

# Summary Basis for Regulatory Action

**Date:** October 20, 2016

**From:** Oumou Barry, Chair of the Review Committee, CBER/OBRR/DBCD/DRB

**BLA/ STN#:**125533/0

**Applicant Name:** Bio-Rad Medical Diagnostics GmbH---U.S. License No. 1845, located in Dreieich, Germany

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

**MDUFA Goal Date:** November 25, 2016

**Proprietary Name:** IH-Anti-D (RH1) Blend

**Established Name** Blood Grouping Reagent, Anti-D (Monoclonal Blend) (Formulated for Automated Testing)

**Intended Use:** The IH-Anti-D (RH1) Blend is intended to be used with the IH-Card AHG Anti-IgG to detect weak D and partial D (DVI) by Indirect Antiglobulin Test (IAT) using the IH-System.

**Recommended Action:** Approval

**Signatory Authorities Action:**

**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.

**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 1**

<b>Material Reviewed/ Consulted</b>	<b>Specific documentation used in developing the SBRA</b>
<b>Reviewer Name – Document(s)</b>	<b>Date</b>
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, provided write-up for this section on 9/8/2016.
CMC Product Review	Oumou K Barry, OBRR/DBCD/DRB Review Memo Date: August 16, 2016  Simleen Kaur, (Microbiology/Bioburden) OCBQ/DBSQC/LMIVTS Review Memo Date: November 3, 2014
Labeling	Dana Jones, OCBQ/DCM/ALP Review Memo
Lot Release Protocols/Testing Plans	Karen Campbell Review Memo Date: February 8,11, 2016
Bioresearch Monitoring Review	Not applicable for these submissions
Establishment Inspection Report	Chad Burger OCBQ/ DMPQ/BII, provided write-up for this

	section on 9/8/2016.
Advisory Committee Transcript	Not applicable
Other (list)	Not applicable

## 1. Introduction

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

The submissions consisted of:

- Three Biologics License Applications (BLAs) for Anti-Human Globulin and Blood Grouping Reagents
- Ten Efficacy Supplements for Anti-Human Globulin, Blood Grouping Reagents, and Reagent Red Blood Cells (RRBCs)
- Four 510(k)s- 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 products, one group containing ten Blood Grouping Reagents, one group containing eight Reagent Red Blood Cells, and one group containing the four 510(k) products.

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

The ABO system was discovered by Landsteiner in the 1900s and is still the most important blood group system in transfusion practice. The ABO system is defined by the presence and or absence of A and / or B antigens on the surfaces of red blood cells with the corresponding antibodies in plasma or serum of the test sample. The Rh system is the second most important blood group system and was first described in the 1940s. There are more than 50 blood group antigens in the Rh system. However, the D, C, E, c, and e antigens are considered to be the most immunogenic and clinically significant. Antibodies to Rh antigens 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 from red blood cells confirmed to have specific antigens.

The IH-System performs ABO grouping, antigen typing, detection and identification of clinically significant red 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 reactive 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 containing (b) (4) containing suspension medium, which is a 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 containing (b) (4) containing buffer, diluent medium, and preservative, which 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): 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 test systems approved for performing manual and automated immunohematology testing 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.
- According to the FDA records, BMD was licensed in 2008 to manufacture Anti-D (RH1) Blend (clones BS232/BS221/H41 11B7) under STN 125223/0 for use as vialled reagent in a manual tube test method.
- BMD is now seeking FDA approval for the IH-Anti-D (RH1) Blend that is intended to be used with IH-Card AHG Anti-IgG for testing weak and partial D antigens (including DVI) in Low Ionic Saline Solution (LISS)-Indirect Antiglobulin Test (IAT) procedures on the IH-1000 Automated Analyzer.

#### *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.
- Bio-Rad uses in vitro substances (IVSs) Anti-D clones (BS232/BS221/H41 11B7) as reactive components to manufacture in vitro product IH-Anti-D (RH1) Blend. The IVSs are manufactured from cell culture supernatant and the final in vitro product is supplied as a 5 ml liquid reagent in a 10mL glass vial. The IH-Anti-D (RH1) Blend is intended to be used with IH-Card AHG Anti-IgG for testing weak and partial D



antigens (including DVI) in Low Ionic Saline Solution (LISS)-Indirect Antiglobulin Test (IAT) procedures on the IH-1000 Automated Analyzer.

