Summary Basis for Regulatory Action

From: Ricardo Espinola, Chair of the Review Committee

BLA/ STN#: IH-Cell Reagent Red Blood Cells to be used on the IH-1000 Automated Analyzer STN 125208/70

Applicant Name: Bio-Rad Medical Diagnostics GmbH License No. 1845

Date of Submission: February 27, 2014

MDUFA Goal Date: October 21, 2016

Proprietary Name: IH-Cell A1 & B, IH-Cell A2, IH-Cell I-II, IH-Cell I-II-III, IH-Cell Pool, IH-Panel 11, IH-Panel 11 Papain, IH-Panel Plus 6

Established Name (common or usual name): Reagent Red Blood Cells

Intended Use: The IH-Cell Reagent Red Blood Cell products are intended to be used for ABO serum grouping, and the detection and identification of unexpected antibodies, based on the principles of agglutination and gel filtration of the IH-Card System. The IH-Cell products and associated reagents are intended to be used together with the fully automated system IH-1000 Automated Analyzer 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.**

Material Reviewed/ Consulted	Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date
Clinical Review	Ricardo Espinola October 31, 2016 August 08, 2016
Statistical Review	Zhen Jiang November 26, 2014 July 14, 2015 October 30, 2015 August 30, 2016
CMC Facility Review	Chad Burger December 17, 2014
CMC Product Review	Ricardo Espinola October 31, 2016 August 08, 2016 Simleen Kaur (Microbiology/Bioburden) November 5, 2014
Labeling	Dana Jones (Labeling) August 26, 2014
Lot Release Protocols / Testing Plans	Karen Campbell (DBSQC – OCBQ) October 28, 2015 (Laboratory Quality Product Testing Plan) November 17, 2015 (Lot Release Protocol Templates)
Bioresearch Monitoring Review	Bioresearch monitoring inspections were not conducted for this BLA
Establishment Inspection Report	Chad Burger October 27, 2015
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 immunohematology test system called the IH-System.

The submissions consist of:

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

The following is a summary 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 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 the 510(k) premarket notifications.

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Millipore was approved by the FDA on August 14, 2008 to supplement their license to supply the following FFMUs to Biotest Medical Diagnostic GmbH, U.S. License No. 1798 under a shared manufacturing arrangement: Anti-C (clone MS-24), STN 103858/5046, Anti-c (Clone MS-33), STN 103860/5048, Anti-K (clone MS-56), STN 103864/5045 and Anti-e (clones MS-16/MS-21/MS-63), STN103866/5055/5056/5057. BMD U.S. License No. 1845 subsequently acquired portions of Biotest and acquired ownership of these FFMU products.

The IH-Cell products are ready to use Reagent Red Blood Cells (RRBCs) for ABO serum grouping, detection and identification of unexpected antibodies together with associated reagents. 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 following table, extracted from the submission, shows the proprietary name and intended use of the eight RRBC products.

Table 1: RRBCs – Proprietary Name and Intended Use

PROPRIETARY NAME	INTENDED USE

IH-Cell A1 & B	For detection of antibodies to ABO blood group antigens on human red blood cells.
IH-Cell A2	For detection of antibodies to ABO blood group antigens on human red blood cells.
IH-Cell I-II	For detection of antibodies to human red blood cell antigens in patient and donor samples using IH-Cards.
IH-Cell I-II-III	For detection of antibodies to human red blood cell antigens in patient- and donor samples using IH-Cards.
IH-Cell Pool	For detection of antibodies to human red blood cell antigens in donor samples using IH-Cards.
IH-Panel 11	For identification of antibodies to human red blood cell antigens in patient and donor samples using IH-Cards.
IH-Panel 11 Papain	For identification of antibodies to human red blood cell antigens in patient and donor samples using IH-Cards.
IH-Panel Plus 6	For identification of antibodies to human red blood cell antigens in patient and donor samples using IH-Cards.

The IH-System consists of:

- IH-Card: a plastic card, consisting of six microtubes containing the active component, i.e., BGR or AHG, in a buffered (b) (4) gel suspension.
- IH-Anti-D Blend: vialed Anti-D reagent for performing weak D and DVI testing using the IH-AHG Anti-IgG card.
- IH-Cell products: vialed RRBCs (i.e., reverse grouping cells, screening cells, pool cells, and identification panel cells).
- IH-1000 Automated Analyzer System: an automated, blood grouping and antibody test system 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 filled 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 containing (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 premarket notification procedures): 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 submissions 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 the 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 to non-US markets. 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.

Device Description and Function

The IH-System is an Immunohematology Test System that consists of an analyzer, software (IH-COM), Anti-Human Globulin (IH-Cards AHG), and supplemental reagents (FDA licensed or cleared) 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.

A suspension of 0.6% RRBCs together with serum or plasma is centrifuged through the gel. In negative reactions, the RRBCs pass through the gel and form a pellet on the bottom of the tube, whereas, in positive reactions, they are trapped on top and in the gel.

The various assays performed by the IH-System provide test results for blood collection establishments, transfusion services, and hospitals for managing donors and patients.

Chronology

CBER received the Reagent Red Blood Cells (RRBCs) BLA Efficacy Supplement on March 07, 2014. CBER issued a Filing with No Deficiencies Letter on May 1, 2014. CBER subsequently received 23 amendments submitted from BMD in response to fourteen information requests for STN 125208/70. A Complete Response Letter was issued on December 31, 2014. A final amendment dated June 30, 2016 completed BMD's responses to all outstanding issues associated with the RRBCs.

3. Chemistry Manufacturing and Controls (CMC)

All manufacturing is carried out according to US Current Good Manufacturing Practices (cGMP) in a controlled environment.

a. Manufacturing Summary

All process steps for the manufacturing of RRBCs are similar to the manufacturing process of BMD licensed RRBCs Biotestcell and Erytypecell. These manufacturing processes were already validated and approved by FDA. On August 11, 2014, BMD submitted a detailed comparison table for the manufacturing of Biotestcell /

Erytypecell and the RRBCs. The only difference in the RRBCs process is (b) (4) .

