-Card Neutral
 - BK140139 IH-Card Control

The above submissions were grouped as follows: one group containing two Anti-Human Globulin reagents, one group containing 10 Blood Grouping Reagents, one group containing eight Reagent Red Blood Cells, and one group containing four 510(k) premarket notifications.

- (b) (4) [REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]
 - [REDACTED]
[REDACTED]

The ABO system was discovered in the 1900 by Karl Landsteiner and associates and it is the most important blood group system in transfusion practice. The importance of the discovery of the ABO system is the recognition that antibodies are present when the corresponding antigens are lacking. The Rh system is the second most important blood group system. There are more than 50 blood group antigens in the Rh system. However, the D, C, E, c, and e antigens are the most immunogenic and clinically significant. Antibodies to Rh antigens can cause hemolytic transfusion reactions and hemolytic disease of the fetus and the newborn. The Kell system is complex, and contains many antigens. The K (KEL1) antigen is the most important in the Kell system from a clinical perspective because it is highly immunogenic. Anti-K is a frequently encountered antibody and can cause hemolytic transfusion reactions and hemolytic disease of the fetus and the newborn. Testing for red blood cell antibodies and antigens is commonly performed by serologic methods using commercially manufactured antisera derived from polyclonal or monoclonal sources, or red blood cells confirmed to have specific antigens.

The IH-System performs ABO grouping, red blood cell antigen typing, detection and identification of clinically significant red blood cell antibodies, crossmatching, and direct antiglobulin testing, based on the principles of agglutination and gel filtration. The IH-System consists of:

- IH-Card: a plastic card, consisting of six microtubes containing the component, (i.e., Blood Grouping Reagent or Anti Human Globulin), in a buffered (b) (4) gel suspension.
- IH-Anti-D Blend: vial of Anti-D reagent for performing weak D and DVI testing using the IH-AHG Anti-IgG card.
- IH-Cell products: vial of Reagent Red Blood Cells (i.e., reverse grouping cells, screening cells, pooled cells, and identification panel cells).
- IH-1000 Automated Analyzer System: a fully automated, walkaway, high throughput analyzer for the IH-Cards.
- IH-COM: stand-alone software to be used for data management, and the evaluation and interpretation of assay results. The software is directly linked to the IH-1000 via a bidirectional interface and can also be interfaced with the customer's Laboratory Information System (LIS).
- IH-Card Neutral: a plastic card, consisting of six microtubes with (b) (4) containing suspension medium, potentiating and preservative medium used for the detection of ABO antibodies during the reverse grouping. (Note: The neutral gel is also contained in single microtubes of certain IH-Cards containing Blood Grouping Reagents).
- IH-Card Control: a plastic card, consisting of six microtubes with (b) (4) containing buffer, diluent medium, and preservative, and is intended for use as a supplemental control for IH-Cards with monoclonal Blood Grouping Reagent without a control well.
- IH-LISS Rack (Class II Exempt from pre-market notification): consists of 10 plastic cards, each with six microtubes, filled with a suspending medium, (i.e., modified Low Ionic Strength Solution). The IH-LISS is used for preparing red blood cell suspensions for use with the appropriate IH-Card.

The IH-System is not a first of its kind device. Other manufacturers have been approved/cleared to market manual and automated immunohematology test systems; using the

column agglutination technique first described by Yves Lapierre in 1985 for the detection of red blood cell agglutination.

2. Background:

Meetings with FDA

FDA held a pre-submission (CRMTS # 8105, PTS PS001492) meeting with BMD on October 6, 2011. The discussion items included performance studies design, statistical analysis and data reporting, instrument changes, and submission strategy. The meeting package indicated that the future submissions would include both manual and automated testing methods and instrumentation. Prior to submitting the respective applications to CBER in February 2014, BMD decided to only submit information and data for automated testing using the IH-1000 Automated Analyzer System.

Marketing History

- The design of the IH-Cards is based on technology transfer from two commercially distributed products manufactured by DiaMed Ltd., and Bio-Rad Laboratories, Inc. The plastic card is used by DiaMed Ltd. (Morat, Switzerland) for the DiaMed ID-Micro Typing System that was introduced to non-US markets in 1988 and is still manufactured and marketed by Bio-Rad in Switzerland. The gel was used by Bio-Rad Laboratories, Inc. in (b) (4) for manufacturing the ScanGel® Cards distributed to non-US markets from the late 1990's to 2014.
- The FDA approved Biotest U.S. License No. 1798 in August of 2008 to use components Anti-e (STN 125203/0), Anti-K (STN 125204/0), Anti-c (STN 125205/0), and Anti-C (STN 125206/0) from Millipore (under shared manufacturing arrangement) and Anti-D (VI+) STN (125097/10) from (b) (4) (contract manufacturing arrangement) as raw materials to manufacture final products for use on the FDA cleared Tango® Automated Analyzer. BMD, U.S. License No. 1845, subsequently

acquired portions of Biotest (b) (4)