- The analyzer is fully automated high throughput and 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. Reaction in the gel microtube are captured by the camera and analyzed by the image evaluation software for grading. The evaluated images are transferred to IH-COM, external data management software for further interpretation and generation of results for the test sample. Every individual result from the analyzer is visually reviewed, validated and manually edited (changed) if questionable. The IH-System is intended for blood collection establishments, transfusion services and hospitals for donor and patient testing.

#### *Chronology*

CBER received a BLA submission for IH Anti-D (RH1) Blend on March 7, 2014. CBER issued a Filing with No Deficiencies Letter on May 1, 2014. CBER subsequently received 28 amendments submitted by BMD in response to various information requests. A Complete Response (CR) letter was issued on December 31, 2014. FDA issued a second CR letter on November 20, 2015 due to unresolved issues with the companion AHG submissions. A final amendment dated August 26, 2016 completed Bio-Rad responses to all outstanding issues associated with this BLA application.

### **3. Chemistry Manufacturing and Controls (CMC)**

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

The manufacturing stages of the IH-Anti-D (RH1) Blend include: manufacturing of the bulk, filtration (b) (4), sub-lotting, filling and packaging. BMD submitted certificates of analysis (CoA) for the raw materials and excipients used to manufacture the final products. The CoAs were reviewed and found acceptable. According to the validation data submitted, the manufacturing process was validated using worst case 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.

*Manufacturing of components*

The IVSs components used to manufacture the new IH-Anti-D (RH1) (b) (4)  
The components used for this product are the same ones used in the licensed Anti-D under (STN 125223/0).

*Manufacturing of the vitro product (IVP)*

All manufacturing including final product release testing of this in vitro product is performed at the BMD facility located in Dreieich, Germany.

*Inspection and testing of the Incoming Goods*

Incoming Goods which include the (b) (4) bovine serum albumin (BSA), the IVSs and other excipients, are checked against the shipping documents and are in-process tested according to the CoAs or based 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 the storage requirement of the material. Incoming goods are released for manufacturing by BMD's Quality Assurance Unit based on testing results.

*Manufacturing of the (b) (4) solution*

(b) (4)

*Filtration and Sub-lotting of the (b) (4) solution*

(b) (4)

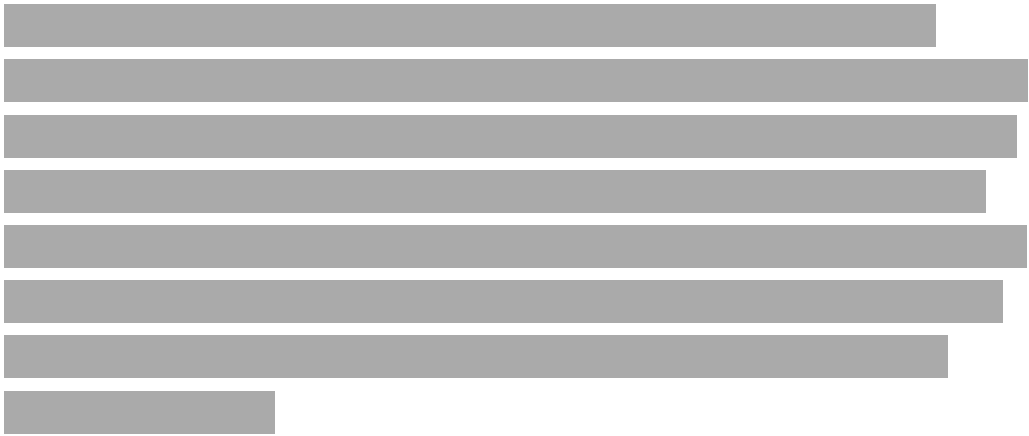
*Date of manufacture (DOM) and Expiration Date*

The date of manufacture for the IH-Anti-D (RH1) is considered to be the date the (b) (4) container is (b) (4) filtered, which can be up to (b) (4) prior to the date of filling. BMD proposes a shelf life of 24 months from the DOM.