In-Vitro Substances

The *in vitro* components are packed human red blood cells (RBCs) of defined phenotype and characteristic antigens. They are used to manufacture different types of Reagent Red Blood Cells (RRBCs). The RBCs *in-vitro substances* are checked after receipt by the BMD's Technical Department and stored at BMD production facility before use. The identity and excipients are checked against accompanying documents (Incoming goods receipts, copy of shipping note, Certificate of Analysis). Accompanying documents are transferred to BMD's Quality Assurance Unit for review and final release.

The RBCs used are of five different types according to antigens of the ABO blood groups and the Rhesus antigen: Type A_1 (Rh Negative), A_2 (Rh Negative), Type B (Rh Negative), Type O (Rh Positive), and Type O (Rh Negative), respectively. The table shown below provides the list of RBCs types used and the respective acceptance criteria. The table was extracted from the submission.

Table 2: Red blood cell types and Acceptance criteria

Red Blood Cell Type	Acceptance criteria
A_1 rr	Determination of red blood cell types with suitable standard test methods Negative for HIV 1 and 2, HCV, and HbsAg Negative for syphilis
B rr	
A_2 rr	
O R_1R_1	
O $R_1{}^wR_1$	
O R_2R_2	
O rr	
R_ZR_1	
R_ZR_2	
O R_0r Fy (a-b-)	
O r´r	
r´^{w}r, kk	
O r"r	
O rr kk, Fy (a+b-)	
O rr K +, Fy (a-b+)	
O Rh, rare antigen configuration	

The human RBCs used for manufacturing the RRBCs are (b) (4) . Blood collections from the US supplier ((b) (4)) are carried out according to national standards established according to 21CFR640 and 21CFR660.

The RBCs *in vitro* components and the solutions are checked and stored at BMD production facility before use. For all incoming goods a visual inspection is carried out. Identity of *in vitro* substance and excipients is checked against accompanying documents (incoming goods receipt, copy of shipping note, Certificate of Analysis). For RBCs, the identity is checked by controlling the donor's number reported in the delivery document. Each single container is labeled at the time of receipt. Received goods are released for manufacturing purposes. Only the batches for *in vitro* products manufactured with RBCs that are negative for infection parameters are released.

(b) (4)

In Vitro Products

All manufacturing and serological testing, including final product release testing of the IH-Cell RRBCs is conducted at BMD, Dreiech, Germany. The facility is registered with FDA under Facility Establishment Identifier number 9610824.

The *in vitro* components, originating from packed human RBCs are used to manufacture eight *in vitro* products. The composition and configuration of the RRBCs products are shown in the table below. The following three tables were extracted from the submission.

Table 3: Composition and configuration of IH-Cell A1,B, IH-Cell A2, IH-Cell I-II, IH-Cell I-II-III, IH-Cell Pool

Product Proprietary Name	Red Blood Cell Type	At least the following antigens are included in each lot	Concen-tration of Red Cell Suspension ± 0.1%	Preservative solution	Intended Use
IH-Cell A_1,B	A_1 rr	N/A	0.6%	(b) (4)	Serum Grouping
	B rr				
IH-Cell A_2	A_2 rr	N/A	0.6%		
IH-Cell I-II	O R_1R_1 or O $R_1^wR_1$	K, k, Fy^a, Fy^b, Jk^a, Jk^b, M, N, S, s, Le^a, Le^b, P_1	0.6%		Antibody Screening
	O R_2R_2				
IH-Cell I-II-III	O R_1R_1 or O $R_1^wR_1$	K, k, Fy^a, Fy^b, Jk^a, Jk^b, M, N, S, s, Le^a, Le^b, P_1	0.6%		Antibody Screening
	O R_2R_2				
	O rr				
IH-Cell Pool	O R_1R_1 or O $R_1^wR_1$ and O R_2R_2	K, k, Fy^a, Fy^b, Jk^a, Jk^b, M, N, S, s, Le^a, Le^b, P_1	0.6%		Antibody Screening

Table 4: Composition and configuration of IH-Panel 11 and IH-Panel 11 Papain

IH-Panel 11 and IH-Panel 11 Papain*	(b) (4)	K, k, Fy^a, Fy^b, Jk^a, Jk^b, M, N, S, s, Le^a, Le^b, P_1	0.6%	(b) (4)	Antibody identification

* Papainized cells

Table 5: Composition and configuration of IH-Panel Plus 6

IH-Panel Plus 6	(b) (4)	N/A	0.6%	(b) (4)	Antibody identification

The manufacturing process of the in vitro products RRBCs, includes the following steps:

of the Packed Red Blood Cells

Papain Treatment of RBC for IH-Panel 11 Papain

[redacted]

[redacted]

Filling of Final Product

(b) (4)

[redacted]

A validation summary and data submitted by BMD support that RBC suspensions remain homogeneous during the entire filling process.

Transport Simulation Studies

These studies evaluated the effects on stability of storage conditions that vary from the recommended storage condition. RRBCs *in-vitro* products are held under storage conditions, which simulate excursions from the recommended storage temperature conditions. The *in-vitro* products were held for 5 days at two storage temperatures, 2 to 8 ºC and (b) (4) and were subsequently tested. The reagents were then stored at 2 to 8 ºC and tested for stability throughout the shelf life, at the same time points as the real time studies. Testing results met the acceptance criteria.

Packaging

Vials are automatically packaged according to SOPs SV-D: PA-4001-03 and SV-D: PG-003-07. Final packaged *in vitro* products are stored at the warehouse at 2 ºC to 8 ºC until release by Final Serological Control and prior to shipping.