Device Description

- The IH-System is an Immunohematology Test System that consists of an analyzer, software (IH-COM), IH-Card BGRs, and supplemental reagents for automated testing. The test principle is based on gel filtration and column agglutination. In gel filtration technique, the gel in the microtube acts as a sieve; after centrifugation of the card, non- agglutinated RBCs settle at the bottom of the microtube while the agglutinated cells are dispersed throughout the gel depending on their size.
- BMD uses the in vitro substances (IVSs) as active components to manufacture the final in vitro gel card products called IH-Cards. The card is made up of plastic material and consists of six microtubes in each card. Some microtubes are filled with buffered (b) (4) gel suspension mixed with different blood grouping specificities used for antigen typing of red blood cells. Some microtubes are filled with the buffered gel suspension alone. These serve as the neutral/control microtubes for reverse ABO typing or control. The BGR cards include two types of controls; the control I diluent is used in the Anti-D (VI-) cards and the control II diluent is used in the Anti-D (VI+). The control diluents are designated based on formulation of the two Anti-D reagents. The control microtubes only contain the gel supernatant and serve as negative controls to ensure the test samples do not spontaneously agglutinate in the gel microtube.
- The analyzer is a fully automated high throughput instrument that performs a variety of assays. The gel cards, reagents and samples are automatically identified by the barcode reader after being placed on the analyzer. Sample pipetting, reagent pipetting and incubation of reaction, if applicable, are all performed automatically without interaction from the operator. Reactions in the gel microtube are captured by the camera and analyzed by the image evaluation software for grading. The

evaluated images are transferred to the IH-COM external data management software for further interpretation and generation of results. Every individual result that is generated from the instrument is reviewed; validated and questionable results are edited (changed) as needed. The IH-System is intended for blood collection establishments, transfusion services and hospitals for blood donor and patient testing.

Table 3 below shows the various (in vitro product) gel card configurations BMD manufactures using the various IVSs.

Table 3: IH-Card Configurations

| | <i>In vitro</i> substance / gel component | Anti-A (15750F7) | Anti-B (X9) | Anti-A+B (AB5-63-A5-A2/X9) | Anti-DVI- (B9A4) | Anti-DVI+ (ESD IM/BS226) | Anti-C (MS24) | Anti-e (MS33) | Anti-e MS16/MS21/MS63 | Anti-K (MS 56) | Anti-E (DEMI) | Control I* | Control II* | Neutral 55/45* | Anti-IgG + C3d** |
|-------------------------------------|---|------------------|-------------|----------------------------|------------------|--------------------------|---------------|---------------|-----------------------|----------------|---------------|------------|-------------|----------------|------------------|
| <i>In vitro</i> product (gel cards) | Configuration | | | | | | | | | | | | | | |
| IH-Card ABO/D(DVI-)+Rev A1.B | A-B-D(DVI-)-ctl1-A1-B | x | x | | x | | | | | | | x | | 2x | |
| IH-Card ABO/D(DVI+)+Rev A1.B | A-B-D(DVI+)-ctl2-A1-B | x | x | | | x | | | | | | | x | 2x | |
| IH-Card ABO/RhD(DVI+) | A-B-AB-D(DVI+)-ctl2, AHG | x | x | x | | x | | | | | | | x | | x |
| IH-Card Group A.B | AB-AB-AB-AB-AB-AB | | | 6x | | | | | | | | | | | |
| IH-Card Group ABO | A-B-A-B-A-B | 3x | 3x | | | | | | | | | | | | |
| IH-Card ABD(DVI-)-Conf | A-B-D(DVI-)-A-B-D(DVI-) | 2x | 2x | | 2x | | | | | | | | | | |
| IH-Card ABD(DVI+)-Conf | A-B-D(DVI+)-A-B-D(DVI+) | 2x | 2x | | | 2x | | | | | | | | | |
| IH-Card Rh-Phenotype+K | C-E-c-e-K-ctl1 | | | | | | x | x | x | x | x | x | | | |
| IH-Card Anti-C | C-C-C-C-C-C | | | | | | 6x | | | | | | | | |
| IH-Card Anti-E | E-E-E-E-E-E | | | | | | | | | 6x | | | | | |
| IH-Card Anti-c | c-c-c-c-c-c | | | | | | | 6x | | | | | | | |
| IH-Card Anti-e | e-e-e-e-e-e | | | | | | | | 6x | | | | | | |
| IH-Card Anti-D (DVI+) | D-D-D-D-D-D (DVI-) | | | | | 6x | | | | | | | | | |
| IH-Card Anti-D (DVI-) | D-D-D-D-D-D (DVI-) | | | | 6x | | | | | | | | | | |
| IH-Card Anti C-E-K | C-E-K / C-E-K | | | | | | 2x | | | 2x | 2x | | | | |
| IH-Card Anti-K | K-K-K-K-K-K | | | | | | | | | 6x | | | | | |
| IH-Card RhD(DVI+)-Phenotype | D(DVI-)-C-E-c-e-ctl1 | | | | x | | x | x | x | | x | x | | | |