*Filling of the final product*

- Filling is carried out at the filling and packaging department in Building (b) (4)

(b) (4)



- Vials are automatically labeled using the (b) (4) label system; the system is connected to the SAP System from which it receives the lot specific information. The first label is printed to check contents and barcode reading before the labeling process is initiated. Also, at the end of labeling, the same check is carried out on the last printed label for correctness of labeling information. Finally, labeled vials undergo a visual examination to check for absence of leakage, visible particles, turbidity, defective/correct fitting of the pipette top closures, and presence of the labels. Vials that do not pass the visual controls are rejected and vials that pass the checks are stored in quarantine at 2-8 °C until release based on final serological control.

#### *Packaging of the IVP*

After the product is released by final serological control, the vials are automatically packaged using an Automatic Packaging Machine; alternatively, a manual process is in place. The Automatic Packaging Machine consists of a cardboard box folding unit, a second unit folding the package insert and a third unit for labeling the outer carton. Final packaged in vitro product is stored at the warehouse at 2-8 °C prior to shipping out to customers. At packaging the visual inspection is performed for particles and defective pipettes, tightness of the closure and correct labeling.

Final Quality Control (QC) Testing

BMD performs final serological QC on the final in-vitro product to verify specifications as well as standards defined for packaging and labeling. Final serological QC testing of the IH-Anti (RH1) Blend includes negative and positive specificity testing, absence of in-vivo coating of test red blood cells (RBCs) and potency testing by means of titer determination. Final QC on the label packed product include a visual check of label content and label positions and instructions for use (IFU) for correctness and completeness. The specifications/ acceptance criteria established for testing IH-Anti-D (RH1) blend at final serological QC are listed below.

**Table 2:** Serological Specifications for IH-Anti-D (RH1) Blend at final QC

Parameter	Method	Acceptance Criteria
Specificity testing against antigen positive cells	(b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted]	(b) (4) [Redacted] [Redacted]
Specificity against antigen negative cells	(b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted]	(b) (4) [Redacted]

	(b) (4) [REDACTED] [REDACTED]	
Direct Antiglobulin Test (DAT) to verify in vivo coating of the test red cells	(b) (4) [REDACTED] [REDACTED] [REDACTED]	(b) (4) [REDACTED]
Potency Testing	(b) (4) [REDACTED] [REDACTED] [REDACTED]	(b) (4) [REDACTED] [REDACTED] [REDACTED]

**Source:** Page 234-235 of 245 of the CMC section original submission.

*Microbiology/Bioburden*

Blood Grouping Reagents are microbiologically controlled products; therefore, they are not considered sterile. CBER found the bioburden test method is qualified in accordance with (b) (4) . And the proposed sodium azide formulation concentration is shown to have effective anti-microbial properties in accordance with (b) (4)

**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 Reagent 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 Reagent 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**

<b>Name/address</b>	<b>FEI number</b>	<b>DUNS number</b>	<b>Inspection/waiver</b>	<b>Results/Justification</b>
<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)	(b) (4)	N/A*	N/A
(b) (4)				
(b) (4)				
(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 IH-Anti-D (RH1) Blend Product is filled in a 10mL glass vial (b) (4) This container is closed with a



polypropylene screw cap that contains a 10 mL glass pipette with natural rubber bulb  
(b) (4)

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) vials at a temperature

(b) (4)

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, (b) (4) after the shelf life of the IH-Anti-D (RH1) Blend Product); all acceptance criteria were met.

#### **f) Transport/Shipping Studies**

Bio-Rad uses FDA previously approved validated shipping containers for shipment of this vial reagent. Also, as part of the stability studies, Bio-Rad tested one conformance lot of IH-Anti-D (RH1) Blend for the transport simulation study. The samples were exposed to various temperature conditions for up to (b) (4) then returned to normal storage for testing up to expiry. The temperature stimulation study was conducted to demonstrate that product performance is not affected by temperature conditions that may be encountered during transport. The data submitted indicate that the temperature excursion samples met specifications up to expiry.