Quality Control (QC) /Release Testing and Specifications

A first QC of packaging and labeling is performed on the final *in-vitro* product after filling and a second QC is performed after packaging. Final packaging and labeling QC comprises tests on packaging, filling and labeling. The inspection includes: label identity (Compliance of product description, expiration date, batch number, item number, label symbols, label version number and release date of version number with batch record requirements), label position (Compliance with batch records requirements), and verification of completeness, and correct version of the Instructions for Use (IFU must be in compliance with batch record requirements). QC testing is performed on the final *in vitro* products after filling and packaging. The samples are pulled randomly. All tests are performed at room temperature 22 ± 4 ºC. The serological methods used for testing comprise manual tests as well as automated tests on the IH-1000 automated analyzer. The serological specifications and test methods are shown in the table below. The information contained in this table was extracted from the submission.

Table 6: Serological specifications and test methods

Parameter	***In Vitro* Product**	**Method**	**Acceptance Criteria**
Determination of Rh-antigens	IH-Cell I-II IH-Cell I-II-III IH-Cell Pool IH-Panel 11 IH-Panel Plus 6 IH-Panel 11 Papain	RRBCs are tested for reaction with these antibodies: Anti-D, -C, -c, -E, -e and -C^w	Reagent must react positive with a reaction strength (b) (4)
Determination of blood group antigens	IH-Cell A 1 & B IH-Cell A2	RRBCs are tested for reaction with the following antibodies: Anti-A, -	Reagent must react positive with a reaction strength (b) (4)

		B, -AB, -A_1 and -H	(b) (4)
Positive Specificity	IH-Cell I-II IH-Cell I-II-III IH-Cell Pool IH-Panel 11 IH-Panel Plus 6 IH-Panel 11 Papain	IH-Panel 11 Papain, IH-Panel 11 and IH-Panel 6 Plus: RRBCs are tested for reaction with four other known antibodies of the IgG type	Reagent must react positive with a reaction strength (b) (4) Exception IH-Panel 11 Papain: because of the papainization the following antigens are destroyed or react weaker with antibodies: F_y^a, F_y^b, M, N, S, s.
Negative Specificity	IH-Cell I-II IH-Cell I-II-III IH-Cell Pool IH-Panel 11 IH-Panel Plus 6 IH-Panel 11 Papain	RRBCs are tested with 6 different blood plasmas or sera, which lack antibodies against tested antigens	Reagents must react negative ((b) (4))
Positive and Negative Specificity	IH-Cell A1 & B IH-Cell A2	RRBCs are tested for reaction with Anti-A and/or –B antibodies RRBCs are tested with 4 blood plasmas or sera, each of which contains either anti-	Reagent must react positive with corresponding antibody with a reaction strength (b) (4) Reagent must react negative with not corresponding antibody

		A, -B or –A and –B antibodies	False negative reactions must be verified by (b) (4)
DAT (to demonstrate the absence of *in vivo* coating of RRBCs with immune-globulin)	IH-Cell I-II, IH-Cell I-II-III IH-Cell Pool IH-Panel 11 IH-Panel Plus 6 IH-Panel 11 Papain	Manual testing using the IH-Card AHG Anti-IgG, -C3d, or IH-Card AHG Anti-IgG, or only for IH-Panel 11 Papain IH-Card AHG Anti-IgG	DAT must react negative ((b) (4))

Batch Release and Issuance of Certificate of Analysis

For each batch of *in vitro* product fully executed batch production records are reviewed for compliance to established manufacturing and testing procedures by BMD' Quality Assurance Unit. The final review at BMD is performed by the Batch Record Review Manager. If all process and release specifications are met, the Batch Record Review Manager releases the product for distribution.

Process Controls

Non-serological in process controls:

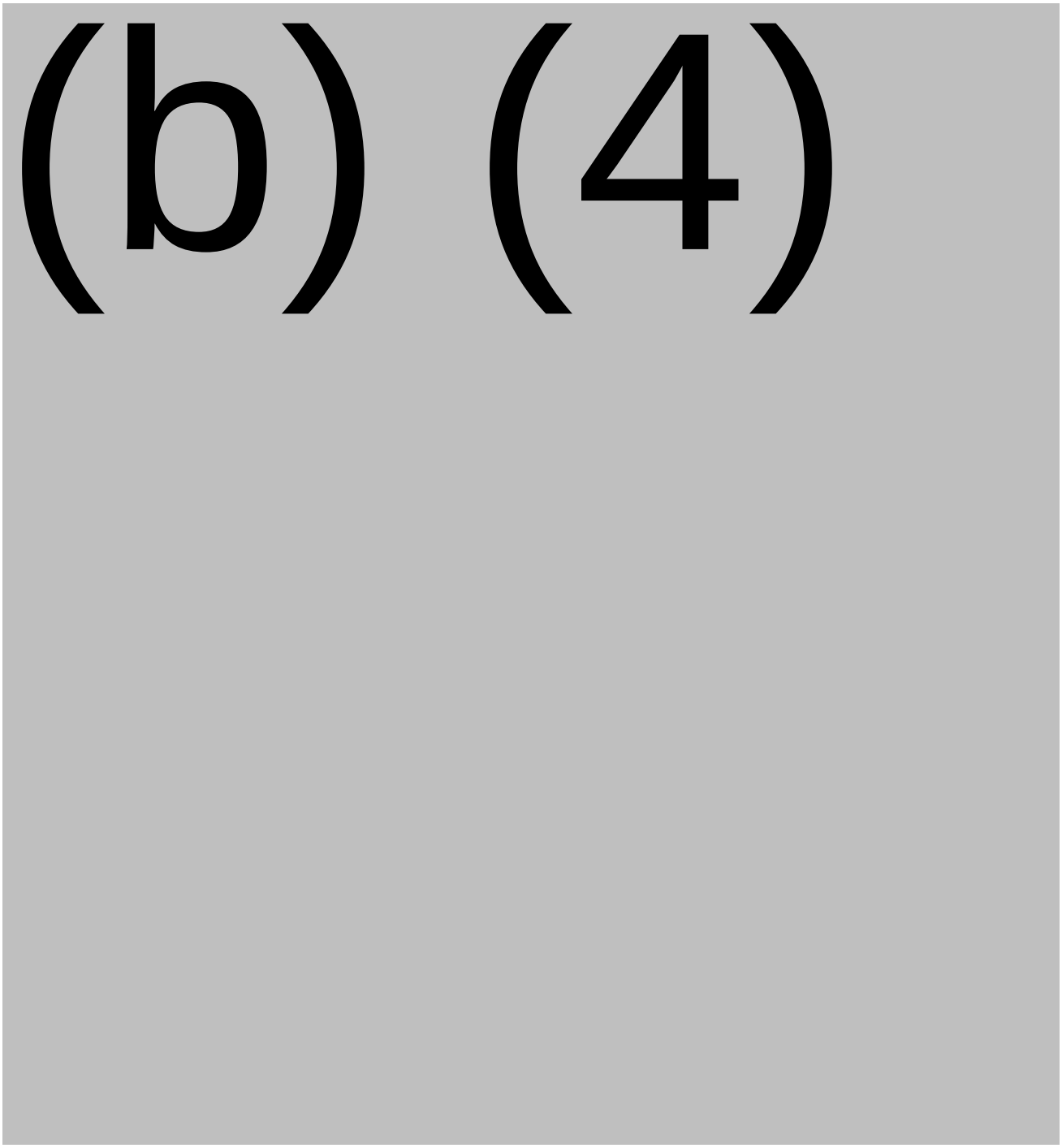
1. (b) (4)
2. (b) (4)