*Control I, Control II and Neutral 55/45 are (b) (4) gels containing suspension medium, potentiators and preservatives.
 **Anti-IgG + C3d is a gel suspension containing Anti-Human Globulin Anti-IgG (Rabbit polyclonal) and Anti-Human Globulin Anti-C3d 053A-714. The manufacturing of this gel suspension is covered by an adjacent BLA submission.

Source: Original submission, Vol-004 CMC section, page 88 of 245

Chronology

CBER received the efficacy supplement submissions and the BLA submissions for the BGRs on March 7, 2014. CBER issued a Filing with No Deficiencies Letter on May 1, 2014. CBER subsequently received 31 amendments submitted by BMD in response to various information requests. A Complete Response (CR) Letter was issued on December 31, 2014. A second CR letter was issued on November 20, 2015 due to unresolved issues

with the companion (b) (4) submissions. A final amendment dated August 26, 2016 completed BMD's responses to all outstanding issues associated with the BGR submissions.

3. Chemistry Manufacturing and Controls (CMC)

All manufacturing is carried out in a controlled environment. The applications were 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

Manufacturing of the BGR submission covered four main stages: the IVSs, (b) (4), production of the gel (b) (4), and filling/packaging of the final product. According to the validation data submitted, the manufacturing process was validated using worst scenarios. The validation data have been reviewed and found acceptable. The submissions indicate that in-process testing and specifications are established up to release of the final product.

Manufacture of the Components/IVSs

- I. Anti-e, Anti-K, Anti-c and Anti-C from Millipore are FDA licensed FFMU products.
- II. Anti-D (VI+) clone (BS226) from (b) (4) : Is an established product;
(b) (4)
- III. (b) (4)

IV. Anti-A 157 50F7, Anti-A,B AB5-63A5A2, Anti-D (VI-) B9A4 are manufactured at Bio-Rad Laboratories located in (b) (4) under a contract manufacturing arrangement with BMD.

- a) The certificates of analysis (CoAs) from Bio-Rad Laboratories for the raw materials used in the manufacture of the components at the (b) (4) facility were reviewed and found acceptable. BMD accepts raw materials that are derived from animal source such the Fetal Calf Serum (FCS) with CoAs verifying the origin is Bovine Serum Encephalitis (BSE) free country.
- b) The components from Bio-Rad Laboratories are derived from cell culture supernatant of immunoglobulin-secreting hybridoma cell lines.
 - i. IVSs Anti-A and Anti-A,B clones are produced by merging murine monoclonal antibody producing cells and mouse (b) (4) cells yielding IgM κ monoclonal antibodies.
 - ii. IVS Anti-D (VI-) clone is produced by merging human antibody producing cells (b) (4) and mouse (b) (4) cells yielding IgM λ monoclonal antibodies.

The monoclonal antibodies were tested and confirmed to be specific for their respective human red cell antigens.

- c) (b) (4)
- (b) (4)

(b) (4) [Redacted]
[Redacted]

d) (b) (4) [Redacted]
[Redacted]
[Redacted] [Redacted] [Redacted]
[Redacted]
[Redacted]

e) (b) (4) [Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

f) (b) (4) [Redacted]
[Redacted]
[Redacted]

Inspection and testing of the incoming goods

Incoming Goods which include the (b) (4) bovine serum albumin (BSA), components and other excipients are checked against the shipping documents and in-process tested according to the CoAs or based on in-process testing established at BMD. During incoming inspections, the raw materials are labeled as “In quarantine” and are stored in separate, monitored locations based on storage requirement of the materials. Incoming

goods are released for manufacturing by BMD's Quality Assurance Unit based on testing results.

(b) (4) *Gel*

- (b) (4) gel used to manufacture the (b) (4) is received from Bio-Rad located in (b) (4). BMD receives the gel and performs incoming testing, which includes (b) (4). Review of the CoAs submitted for the various gel concentrations show that specifications for incoming testing were met.

- (b) (4)
(b) (4)

(b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)

(b) (4) [Redacted text block]

Production of the Gel (b) (4)

(b) (4) [Redacted text block]

Filling of the final container

(b) (4) [Redacted text block]

(b) (4) [Redacted]

Date of Manufacture (DOM)

The DOM for the in vitro products is the day the (b) (4) [Redacted] the cards. BMD proposes a shelf life of 16 months for the BGR cards from the DOM.

