Summary Basis for Regulatory Action Template

From: Annette Ragosta, Chair of the Review Committee

BLA STN#: 125342/15

Applicant Name: Alba Bioscience Limited (Alba)

Date of Submission: September 1, 2014; application received in CBER on September 8, 2014

MDUFA Goal Date: March 14, 2017

Proprietary Name/ Established Name: Ortho™ Sera Anti-Fy^b/Blood Grouping Reagent

Intended Use: (*Copied from page one of the Instructions for Use document)*

> For *in vitro* diagnostic use only
> For use with the ID-Micro Typing System™ Anti-IgG Card
> For Indirect Antiglobulin Test
> The Anti-Fy^b reagent (Anti-FY2) is for the qualitative *in vitro* detection of human Fy^b positive red blood cells by the indirect antiglobulin test.

Recommended Action:
The Review Committee recommends approval of Alba's Anti-Fy^b reagent for use with the Ortho ID-Micro Typing System™ Anti-IgG Gel Card column agglutination test method.

Review Office(s) Signatory Authority(ies): Orieji Illoh, MD, Director, Division of Blood Components and Devices, Office of Blood Research and Review

> ☐ **I concur with the summary review.**
>
> ☐ **I concur with the summary review and include a separate review to add further analysis.**
>
> ☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

TABLE 1

Document title	**Reviewer name, Document date**
Clinical Review(s) • *Clinical (product office)*	• Annette Ragosta, OBRR/DBCD/DRB 25 APR 2016 • Joyce Rockwell, OBRR/DBCD/DRB 13 FEB 2015, 20 MAR 2015, 03 JUN 2015
• Non-Clinical Review	• Annette Ragosta, OBRR/DBCD/DRB 25 APR 2016 • Joyce Rockwell, OBRR/DBCD/DRB 13 FEB 2015, 20 MAR 2015, 03 JUN 2015
Statistical Review(s)	Chunrong Cheng, OBE/DB/TEB 02 JUN 2015
CMC Product Review	• Joyce Rockwell, OBRR/DBCD/DRB 13 FEB 2015, 20 MAR 2015, 03 JUN 2015 • Hyesuk Kong, OCBQ/DBSQC/LMIVTS Microbiology/Bioburden 27 OCT 2016
CMC Facility Review	Priscilla Pastrana OCBQ/DMPQ/BII
Labeling Review(s) • *Product Office* • *APLB (OCBQ/APLB)*	• Annette Ragosta, OBRR/DBCD/DRB 25 APR 2016 • Joyce Rockwell, OBRR/DBCD/DRB 13 FEB 2015, 20 MAR 2015, 03 JUN 2015 • Dana Jones, OCBQ/DCM/ALP 07 APR 2015
Lot Release Protocols/Testing Plans	Karen Campbell (Lot Release)
Establishment Inspection Report	Not applicable for these submissions
Bioresearch Monitoring Review	Not applicable for these submissions

1. Introduction

Alba Bioscience Limited (Alba) submitted this efficacy supplement requesting approval of the Anti-Fy^b reagent for use with the Ortho ID-Micro Typing System™ (MTS) Anti-IgG Gel Card.

This supplement is the second of three bundled submissions of Rare Antisera for Column Agglutination Technology (RASCAT) Blood Grouping Reagents for use with the gel cards. The Anti-Fy^b blood grouping reagent is manufactured by Alba at their licensed Ellen's Glen Road facility, a multi-use facility that manufactures FDA licensed and 510(k) cleared products, as well as blood grouping reagents, red blood cell products, and controls for the rest of the world. The RASCAT reagents will be distributed by Ortho Clinical Diagnostics (FDA License 1236) (Ortho) under the trade name Ortho™ Sera.