Serological in-process controls:

(b) (4)

(b) (4)

Table 7: Serological in process controls – Tested antigens



Validation

The process steps and equipment have been successfully validated through performance qualifications and validations. A validation study was performed for the *in vitro* product IH-Panel 11 Papain. The results were acceptable.

Environment Conditions

A clean room classification concept was established for the BMD manufacturing facilities. The clean room concept defines clean room attributes, control parameters, acceptance criteria, monitoring programs, and hygiene and clothing procedures. It is applicable to all BMD production and quality control facilities in Dreieich. Specific clean room categories are defined for the different activities within BMD facilities.

Air Quality Monitoring

Sample sites, alert (warning) limits and action limits for viable airborne microbes and particles are set out in SOP SV-D: PH-5023-00 “Hygiene monitoring plan for the transfusion manufacturing area”. Air samples are collected at prescribed locations.

- Surface Monitoring. Sample sites, alert (warning) limits and action limits for viable

surface microbes are set out in SOP SV-D:PH-5023-07 “Hygiene monitoring plan for the transfusion manufacturing area”. Critical points are monitored; samples are collected before cleaning and disinfecting operations.

- Reprocessing and Reworking. No reprocessing or reworking is foreseen for

manufacturing of the IH-Cell dilution (Bulk). Reprocessing and Reworking of filled and packaged *in vitro* products comprises of relabeling of final vials, outer cartons and exchange of package inserts. This process is described in SOP SV-D: P:002-00 “Repackaging of intermediate and final products”. This SOP was reviewed and found appropriate.

Visual Inspection

A visual inspection is performed on unopened QC samples. The test vials must meet the following acceptance criteria: (b) (4) .
Unopened vials are then stored at (b) (4)
.

Measurement of (b) (4)

(b) (4)

Microbiology: Product Bioburden Testing and Preservative Effectiveness

The bioburden test method was qualified in accordance with (b) (4) and the RRBCs product matrix is suitable for the intended test method. In addition, the proposed sulfamethoxazole and trimethoprim formulation concentrations were shown to have effective anti-microbial properties in accordance with (b) (4) . The shelf-life of the stabilizer solution (b) (4) of (b) (4) is supported by validation summary and data provided by BMD.

Batch Production Records

I reviewed the batch records for IH-Cell A1 & B, IH-Cell A2, IH-Cell Pool, IH-Cell I-II, IH-Cell I-II-III, IH-Panel Plus 6, IH-Panel 11, and IH-Panel 11 Papain, (b) (4) , expiry 05 March, 2013. The batch records appeared completed and accurate. There were some deviations reported in the batch records, with no impact in the final product.

b. Facilities Review/Inspection

Purified Water

Water quality system, and environmental monitoring, of *in vitro* substance samples are outsourced to (b) (4) A (b) (4) system is used at BMD for producing purified water in compliance with (b) (4) specifications for Purified water.

The water quality testing includes testing for (b) (4) . More information about purified water can be found in the approval review memo from the DMPQ reviewer.

Facility Information

The following information was provided by the DMPQ reviewer. Facility information and data provided for the manufacture of the Reagent Red Blood Cells was reviewed by CBER and found to be sufficient and acceptable. The activities performed at the Bio-Rad Dreieich facility and the inspectional history are noted in the table below and are further described in the paragraphs that follow. This table was provided by DMPQ.

Table 8: Manufacturing facilities for Reagent Red Blood Cells

Name/address	**FEI number**	**DUNS number**	**Inspection/ waiver**	**Results/ Justification**
Final device 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

CBER performed a Pre-License Inspection (PLI) of this facility on 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 BMD 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).

A (b) (4) system is used at BMD for producing purified water in compliance with (b) (4) specifications for Purified water. The water quality testing includes testing for (b) (4) .

c. Environmental Assessment

The following information was provided by the DMPQ reviewer. 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.

d. Container Closure System

The following information was provided by the DMPQ reviewer. The *in vitro* substance RBCs are provided to Bio-Rad Medical Diagnostics (BMD) in (b) (4) . The reagent red blood cells are filled into 10mL (b) (4) glass bottles ((b) (4)). The closure consists of a glass pipette with a rubber bulb and plastic screw cap ((b) (4)).

The final *in vitro* product is provided in (b) (4) glass ((b) (4)) 10 mL clear bottle. The closure consists of an (b) (glass pipette with a white rubber bulb and plastic screw cap. BMD provided information for the 10 ml bottles, but did not provide information for the 4 ml bottles used in some of the product closures. The container closure testing integrity (CCTI) of the submission only included information for the 10 ml vials. BMD did not provide a date for the completion of the CCIT that was performed on the 4 ml vials. FDA requested BMD to provide the CCTI that was performed on the 4 ml vials used with the RRBC products and to provide date of completion of the CCIT studies that were mentioned in the submission. BMD's response was appropriate.