Labeling and Packaging of IH-Cards

(b) (4) [Redacted]

Quality Control (QC) Testing/Specifications:

(b) (4) [Redacted]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Final serological QC of the in vitro products is carried out after [REDACTED] and sealing to allow sedimentation of the gel particles. Final serological QC of the in vitro products include specificity testing with antigen positive RBCs, negative specificity and absence of contaminated antibodies using antigen negative cells, and visual inspection. The visual inspections include checking for intact sealing, presence of gel and supernatant, and homogeneity. The table below lists the group of cells and acceptance criteria established for positive specificity testing of each BGR.

Table 5: Positive specificity testing at final serological QC

| IVS | Clone | Method | Acceptance Criteria |
|--------|---------|-------------------------------------|-------------------------------------|
| Anti-A | 15750F7 | (b) (4) [REDACTED] [REDACTED] | (b) (4) [REDACTED] [REDACTED] |
| Anti-C | MS24 | (b) (4) [REDACTED] [REDACTED] | (b) (4) [REDACTED] |
| Anti-c | MS33 | (b) (4) [REDACTED] | (b) (4) [REDACTED] |

| | | | |
|-----------------|-------------------------|---------|---------|
| | | (b) (4) | |
| Anti-A, B | AB5-63- A5- A2/X9 | (b) (4) | (b) (4) |
| Anti-E | DEM-1 | (b) (4) | (b) (4) |
| Anti-e | MS16/ MS21/ MS63 | (b) (4) | (b) (4) |
| Anti-K | MS56 | (b) (4) | (b) (4) |
| Anti-D (VI-) | B9A4 | (b) (4) | (b) (4) |
| Anti-D (VI+) | BS226/ ESD1M | (b) (4) | (b) (4) |

| | | |
|--|--|---------|
| | | (b) (4) |
|--|--|---------|

Source: Table D-4, on page 166 CMC section of the original submission

The table below lists the group of cells and acceptance criteria established for negative specificity and absence of contaminating antibodies for each BGR.

Table 6: Negative specificity testing at final serological QC

| IVS | Clone | Method | Acceptance Criteria |
|-----------------|---------------------|---------|---------------------|
| Anti-A | 15750F7 | (b) (4) | (b) (4) |
| Anti-C | MS24 | (b) (4) | (b) (4) |
| Anti-c | MS33 | (b) (4) | (b) (4) |
| Anti-A, B | AB5-63-A5- A2/X9 | (b) (4) | (b) (4) |
| Anti-E | DEM-1 | (b) (4) | (b) (4) |
| Anti-e | MS16/MS21/M S63 | (b) (4) | (b) (4) |
| Anti-K | MS56 | (b) (4) | (b) (4) |
| Anti-D (VI-) | B9A4 | (b) (4) | (b) (4) |

| | | | |
|--|-------------|---------|---------|
| | | (b) (4) | |
| Anti-D (VI+) | BS226/ESD1M | (b) (4) | (b) (4) |
| <p>Note: The RBCs to be tested for negative specificity may not express antigen to the corresponding antibody being tested and must cover the following antigens : C, c, D, E, e, K, k, Kp^b, Js^b, Fy^a, Fy^b, Lu^b, Jk^a, Jk^b, M, N, S, s, Le^a, Le^b, P₁</p> | | | |

Source: Table D-5, page 168 CMC section of the original submission.

Microbiology/Bioburden

Blood Grouping Reagents are microbiologically controlled products; they are not considered sterile. The manufacturing of the in-vitro products includes addition of sodium azide as preservative and filtration using [REDACTED]. The bioburden test method was qualified in accordance with [REDACTED]. The proposed sodium azide formulation concentration was shown to have effective anti-microbial properties in accordance with [REDACTED].

b. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A 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 for the BLAs for the manufacture of Blood Grouping Reagents was reviewed by CBER and found to be sufficient and acceptable. The following Blood Grouping Reagents associated with this bundled BLA are listed below.

| |
|--|
| Anti-B (clone X9) (IgG3Murine Monoclonal (Formulated for Automated Testing)) |
|--|

| |
|--|
| Anti-D (clones BS232/BS221/H41 11B7) (Human Monoclonal Blend IgM/IgG/IgG) (Formulated for Automated Testing) |
| Anti-A (clone 15750F7) (IgM Murine Monoclonal) (Formulated for Automated Testing) |
| Anti-A,B (clone AB5-63-A5-A2/X9) (IgM Murine Monoclonal) (Formulated for Automated Testing) |
| Anti-D(VI-) (clone B9A4) (IgM Human Monoclonal) and Anti-D(VI+) (clone BS226/ESD1-M) (IgM Monoclonal) (Formulated for Automated Testing) |
| Anti-E (clone DEM-1) (IgM Human Monoclonal) (Formulated for Automated Testing) |
| Anti-e (clone MS16/MS21/MS63) (IgM Human Monoclonal) (Formulated for Automated Testing) |
| Anti-K (clone MS-56) (IgM Human Monoclonal) (Formulated for Automated Testing) |
| Anti-c (clone MS-33) (IgM Human Monoclonal) (Formulated for Automated Testing) |
| Anti-C (clone MS24) (IgM Monoclonal) (Formulated for Automated Testing) |