## **4. Analytical Studies**

Analytical studies included a lot-to-lot precision study, reproducibility study, interfering substances study, stability (shelf life /on-board) studies, sample aging and anticoagulant studies, and weak D testing.

### *Lot-to-Lot Studies*

BMD conducted the Lot-to-Lot Study internally using three conformance lots of IH-Anti-D (RH1) Blend 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 manually edit (change) the instrument result if questionable. Review of edited data submitted indicates that all three lots of the selected BGR products demonstrated 100% agreement for expected positive and negative samples.

#### *Reproducibility Study*

This study was conducted at three sites (two external and one internal) using one conformance lot of IH-Anti-D (RH1) Blend to test identical panel 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 × 2 duplicates × 2 runs × 5 days). Review of the edited data indicates that sample panel #1 showed a (1+)/ not interpretable reaction at one external site on day 5. According to BMD, a 1+ reaction for BGR is considered as a not interpretable or equivocal (EQV) result by the IH-Com Software. BMD stated that image of the result was later reviewed and found to be negative.

#### *Interfering substances*

Review of the data submitted for the performance studies demonstrate that samples with light-moderate lipemic. Hemolysis and icterus were tested using the IH-Anti-D (RH1) Blend. BMD also conducted a study internally to assess the effect of testing grossly hemolyzed, icteric and lipemic samples on the IH-1000 Analyzer. For the internal study, BMD tested 12 samples of each category with the IH-Anti-D (RH1) Blend. The data obtained from these studies demonstrated that higher than normal

concentrations of triglycerides, bilirubin and hemoglobin do not have adverse effect on performance of the final product.

#### *Stability studies*

BMD conducted a stability study to establish the dating period for the in vitro product using three conformance lots of IH-Anti-D (RH1) Blend. The stability samples were stored 2-8 °C and tested for potency and specificity every (b) (4) up to (b) (4). BMD proposes a shelf life of 24 months for IH-Anti-D (RH1) Blend when stored at 2-8 °C. The latest stability report submitted in the amendment received on June 1, 2015, verifies stability of the IH-Anti-D (RH1) Blend up to (b) (4) when stored at 2-8 °C. The proposed shelf life of 24 months is acceptable.

#### *On-board stability*

BMD claims in the labeling that reagents, including IH-Anti-D (RH1) Blend, can be stored on the analyzer for up to 48 hours. BMD conducted on-board stability and the study involved storing samples from the lot used for the transport simulation study on the IH-1000 Analyzer for 48 hours. The “on-board samples” were tested in parallel with the “non-on-board” samples for serological reactivity after expiry (24 months) and compared. Review of the data submitted indicates that specifications were met.

#### *Sample Aging and Anticoagulant Studies*

The sample aging and anticoagulant studies were conducted both internally at Bio-Rad and at the clinical sites. For the internal study, BMD tested a minimum of (b) (4) EDTA samples up to 5 days post collection to support the 5-days claim post collection. The performance studies data indicate that EDTA samples and donor segment (CP2D) with preservative solution (AS-3) were tested with the IH-Card Anti-D (RH1) Blend at the clinical trial sites and covered sample ages one to 32 days. The data submitted indicate the results obtained with the fresh and stored samples were comparable.

### *Weak D Testing*

BMD conducted this study internally to determine if the IH-Anti-D (RH1) Blend is capable of detecting weak D samples because this reagent has a weak D labeling claim. For this study, BMD tested 54 known weak D samples using IH-Anti-D (RH1) Blend and compared the results with FDA-licensed Anti-D reagents. IH-Anti-D (RH1) Blend detected all 54 weak D samples as expected.