Anti-Fy^a and anti-Fy^b (Anti-FY1 and Anti-FY2) were described in 1950 and 1951 respectively. Fy^a and Fy^b are a pair of alleles on the long arm of chromosome 1, giving rise to three commonly encountered phenotypes: Fy (a+b-), Fy (a+b+) and Fy (a-b+). These antigens are fully developed at birth. The Fy^a antigen occurs in approximately 66% of Caucasians and 10% of the Black population. The Fy^b antigen occurs in approximately 83% of Caucasians and 23% of the Black population. Antibodies directed against the Duffy antigens can cause hemolytic transfusion reactions and hemolytic disease of the newborn.

Clinical laboratories commonly perform blood group determination using hemagglutination methods. The principle of the hemagglutination test dates back to the 1900's when Karl Landsteiner identified the A, B, and O blood groups. The same principle applies to the other blood group systems. When reagent antiserum is added to red blood cells containing the corresponding antigen, agglutination occurs.

2. Background

Meetings with FDA:

Alba submitted a pre-submission meeting request to FDA (reference PTS # PS002250) on September 5, 2013, to discuss 14 Blood Grouping Reagents (BGR), both monoclonal and polyclonal, to be marketed under the trade name ORTHO™ Sera for use with the Ortho ID-Micro Typing System™ gel cards manufactured by

Ortho-Clinical Diagnostics. The meeting was held on October 24, 2013. FDA had a follow up teleconference with Alba on November 12, 2013.

Marketing History:

The Anti-Fy^b blood grouping reagent was approved in 2012 under BL 125342/0 for use with the standard tube test method and the MTS Anti-IgG Gel Card was approved in 1994 under BL 103461/0. Both devices have been distributed in the US since their approval dates. This submission does not request any changes to the manufacturing processes or facilities used for the Anti-Fy^b blood grouping reagent or the MTS Anti-IgG Gel Card.

Device Description:

The Anti-Fy^b blood grouping reagent is manufactured from human plasma. Plasma donations used in the manufacture of polyclonal antibody derived blood grouping reagents are in limited supply due to the scarcity of stimulated donors; therefore Anti-Fy^b plasma is purchased from various suppliers. The Anti-Fy^b reagent is formulated and filled into a five milliliter glass vial. The end user manually adds the reagent to the MTS Anti-IgG Gel Card for detection of the Fy^b antigen by the indirect antiglobulin test. The MTS Anti-IgG Gel Card contains six microtubes of Anti-IgG reagent suspended in a diluent and a buffered gel solution. The Anti-Fy^b reagent will react with red blood cells that are positive for the Fy^b antigen. These sensitized red blood cells will then react with the Anti-IgG gel during centrifugation. Strongly positive agglutination reactions produce a line of red blood cells layered at the top of the gel. Positive reactions will have varying degrees of visible red blood cell agglutinates suspended in the gel. Uncoated (unsensitized) red blood cells or red blood cells coated only with complement are not agglutinated by the Anti-IgG and will form a button at the bottom of the microtube.

Chronology:

CBER received this efficacy supplement on September 8, 2014. CBER issued a Filing with Deficiencies Letter on October 29, 2014. CBER subsequently received

16 amendments from Alba in response to various information requests and two Complete Response (CR) letters issued on June 19, 2015 and May 11, 2016.

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

In Vitro Substance (IVS)

The raw material used in the IVS is a human derived polyclonal antibody specific for the human red blood cell antigen Fy^b. The raw material is supplied by blood collection facilities and brokers on Alba's approved suppliers list. A Certificate of Analysis (CoA) is obtained from the supplier to show the material has been tested and found to be non–reactive for HBsAg, Anti-HIV1/2, Anti-HCV and Syphilis (21 CFR 610.40). (b) (4)

(b) (4)

(b) (4)

Alba provided a comprehensive list of these products in the submission. Cross contamination of the products is controlled by (b) (4) In addition, sodium azide (0.1g/L) is added to minimize bacterial growth.