The facilities involved in the manufacture of the Blood Grouping Reagents are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for Bio-Rad Blood Grouping Reagents

| Name/address | FEI number | DUNS number | Inspection/waiver | Results/Justification |
|--|------------|-------------|---|---|
| <i>Final device</i> Manufacturing and Testing Bio-Rad Medical Diagnostics GmbH Industriestr. 1 Dreieich, Hessen, Germany | 3002806595 | 312576506 | Surveillance Inspection Pre-License Inspection | Team Biologics March 16 - 24, 2015 VAI CBER October 1 - 10, 2014 VAI |
| <i>Component</i> Manufacturing Bio-Rad Laboratories, (b) (4) [REDACTED] | (b) (4) | (b) (4) | N/A* | N/A |
| <i>Component</i> (b) (4) | (b) (4) | (b) (4) | N/A* | N/A |

| | | | | |
|---------|--|--|--|--|
| (b) (4) | | | | |
| | | | | |
| | | | | |
| | | | | |

* Due to the nature of this product the *in vitro* substance manufacturer facilities were not required to be inspected.

CBER performed a Pre-License Inspection of the Dreieich, Germany facility from October 1-10, 2014. At the end of the inspection, a Form FDA 483 with seven observations was issued. The firm responded adequately addressing all 483 observations.

Subsequent to the PLI, Team Biologics performed a surveillance inspection of the Bio-Rad Medical Diagnostics GmbH manufacturing facility from March 16-24, 2015. The corrective actions were found to be acceptable and the inspection was classified as Voluntary Action Indicated (VAI).

d. Environmental Assessment

Bio-Rad Medical Diagnostics GmbH included a request for categorical exclusion from performing an Environmental Assessment under 21CFR Part 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 System

The blood grouping reagent (with the exception of IH-Anti-D RH1 Blend) is filled into polypropylene plastic cards (IH-Cards) with overall dimensions of 70 x 9 x 53 mm ((b) (4)). Each gel card has six small columns (micro tubes) integrated into them, which is filled with the blood grouping reagent and (b) (4) gel. The

opening of the columns is covered with a heat sealing lacquered aluminum foil ((b) (4) [REDACTED]).

Bio-Rad Medical Diagnostics GmbH conducted the container closure integrity testing for the IH-Cards at their Dreieich location. This testing consisted of the ((b) (4) [REDACTED]) and upright IH-Cards at a temperature between 18°C to ((b) (4) [REDACTED]). Then, the cards were tested for serological reactivity, bioburden, and visual inspection for the detection of leaks at 0, 3, 6, 9, 12, 16 ((b) (4) [REDACTED]) of the IH-Cards); all acceptance criteria were met.

The blood grouping reagent IH-Anti-D (RH1) Blend Product is filled in a 10mL glass vial ((b) (4) [REDACTED]). This container is closed with polypropylene screw cap that contains a 10 mL glass pipette with natural rubber bulb ((b) (4) [REDACTED]).

Bio-Rad Medical Diagnostics GmbH conducted the container closure integrity testing for the IH-Anti-D (RH1) Blend Product at their Dreieich location. This testing consisted of the ((b) (4) [REDACTED]) vials at a temperature ((b) (4) [REDACTED]). Then the vials were tested for serological reactivity and potency, bioburden, and visual inspection for the detection of leaks at 0, 3, 6, 9, 12, 18, 24 ((b) (4) [REDACTED]) IH-Anti-D (RH1) Blend Product); all acceptance criteria were met.

f. Transport/Shipping Studies

- Bio-Rad tested one conformance lot of each IH-Card product for the transport simulation study. The study was conducted to demonstrate that product performance is not affected by temperature conditions that may be encountered during shipment. The data submitted for the transport simulation study were acceptable.

- Bio-Rad also conducted simulation shipping validation studies which covered shipment of the IH-Card BGRs from Germany to the US distribution center and from the distribution center to customers. (b) (4)

[REDACTED]

4. Analytical Studies

Analytical studies performed included reproducibility study, lot-to-lot study, stability studies (shelf life and on-board), sample aging and anticoagulant studies and interfering substances study.

Reproducibility Study

This study was conducted at three sites (two external and one internal) using one lot of selected representative BGR products to test identical panel of samples on the IH-1000 Analyzer. One operator tested the panel samples on five non-consecutive test dates over a 20 day period, in duplicate, twice a day providing 60 data points (i.e., one lot of reagent x 3 sites x 2 duplicates x 2 runs x 5 days). The operator had the ability to manually edit (change) the instrument result if questionable. The edited data submitted showed 100% agreement.