## **5. Clinical Studies**

### **a) Clinical Program**

BMD conducted a clinical study to evaluate the 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 United State (US) clinical sites: Puget Sound Blood Center, located in Renton, Washington, Transfusion Services Vanderbilt University Medical Center, located in Nashville, Tennessee, Miriam Hospital located in Providence, Rhode Island, and LifeSource Testing Laboratory located in Rosemont, Illinois. There was also one internal site at Bio-Rad Laboratories located in Cressier, Switzerland. According to the study data, 3,508 leftover de-identified clinical specimens (patient, donor and cord blood) were tested to demonstrate sensitivity and specificity of the IH-Anti-D (RH1) Blend. Performance of the IH-Anti-D (RH1) Blend was evaluated for correctly identifying weak D samples using IH-Card AHG Anti-IgG in LISS-IAT technique. The results from the IH-1000 were compared to the FDA licensed reagents and cleared instruments for concordance.

BMD used at least two conformance lots of IH-Anti-D (RH1) Blend for the clinical study. The clinical study started in October of 2012 and concluded in November of 2013. The sites were instructed to run Quality Control (QC) at least once a day and proceed with testing only when QC results are acceptable. Each result transferred for

the IH-1000 to the IH-Com software was reviewed and validated by the end-user; equivocal (EQV) results were manually edited (changed) as needed. 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 is not resolved on the repeat, a third licensed reagent or a molecular technique was used as a reference. The table shows the reference methods and reagents used at each clinical site:

**Table 3:** Reference methods and reagents used

Site	Reference Method/Reagents Used
Vanderbilt University Medical Center	Immucor Anti-D, Series 4, Tube IAT, Immucor Anti-IgG and Ortho Coombs Control <sup>®</sup> , using package insert (PI) instructions.
Puget Sound Blood Centers	Beckman Coulter PK7300 <sup>™</sup> , using Diagast Anti-D/Anti-D PK1 reagent. Manual tube method using Ortho Anti-D BioClone and Immucor Anti-IgG, using PI and instrument operator's manual instructions.
Miriam Hospital	Tube Method Ortho <sup>®</sup> Anti-D BioClone <sup>®</sup> (Monoclonal/Polyclonal Blend) Ortho <sup>®</sup> Anti-IgG Ortho Coombs Control, using PI instructions.
LifeSource Testing Laboratory	Beckman Coulter PK7300 <sup>™</sup> using Diagast Anti-D/Anti-D PK2 reagent. And Manual tube method using Bio-Rad Seraclone <sup>®</sup> Anti-D Blend and Bio-Rad AHG Anti-IgG reagent using PI and instrument operator's manual instructions.

**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 percent agreement with the comparison device or method has to exceed 0.99. Review of the data submitted indicates that the edited results met the acceptance criteria. The point Estimate and Lower Confidence Limits (LCL) for

Positive (PPA), Negative (NPA), and Overall Agreement (OPA) for the IH-Anti-D (RH1) Blend can be found in the table below.

**Table 4:** Point Estimates and Lower Confidence Limits for PPA, NPA and OPA

<b>BGR</b>	<b>PPA (Edited)</b>	<b>NPA (Edited)</b>	<b>OPA (Edited)</b>
IH-Anti-D (RH1) Blend	99.97% 2879/2880 [ 99.84%]	99.68% 626/628 [99.00%]	99.91% 3505/3508 [ 99.78%]

**Source:** FDA Statistician’s Memo

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

According to the data submitted, performance evaluation of the IH-Anti-D (RH1) Blend included 196 cord blood samples and 648 elderly samples in the age range of (65-103 years).

**c) Overall Comparability Assessment**

- The data submitted indicates that instructions in the labeling were followed to successfully carry out the clinical performance study. The study data demonstrates safety and efficacy for the IH-Anti-D (RH1) Blend.
- 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 GmbH 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 resolved any issues through information requests with BMD GmbH. 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-Anti-D (RH1) Blend contained in the BLA submission.

No postmarketing commitments are associated with this BLA.

## **8. Labeling**

The Advertising and Promotional Labeling Branch (APLB) reviewed the instruction 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 has been reviewed and found acceptable. Unique Device Identification (UDI) review performed by CBER found the required elements to comply with Title 21 CFR 830 have been met. 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 content of the of the BLA submission, 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 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 stored test results, if necessary.
- Features of this test system that impact the timely availability of transfusion products, include a 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 the IH-Anti-D (Blend) included in this BLA submission.