For testing of container closure integrity, one lot of each IH-Cell representative was tested according to protocol DPPQF-0588/02 "Stability Testing of the Reagent Red Blood Cells IH-Cell". The results were acceptable.

e. Additional Information provided by DMPQ Reviewer.

Shipping Validation for RRBCs

A summary report for the shipping validation for RRBCs had been submitted to FDA in October 2012 (STN 125213/33). BMD confirmed on December 17, 2014, that there had been no changes to the bottles or the shipping method for the RRBCs. The results of that study were considered acceptable.

4. Analytical Studies

Analytical studies performed with RRBCs, included the following studies:

- Lot-to-Lot
- Reproducibility
- Interference Substances
- Shelf Life Stability
- In Use Stability
- On Board Stability

Lot-to-Lot Study

This was conducted in house at BMD using three lots of each of the representative products including IH-Card ABO+D(VI+)+RevA1B, IH-Card A,B, IH-Card Rh+K Type, IH-Anti-D Blend, IH-AHG Anti-IgG, IH-Cell A1&B, IH-Cell A2, IH-Cell Pool, IH-Cell I-II, IH-Panel 11 Papain. Each product was tested using a panel of samples on the IH-1000 Analyzer. Testing occurred on five non-consecutive test dates over a 20 day period. On each day of testing, one operator tested in duplicate twice a day: 3 lots x 1 site x 5 days x 2 runs (AM and PM) x 2 replicates.

The results showed that the percentage agreement after validation for all three lots combined for each BGR, AHG and RRBCs was 100% (95% Lower Confidence Interval: 95.13%. For the expected positive results, the agreement after validation was 100% and for the expected negative results, the agreement after validation was 100%.

Reproducibility Study

This study was conducted at three sites (two external and one internal) using one lot each of IH-Card ABO+D(VI+)+RevA1B, IH-Card A,B, IH-Card Rh+K Type, IH-Anti-D Blend, IH-AHG Anti-IgG, IH-Cell A1&B, IH-Cell A2, IH-Cell Pool, IH-Cell I-II, IH-Panel 11 Papain. At each site, each product was tested using

an identical panel of samples on the IH-1000 Analyzer. Testing occurred on five non-consecutive test dates over a 20 day period. On each day of testing, one operator tested in duplicate twice a day: one lot of reagents x 3 sites x 5 days x 2 runs (AM and PM) x 2 replicates.

Results showed that the percentage agreement after validation for all three sites combined for each BGR, AHG and RRBCs was 100% (95% Lower Confidence Interval: 95.13%.

Shelf Life Stability

The shelf life of the RRBCs products is 63 days. The date of manufacture of the *in-vitro* products is the date of the earliest collection of the donor blood. The 63 day expiration date for RRBCs is established from the date of manufacture. The test methods (potency and specificity) used to verify product stability, are the same serological methods used for release testing.

A stability study report (DSTQF-0588/02) submitted by BMD on August 19, 2014 describes the stability testing performed to verify the proper reactivity and specificity over the entire shelf-life of 63 days.

(b) (4)

In Use Stability Study

The stability of the RRBCs were tested by detecting antibodies in twofold serial dilutions with (b) (4) containing (b) (4) bovine albumin as dilution medium. The antibodies to detect were selected by BMD to create a "worst case scenario" since some antigens deteriorate more rapidly than others during storage . Each representative RRBC was tested (b) (4) .
All results met the acceptance criteria.

On-Board Stability

The study was performed with one lot of each representative IH-Cell product. The stability of 48 hours IH-1000 on-board storage was verified with each one lot of the representative IH-Cells. Test intervals defined for this study were as follows:

1. $t_{end:}$ After 63 days of shelf life
2. $t_{end + 24h:}$ After 63 days of shelf life and 24 h on-board storage condition (tolerance + 3 h allowed)
3. $t_{end:}$ After 63 days of shelf life and 49 h on-board storage condition (tolerance + 3h allowed)

Testing was performed on the IH-1000 analyzer according to the IH-1000 user manual and RRBCs package inserts. Only visually verified results were used for the stability evaluation. For visual control, one vial of each representative cell was investigated for (b) (4) on each defined test interval. The results met all the acceptance criteria.

Interference Substances

The testing of these samples was conducted internally at BMD with investigational reagents in comparison to FDA licensed comparative products. Blood samples with grossly hemolyzed, and high levels of lipid and bilirubin levels were included. Clinical Laboratory Standards Institute document EP7-A2, "Interference Testing in Clinical Chemistry" was used as a reference guide for preparation of samples. The obtained results demonstrated that higher than normal concentrations of triglycerides, bilirubin or hemoglobin did not have an adverse effect on the performance of the investigational reagents.

5. Performance Studies

a) Clinical Studies

BMD conducted a clinical comparison study to evaluate the RRBCs performance on the IH-System in a clinical setting. The studies were performed at four external United States testing sites: Puget Sound Blood Center (PSBC) located in Renton, Washington, Miriam Hospital (MH) located in Providence, Rhode Island, Vanderbilt University Medical Center (VUMC) located in Nashville, Tennessee, and LifeSource Testing Laboratory (LSTL) located in Rosemont, Illinois. In addition internal studies were conducted at the Bio-Rad

Research and Development Laboratory in Cressier, Switzerland. These sites used Bio-Rad Medical Diagnostics IH- reagents and FDA licensed comparator reagents. Samples consisted of patient and donor blood samples. Results from the investigational method and the reference assay were compared for concordance. If the results of the investigational and reference method were discordant, testing was repeated. If the results were still discordant after repeat testing, then a third FDA licensed reagent was used as a referee. If the antibody identification results were discordant after repeat testing, antigen dosage and profile were evaluated as potential cause for discrepancy.

BMD used the following acceptance criteria for the studies:

- ABO Blood Grouping – RRBCs A1 & B and A2 Cell: The lower bound of the one-sided 95% confidence intervals for the positive percent agreement and the negative percent agreement had to exceed 0.99.
- Antibody Detection, Antibody Identification: The lower bound of the one-sided 95% confidence intervals for the positive percent agreement and the negative percent agreement had to exceed 0.95.