Lot-to-Lot Study

BMD conducted the Lot-to-Lot Study internally using three lots of representative IH-Card BGR Products to test a panel of samples on the IH-1000 Analyzer. One operator tested each sample in duplicate, with two runs per day on five non-consecutive days over a 20 day period, providing 60 data points (i.e., 3 lots × 2 duplicates × 2 runs × 5 days). The operator had the ability to validate or edit (change) the instrument result if the initial result is questionable. The edited results for the selected products show 100% agreement.

Shelf life Stability

BMD conducted a shelf life stability study for establishing the dating period for the in vitro products. BMD used at least three conformance lots of each in vitro product for the shelf life stability study. The stability samples were stored at 18-25 °C and tested for specificity every three months until expiry and beyond. Based on the stability data, BMD proposes a 16 month shelf life for the in vitro IH-Cards when stored at 18-25 °C. The latest stability reports included in the amendment received on December 24, 2014 have been reviewed and found acceptable. The proposed shelf life of 16 months for the IH-Card BGRs is acceptable.

On-Board Stability

BMD's labeling claims that the IH-Cards can be stored on the IH-1000 for seven days and opened cards are stable on the analyzer for two hours. Bio-Rad performed on-board simulation study on one lot of each IH-Card BGR. (b) (4)

[REDACTED]

[REDACTED] The data submitted indicate that specifications were met for the simulation on-board cards.

Sample aging and anticoagulant studies

The sample aging and anticoagulant studies were conducted both internally at BMD and at the clinical sites. For the internal study, per protocol, BMD tested a minimum of (b) (4) EDTA samples up to 5 days post collection to support 5-days claim post collection. The performance studies data indicate that EDTA samples and donor segments containing (CP2D, CPD) anticoagulants with preservative solutions (AS-3 and AS-1) were tested with selected card configurations at the clinical trial sites and covered sample ages (one to 39 days). The data submitted indicate the results obtained with the fresh and stored samples were comparable.

Interfering substances

The data from the performance studies demonstrate that samples with light-moderate lipemia, hemolysis and icterus were tested using the IH-Card BGRs. BMD also conducted study internally to assess the effect of testing grossly hemolyzed, icteric and lipemic samples on the IH-1000 Analyzer. The data obtained from these studies demonstrate that higher than normal concentrations of triglycerides, bilirubin and hemoglobin do not have adverse effect on the performance of the IH-Card BGRs on the IH-System.

5. Clinical Studies

a) Clinical Program

BMD conducted clinical study to evaluate performance of the IH-System for its intended use in the hands of end-users in clinical settings. The clinical study was performed at four external United States (U.S.) sites: Puget Sound Blood Center, located in Renton, Washington, Vanderbilt University Medical Center located in Nashville, Tennessee, Miriam Hospital located in Providence, Rhode Island, LifeSource Testing Laboratory located in Rosemont, Illinois. There was one internal testing at Bio-Rad Laboratories located in Cressier, Switzerland. Over 6,400 leftover de-identified clinical specimens that included patient, donor, and cord bloods were tested to demonstrate sensitivity and specificity of the IH-Card BGRs. In the clinical study, the

performance of the IH-Card BGR was evaluated on the IH-1000 Analyzer for ABO grouping and RH phenotyping and the results were compared to FDA licensed reagents and cleared instruments for concordance. The table below shows the number of samples tested to evaluate the BGRs at the clinical sites.

Table 7: Number of Samples Collected and Analyzed per Site – BGRs

| Site | ABO Forward Testing | ABO Reverse (A1&B) | Anti-A,B | A2 RRBCs | Anti-D (DVI-) | Anti-D(DV I+) | Anti-D Blend | Rh-Phenotyping + K * |
|---|---------------------|--------------------|--------------|--------------|---------------|---------------|--------------|----------------------|
| Puget Sound Blood Center | 300 | 3,620 | 1,799 | 750 | 1,150 | 2,770 | 2,069 | 1,130 |
| Miriam Hospital | 497 | 1,000 | 599 | 150 | 1,250 | 247 | 301 | 249 |
| Vanderbilt University Medical Center | 0 | 994 | 600 | 150 | 994 | 0 | 316 | 130 |
| LifeSource Testing Laboratory | 199 | 725 | 200 | 0 | 100 | 824 | 822 | 0 |
| Total | 996 | 6,339 | 3,198 | 1,050 | 3,494 | 3,841 | 3,508 | 1,509 |

** Additional 55 selected known e antigen negative and 55 selected K antigen positive samples are tested in three sites*

Source: FDA Statistician’s memorandum

BMD used at least two conformance lots of each IH-Card BGR, and associated IH-System reagents to include BMD’s 0.6% RRBCs, IH-LISS Rack, IH-Card neutral for the performance evaluation studies. The clinical study started in October of 2012 and concluded in November of 2013. The sites were instructed to run QC at least once a day and proceed with testing only when the QC results were acceptable. Each result transferred for the IH-1000 to the IH-Com software was reviewed and validated by the end-user. A discrepancy between the reference method and the investigational method was repeated using both methods. If the repeat testing resolved the discrepancy no further testing was performed; if the discrepancy was not resolved on the repeat testing, a third licensed reagent or a molecular technique was used as a referee. The table shows the reference methods and reagents used at each clinical site:

Table 8: Reference methods and reagents used

| Site | Reference Method/Reagents Used |
|--------------------------------------|--|
| Vanderbilt University Medical Center | Immucor [®] Galileo Neo, Galileo Echo, manual gel or manual tube method (non-automated) according to package inserts (PIs) and the instrument operator's manual instructions. (ABO/D + Reverse typing). Bio-Rad Seraclone [®] reagents (Rh Phenotyping + K typing cards) |
| Puget Sound Blood Centers | Beckman Coulter PK7300 [™] using Diagast reagents (all IH-Cards). Selected weak D samples tested with the manual tube method using Ortho Anti-D according to PI instructions and instrument operator's manual instructions. |
| Miriam Hospital | Ortho Provue [®] using MTS [™] reagents and manual tube method using Ortho [®] BioClone [®] reagents (all IH-Cards) according to package PI or instruments operator's manual instructions. |
| LifeSource Testing Laboratory | Beckman Coulter PK7300 [™] using Diagast reagents and Manual Method using Bio-Rad Seraclone [®] reagents (ABO grouping cards) according to PI or instrument operator's manual instructions. Rh Phenotyping + K cards were not tested at this site. |

Source: Data obtained from individual site report, VoL-002-Clinical Section

Acceptance criteria for the BGRs: The lower bound of the one-sided 95% confidence interval for the positive and negative agreement with the comparison device/method has to exceed 0.99. The one-sided exact 95% Lower Confidence Limits (LCL) for Positive (PPA), Negative (NPA), and Overall Agreement (OPA) for the BGRs can be found in the table below.

Table 9: Point Estimates and Lower Confidence Limits for PPA, NPA and OPA

| BGR | PPA (Edited) | NPA (Edited) | OPA (Edited) |
|--------|--------------|--------------|--------------|
| Anti-A | 99.93% | 99.91% | 99.90% |

| | | | |
|---|--|--|----------------------------------|
| | 2940/2942 [99.79%] | 4388/4392 [99.79%] | 7328/7335 [99.82%] |
| Anti-A,B | 99.88% 1601/1603 [99.61%] | 99.94% 1592/1593 [99.70%] | 99.84% 3193/3198 [99.67%] |
| Anti-D (DVI-) No weak D claim | 99.86% 2940/2944 [99.69%] | <i>99.64%</i> <i>548/550</i> <i>[98.86%]</i> | 99.83% 3488/3494 [99.66%] |
| Anti-D (DV+) No weak D claim | 100% 3169/3169 [99.91%] | <i>99.40%</i> <i>668/672</i> <i>[98.64%]</i> | 99.90% 3837/3841 [99.76%] |
| Anti-C | 100% 1010/1010 [99.70 %] | <i>99.40%</i> <i>495/498</i> <i>[98.45%]</i> | 99.73% 1505/1509 [99.39 %] |
| Anti-c | 100 % 1207/1207 [99.75 %] | <i>99.67%</i> <i>301/302</i> <i>[98.44%]</i> | 99.93% 1508/1509 [99.69%] |
| Anti-E | 100% 431/431 [99.31%] | 99.72% 1075/1078 [99.28%] | 99.80% 1506/1509 [99.49 %] |
| Anti-e | 100% 1470/1470 [99.80%] | <i>97.87%</i> <i>92/94</i> <i>[93.45%]</i> | 99.87% 1562/1564 [99.60%] |
| Anti-K | <i>100%</i> <i>180/180</i> <i>[98.35%]</i> | 99.93% 1382/1383 [99.66%] | 99.87% 1562/1564 [99.60%] |
| <p>a: Lower confidence limits for one-sided 95% confidence intervals are listed in “[]”.</p> <p>b: The agreements that didn’t meet the acceptance criteria are in <i>Italic</i>.</p> | | | |

Source: FDA Statistician’s memo

A summary of the BGRs that did not meet the acceptance criteria for negative or positive percent agreement is listed below:

- BGR Anti-e did not meet the NPA because the “e” antigen is a high frequency antigen approximately (98%) of the general population. Anti-K did not meet the PPA because the “K” antigen is low frequency antigen approximately (2-9%) of the general population. During the Type B meeting referenced above, FDA agreed that BMD does not have to meet NPA for Anti-e and PPA for Anti-K as long as BMD tests 30 samples of each category. The data submitted indicate that the requirement to test 30 samples was met for both Anti-e and Anti-K.
- Two samples were discordant for Anti-e, positive on the investigational and negative on the licensed reference method. Both samples were confirmed to be heterozygous for the “e” antigen by molecular typing. This possibly caused the false negative on the reference method.