Some of the testing results in the clinical sites failed to meet the acceptance criteria to support approval. In a submission issue meeting held on January 14, 2016, FDA asked BMD to perform additional testing in an In-House Performance Study. In addition, FDA recommended that the result verification process should include reviewing and editing (if necessary) of the camera images and assay interpretation. Editing of the results was not limited to indeterminate results, initially positive or negative reactions would have to be edited after visual review. Initial and edited agreement results of the studies performed at the clinical sites are described below.

A) <u>ABO Blood Grouping - RRBC A1 & B, and A2</u>

The table shown below presents the point estimates and lower confidence limits for positive (PPA), negative (NPA) and overall Agreement (OA) for RRBCs.

This table was extracted from the FDA Statistical Review Memo with permission obtained from the statistical reviewer.

Table 9: Point Estimates and Lower Confidence Limits for Positive (PPA), Negative (NPA) and Overall Agreement (OA) for RRBCs [a,b]

Reagent Red Blood Cell	Initial PPA	Initial NPA	Initial OPA	Edited PPA	Edited NPA	Edited OPA
A1 RRBC	99.89% 3801/3805 [99.76%]	99.56% 2514/2525 [99.28%]	99.62% 6315/6339 [99.47%]	99.76% 6315/6330 [99.64%]	99.80% 2520/2525 [99.58%]	99.72% 6321/6339 [99.58%]
B RRBC	99.81% 5302/5312 [99.68%]	*98.61%* *993/1007* *[97.84%]*	99.31% 6295/6339 [99.11%]	99.85% 5304/5312 [99.73%]	*99.21%* *999/1007* *[98.57%]*	99.43% 6303/6339 [99.25%]
A2 RRBC	*98.85%* *600/607* *[97.84%]*	*97.29%* *431/443* *[95.65%]*	98.19% 1031/1050 [97.36%]	*98.85%* *600/607* *[97.84%]*	*97.52%* *432/443* *[95.92%]*	98.29% 1032/1050 [97.47%]

[a]: *Lower confidence limits (LCL) for one-sided 95% confidence intervals are listed in "[]".*

[b]: *The agreements that did not meet the acceptance criteria are in Italic.*

Conclusions:

- There were inconsistencies with the interpretation of study results when camera images alone were used.
- For the IH-Cell A1 RRBC, the PPA, and the NPA met the acceptance criteria.
- For the IH-Cell B RRBC, the PPA met the acceptance criteria but the NPA did not meet the acceptance criteria. Four samples with discordant edited results were blood group O or A, and therefore the reference method gave false negative results.
- For the IH-Cell A2 RRBC, the PPA, and the NPA did not meet the acceptance criteria. Ten discordant edited results in NPA were false negative by the reference method, and 5 discordant edited results in PPA were false negative by the investigational method due to weak agglutinins.

B) Detection of Unexpected Antibodies

The detection of unexpected antibodies was conducted using IH-Card AHG Anti-IgG and IH-Card Anti-IgG, -C3d with three different RRBCs products (IH-Pool, IH-Cell I-II and IH-Cell I-II-III). The PPA, NPA and OA were calculated separately for each RRBCs screen product and for all three RRBCs screen products combined per IH-Card AHG Anti-IgG and IH-Card AHG Anti-IgG,-C3d respectively. The performance evaluations were based on the combined results. The following table was extracted from the FDA Statistical Review Memo with permission obtained from the statistical reviewer.

Table 10: Point Estimates and Lower Confidence Limits for PPA, NPA and OA for Detection of Unexpected Antibodies[a,b]

IH-Cards	RRBCs	Initial PPA	Initial NPA	Initial OPA	Edited PPA	Edited NPA	Edited OPA
IH -Card AHG Anti-IgG	IH-Pool	89.53% 77/86 [82.45%]	99.05% 2914/2942 [98.70%]	98.49% 2991/3028 [98.07%]	89.53% 77/86 [82.45%]	99.12% 2916/2942 [98.78%]	98.55% 2993/3037 [98.14%]
	IH-Cell I-II	100% 12/12 [77.91%]	94.70% 1125/1188 [93.50%]	94.75% 1137/1200 [93.56%]	100% 12/12 [77.91%]	97.22% 1155/1188 [96.30%]	97.25% 1167/1200 [96.34%]
	IH-Cell I-II-III	98.53% 67/68 [93.21%]	95.74% 449/469 [93.86%]	96.09% 516/537 [94.42%]	98.53% 67/68 [93.21%]	97.23% 456/469 [95.63%]	97.39% 523/537 [95.95%]
	Total	*93.98%* *156/166* *[90.00%]*	97.59% 4488/4599 [97.18%]	97.28% 4644/4774 [96.86%]	*93.98%* *156/166* *[90.00%]*	98.43% 4527/4599 [98.10%]	98.09% 4683/4774 [97.74%]
IH-Card AHG Anti-IgG, -C3d	IH-Pool	93.06% 67/72 [85.95%]	98.76% 556/563 [97.68%]	97.80% 623/637 [96.59%]	93.06% 67/72 [85.95%]	98.76% 556/563 [97.68%]	97.80% 623/637 [96.59%]
	IH-Cell I-II	100% 6/6 [60.70%]	98.90% 1974/1996 [98.43%]	98.90% 1980/2002 [98.73%]	100% 6/6 [60.70%]	99.35% 1983/1996 [98.97%]	99.35% 1989/2002 [98.97%]
	IH-Cell I-II-III	97.37% 74/76 [91.95%]	95.96% 1210/1261 [94.92%]	96.04% 1284/1337 [95.04%]	97.33% 73/75 [91.84%]	97.86% 1235/1262 [97.06%]	97.83% 1308/1337 [97.05%]
	Total	*95.45%* *147/154* *[91.63%]*	97.91% 3740/3820 [97.48%]	97.76% 3887/3976 [97.34%]	*95.42%* *146/153* *[91.58%]*	98.77% 3774/3821 [98.43%]	98.59% 3920/3976 [98.24%]

[a]: Lower confidence limits (LCL) for one-sided 95% confidence intervals are listed in "[]".

[b]: The agreements that did not meet the acceptance criteria are in *Italic*.

Conclusions:

For the RRBCs tested in IH-Card AHG Anti-IgG, the performance evaluation on the combined results showed that the PPA did not meet the acceptance criteria. Further investigation indicated that 8 samples with discordant edited results in the PPA did not have red cell antibodies identified.

For the RRBCs tested in IH-Card AHG Anti-IgG,-C3d, the performance evaluation on the combined results showed that the PPA did not meet the acceptance criteria. Further investigation indicated that the 5 samples with discordant results in PPA did not have red cell antibodies identified.

C) Antibody Identification

The testing was conducted using IH-Card AHG Anti-IgG and IH-Card AHG Anti-IgG,-C3d with different RRBC (IH-Panel 11, IH-Panel 11 Papain and IH-Panel Plus 6). Due to limited availability of positive samples and other potential issues in determining positive agreement, CBER agreed in a Type B meeting held on October 6, 2011 to only perform statistical analysis on samples that reacted negative in the antibody identification with the reference method (i.e., only negative percent agreement were calculated).

Table 11: Point Estimates and Lower Confidence Limits for NPA for Antibody Identification [a,b]

IH-Cards	RRBCs	Initial NPA	Edited NPA
IH-Card AHG Anti-IgG	IH-Panel 11	94.16% 1564/1661 [93.12%]	94.76% 1574/1661 [93.77%]
	IH-Panel 11 Papain	98.64% 2029/2057 [98.14 %]	98.69% 2030/2057 [98.19%]
	IH-Panel Plus 6	97.12% 472/486 [94.90%]	97.53% 474/486 [96.03%]
	Total	96.69% 4065/4204 [96.20%]	97.00% 4078/4204 [96.53%]
IH-Card AHG Anti-IgG, -C3d	IH-Panel 11	96.39% 1760/1826 [95.58 %]	96.71% 1766/1826 [95.94 %]
	IH-Panel Plus 6	95.63% 459/480 [93.76%]	95.83% 460/480 [94.00%]
	Total	96.23% 2219/2306 [95.51%]	96.53% 2226/2306 [95.84%]

[a]: *Lower confidence limits (LCL) for one-sided 95% confidence intervals are listed in "[]".*

[b]: *The agreements that did not meet the acceptance criteria are in Italic.*

This table was extracted from the FDA Statistical Review Memo with permission obtained from the statistical reviewer.

Conclusions:

For the RRBCs tested in IH-Card AHG Anti-IgG and the IH-Card AHG Anti-IgG,-C3d the performance evaluation on the combined results met the predetermined acceptance criteria.

Summary of Clinical Studies Results

During the clinical comparison study the test results obtained with the following assays failed to meet the primary endpoint:

1. Serum ABO Blood Grouping with B RRBCs:
    - The negative percent agreement did not meet the 99% acceptance criteria.
2. Serum ABO Blood Grouping with A2 RRBCs:
    - The positive percent agreement and the negative percent agreement did not meet the 99% acceptance criteria.
3. Detection of Unexpected Antibodies with IH-Card AHG Anti-IgG
    - For the IH-Cell Pool the positive percent agreement did not meet the 95% acceptance criteria.
    - For the IH-Cell I-II the positive percent agreement did not meet the 95% acceptance criteria.
    - For the IH-Cell I-II-III the positive percent agreement did not meet the 95% acceptance criteria.
4. Detection of Unexpected Antibodies with IH-Card AHG Anti-IgG,-C3d
    - For the IH-Cell Pool the positive percent agreement did not meet the 95% acceptance criteria.
    - For the IH-Cell I-II the positive percent agreement did not meet the 95% acceptance criteria.
    - For the IH-Cell I-II-III the positive percent agreement did not meet the 95% acceptance criteria.
5. Antibody Identification with IH-Card AHG Anti-IgG
    - For the IH-Panel 11: the positive percent agreement and the negative percent agreement did not meet the 95% acceptance criteria.

- For the IH-Panel 11 Papain: the positive percent agreement and the negative percent agreement did not meet the 95% acceptance criteria.
- For the IH-Panel Plus 6: the negative percent agreement did not meet the 95% acceptance criteria.

6. Antibody Identification with IH-Card AHG Anti-IgG,-C3d
    - For the IH-Panel 11: the positive percent agreement and the negative percent agreement did not meet the 95% acceptance criteria.
    - For the IH-Panel Plus 6: the positive percent agreement and the negative percent agreement did not meet the 95% acceptance criteria.

Because the assays mentioned above failed to meet the primary endpoint, on January 14, 2016, FDA asked BMD to perform an in-house accuracy study (In-House Performance Study) using well-characterized and/or contrived samples for investigational products that did not meet the acceptance criteria. It was agreed to only test positive samples if PPA did not meet the criteria and only test negative samples if the NPA did not meet the criteria. In the in-house study, the test results were compared to the expected results. FDA requested that both the original clinical comparison results and the new in-house accuracy study results to be included in the package inserts of the products.

For this study, BMD used the following acceptance criteria. For antibody detection and for antibody identification, the lower bound of the one-sided 95% confidence intervals for the positive percent agreement and the negative percent agreement had to exceed 0.95.

Results

The following two tables were extracted from the final Statistical review memo with permission from the statistical reviewer.