BGR Anti-D (VI-) did not meet NPA; factors contributing to this BGR not meeting the NPA include:

- Four specimens had initial negative on the reference method but initial equivocal (EQV) on the investigational.
- After editing the results and repeating the test, two specimens-remained discrepant, negative on the reference method but positive on the investigational. The two EDTA specimens were tested using a third licensed reagent; they were both confirmed to be weak D positive.

BGR Anti-D (VI+) did not meet NPA; factors contributing to this BGR not meeting the NPA include:

- Three specimens were negative on the reference method but positive on the investigational.
- Two specimens were negative on the reference method but EQV on the investigational.
- After editing the results and repeating the test, one specimen was confirmed to be negative on both methods and four remained discrepant.

- Three specimens (two cord bloods, one donor segment) were confirmed to be Weak D positive by a third licensed reagent. The fourth specimen was a cord blood; the investigation concluded the specimen to be contaminated with maternal blood.

BGR Anti-C did not meet NPA; factors contributing to this BGR not meeting the NPA include:

- Two specimens were negative on the reference method but EQV on the investigational.
- One specimen was initially negative on the reference method but positive on the investigational. This specimen was edited to EQV on the investigational. Upon repeat, the reference result changed to positive and the investigational remained EQV; sample issue was reported by the testing tech.
- After editing the results and repeating the test, two samples were confirmed to be positive on both methods; however, a transfusion history was reported in both cases following an observation of mixed field reactions.

BGR Anti-c did not meet NPA; factors contributing to this BGR not meeting the NPA include:

- One specimen was negative on the reference method but EQV on the investigational.
- After editing and repeating the test, the result remained the same. Review of the patient history did not indicate any recent transfusion. Investigation indicates that the specimen showed a mixed field reaction with BGR Anti-E as well. The investigation concluded that there was a specimen issue.

b) Other Special Populations (*Elderly, Pediatrics*)

According to the data submitted, evaluation of the BGRs included testing of minimum 396 cord blood samples and over 1000 elderly samples (65-103 years) age range.

c) Overall Comparability Assessment

- The data submitted indicate that instructions in the labeling were followed to successfully carry out the clinical performance study. The study data demonstrate safety and efficacy for the IH-Card BGRs.
- The submissions indicate that all critical manufacturing stages of the final products were properly validated. The data submitted for the conformance lots show that specifications were met for the in-process testing, and the lots remained stable through expiry.

6. Advisory Committee Meeting

The BMD IH-System does not include novel technology; therefore, an advisory committee meeting was not held or required.

7. Other Relevant Regulatory Issues

The review committee members from DBCD, DMPQ, DB, DCM, and DBSQC reviewed their specific sections of the BLA and Efficacy Supplement and resolved any issues through information requests with BMD. 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 IH-Card BGRs included in the efficacy supplement and BLA submissions.

No postmarketing commitments are associated with this BLA.

8. Labeling

The Advertising and Promotional Labeling Branch (APLB) reviewed the draft labeling for the instructions for use (IFU), the final container labels and the package labels. Review of

the labels indicates that the labels were made in accordance with (21 CFR 660.28 and 21 CFR 809.10). The final revised label submitted have been reviewed and found acceptable. Unique Device Identification (UDI) review performed by CBER found the required elements to comply with Title 21 CFR 830. The labeling met the UDI requirements ahead of the September 24, 2016 compliance date for this classification of medical devices.

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 the content of the efficacy supplements submission, issues satisfactorily resolved during the review cycle, and concurrence by their respective management. No internal or external disagreements were brought to the attention of the chairperson.

b) Risk/ Benefit Assessment

- The IH-1000 Automated Analyzer and the reagents used by the IH-System, provide potential advantages to support transfusion medicine.
- The clinical benefits using the IH-System include greater patient safety and timely availability of transfusion products to the patient through improved productivity.
- Features that impact patient safety include reduction in errors associated with subjective interpretation due to manual testing, transcription errors, test errors (i.e., using expired reagents or the wrong reagent), and the capability to review of stored test results, if necessary.
- Features that impact timely availability of transfusion products include reduction in hands-on technologist time by automating the process, time

required for recording assay reagents, controls, and equipment, as well as turn-around time.

c) **Recommendation for Postmarketing Activities**

There are no postmarketing commitments associated with these IH-Card Blood Grouping Reagents (Formulated for Automated Testing) submitted in the efficacy supplement submissions.