Table 12: Performance Results Summary for IH-Cell Pool, IH-Cell I-II, IH-Cell I-II-III in Clinical Comparison Study and Internal Performance Study [a] (Edited Agreements)

Test	Tested on	Results from Clinical Study				Results from In-House Study			
		NPA		PPA		NPA		PPA	
		N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)
IH-Cell Pool	**IH-Card AHG Anti-IgG**	2,942	99.12% (98.78%)	86	89.53% (82.45%)	Not Tested	NA	64	**100% (95.43%)**
	IH-Card AHG Anti-IgG,-C3d	563	98.76% (97.68%)	72	93.06% (85.95%)	Not Tested	NA	64	**100% (95.43%)**
IH-Cell I-II	**IH-Card AHG Anti-IgG**	1,188	97.22% (96.34%)	12	100% (77.91%)	Not Tested	NA	64	**100% (95.43%)**
	IH-Card AHG Anti-IgG,-C3d	1,996	99.35% (98.97%)	6	100% (60.70%)	Not Tested	NA	64	**100% (95.43%)**
IH-Cell I-II-III	**IH-Card AHG Anti-IgG**	469	97.23% (95.63%)	68	98.53% (93.21%)	Not Tested	NA	64	**100% (95.43%)**
	IH-Card AHG Anti-IgG,-C3d	1,262	97.86% (97.06%)	75	97.33% (91.84%)	Not Tested	NA	63	**100% (95.36%)**

[a]: Acceptable PPA and NPA results are not tested in accuracy study.

Conclusion: The In-House study results for IH-Cell Pool, IH-Cell I-II and IH-Cell I-II-III, used for antibody screening and antibody identification, met the acceptance criteria for the PPA.

Table 13: Performance Results Summary for IH-Panel 11, IH-Panel 11 Papain, IH-Panel Plus 6 in Clinical Comparison Study and Internal Performance Study [a]

Test	Tested on	Results from Clinical Study				Results from In-House Study			
		Negative Agreement		Positive Agreement		Negative Agreement		Positive Agreement	
		N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)	N	Point Estimate (one-sided Exact 95% LCL)
IH-Panel 11	IH-Card AHG Anti-IgG	150	88.00% (82.73%)	106	98.11% (94.18%)	212	**98.11% (95.73%)**	64	**100% (95.43%)**
	IH-Card AHG Anti-IgG, -C3d	167	91.02% (86.51%)	39	100% (92.61%)	212	**98.11% (95.73%)**	64	**100% (95.43%)**
IH-Panel 11 Papain	IH-Card AHG Anti-IgG	201	92.54% (88.74%)	154	90.91% (86.15%)	284	**96.48% (94.10%)**	62	**100% (95.28%)**
IH-Panel Plus 6	IH-Card AHG Anti-IgG	81	91.36% (84.38%)	61	100% (95.21%)	213	**99.06% (97.07%)**	Not Tested	N/A
	IH-Card AHG Anti-IgG, -C3d	80	92.50% (85.73%)	9	88.89% (57.09%)	213	**98.59% (96.40%)**	64	**100% (95.43%)**

[a]: Acceptable PPA and NPA results are not tested in accuracy study.

Conclusion: The results for IH-Panel 11, and IH-Panel Plus 6 met the acceptance criteria for the PPA and the NPA.

For IH-Panel 11 Papain, the NPA did not meet the 95% acceptance criteria (94.10%). Ten (10) of 284 expected negative samples were positive on the IH-1000 after result verification. Blood group antibodies could not be identified in any of 10 samples that were unexpectedly positive with IH-Panel 11 Papain. Eight (8) of these 10 samples were also tested on IH-Card AHG Anti-IgG and IH-Card AHG Anti-IgG,-C3d with both non-enzyme treated IH RRBCs (IH-Panel 11 and IH-Panel 6). All 8 samples were negative in antibody identification tests with non-enzyme treated IH-RRBCs. These findings are reflected in the package insert of the product under Specific Performance Characteristics section.

b) Pediatrics

The Bio-Rad Medical Diagnostics GmbH IH-System is an in vitro diagnostic; therefore, a review by the Pediatrics Review Committee was not required.

c) Other Special Populations

N/A

f. Overall Comparability Assessment

The results of the clinical comparison study and product labeling support the conclusion that the RRBCs formulated for automated testing on the IH-1000 Analyzer are safe and effective. In addition, the lots manufactured in support of these submissions, demonstrate the reliability of the manufacturing process to consistently produce RRBCs that meet established specifications, perform as intended, and remains stable throughout its shelf life.

a. Advisory Committee Meeting

The Bio-Rad Medical Diagnostics GmbH IH-System does not include novel technology; therefore, an advisory committee meeting was not held or required.

b. 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 via information requests and resolved issues with the expertise of the their respective management, if applicable. No internal or external disagreements were communicated to the regulatory project manager or chairperson. All reviewers recommended approval of the Reagent Red Blood Cells Efficacy Supplement.

No postmarketing commitments are associated with the Reagent Red Blood Cells Efficacy Supplement.

c. Labeling

The labeling for Reagent Red Blood Cells complies with Title 21 CFR 610.62, 610.63, 610.64, 610.65, 660.55 and 809.10.

In the teleconference held on June 8, 2016, BMD agreed to include in the final labeling all the recommendations provided by FDA. The final labeling for Reagent Red Blood Cells includes the following changes.

- The use of a table format to represent the results from the clinical study and the results from the in-house performance study in the package insert of RRBCs, under the Specific Performance Characteristics section. As clarified by BMD that visual reading and editing of the image results by the operator is a mandatory steps for using the IH-1000 system, FDA suggested to present the "edited results" rather than the "initial results" of the clinical comparison study and the in-house performance study.
- The package insert is revised to define visual reading and editing (if applicable) as a required process. In Specific Performance Characteristics section, BMD added: "See the IH-1000 User Manual NA and IH-Com User Manual NA for more information on verification of results". In the User Manual for IH-1000, page A2 Chapter 1 states, "Intended Use ….It generates results from individual images that must be verified by visual inspection by a qualified operator."
- As in the in-house performance study for IH-Panel 11 Papain, the product testing did not meet the 95% acceptance criteria, the labeling will reflect this finding in the Specific Performance Characteristic section of the package insert.

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.

The revised final labeling was submitted in Amendment 125208/70/23 on June 30, 2016. It was reviewed and found acceptable.

d. 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 Efficacy Supplement, 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 of stored test results, if necessary.

- Features that affect 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 this Reagent Red Blood Cells Efficacy Supplement.