The IVS is not subject to (b) (4)

The following tests are performed prior to release of the IVS for manufacturing of the final Anti-Fy^b reagent:

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

Alba uses a (b) (4) product that has met all final product specification requirements as the in-house reference standard.

The hold times for the IVS; (b) (4) were established through data review of previously manufactured lots of polyclonal derived IVS. A validation study demonstrated that subjecting the (b) (4) IVS to (b) (4) had no impact on the stability of the final product manufactured from the (b) (4) IVS. Due to the scarcity and variability of the raw materials used in the manufacture of the IVS and consequently the volumes of IVS available, the material is not subject to a formal stability program. The IVP subsequently manufactured from the IVS is subject to formal stability studies.

In Vitro Product (IVP)

Alba manufactures the IVP at their licensed facility, located at 21 Ellen's Glenn Road, Edinburgh, UK. The process includes formulation, (b) (4), filling, and in-process and final Quality Control (QC) testing. (b) (4) (b) (4) testing of (b) (4) water and (b) (4) water is carried out by a subcontractor. As with the IVS, multiple products are manufactured in the same rooms as the Anti-Fy^{b} IVP; Alba provided a comprehensive list of these products in the submission. Cross contamination of the products is controlled by campaign manufacturing; full line clearance is

required before commencing production steps. All raw materials used for the manufacture of the Anti-Fy^{b} IVP are provided by qualified suppliers and accepted based upon the supplier CoA and qualifying tests, as applicable.

(b) (4) [redacted]. Autoclaved equipment and aseptic techniques are used throughout this procedure to avoid contamination.

(b) (4) [redacted].

(b) (4) [redacted]. Alba validated the hold times (b) (4) [redacted] using the three conformance lots. The maximum validated hold time at (b) (4) [redacted]. Based on the validation data, Alba has assigned a (b) (4) hold time for the Fy^{b} in-process material. The filling machine is a semi-automatic filling machine and caps are applied then tightened using a capping machine. Filled, unlabeled containers are transferred to cold storage.

Specificity and potency testing are performed on the filled product using the Column Agglutination Technology (CAT) method. (b) (4) [redacted], and bioburden testing are also performed on the filled product. The product progresses to the labeling stage if all required tests meet the pre-determined

acceptance criteria. The product is labeled and an identity check is performed (confirmation of reactivity). The product is stored at 2 to 8°C until it is released for distribution by Quality Assurance.

Specifications and Test Methods

The following table includes the required tests and acceptance criteria for the Anti-Fy^b IVP:

TABLE 2

Test Method	**Acceptance Criteria/Range**
MTS Anti-IgG Column Agglutination Test (CAT), Confirmation of Reactivity	(b) (4) (b) (4)
MTS Anti-IgG CAT, Exclusion of contaminating antibodies	(b) (4) (b) (4)
MTS Anti-IgG CAT, Potency testing using two Fy(a+b+) red blood cells	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Bioburden	(b) (4)

Microbiology

Anti-Fy^b blood grouping reagent is a microbiologically controlled product and is considered a non-sterile, multiple use device. The acceptable level of micro-organisms which the product may contain is (b) (4) . Microbiological control of the final product is accomplished as follows:

- The final product contains the preservative (bacteriostatic agent) Sodium Azide (NaN3) at a concentration of 1 g/L, to inhibit growth of micro-organisms which may be introduced subsequent to the manufacturing

process.

- Environmental and in-process controls are in place to limit the presence of micro-organisms, and therefore limit potential contamination of the product through environmental control and aseptic technique.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. The 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 in the PAS were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of Polyclonal Antibody Anti-Fy^b (Re-calcified human plasma containing anti-Fy^b), product code FD153M is listed in the table below.

Name/Address	FEI number	DUNS number	Results/Justification
in vitro Substance *in vitro Product* *Release Testing* Alba Biosciences Limited 21 Ellen's Glen Road Edinburgh EH17 7QT Scotland, UK	3003580203	719392867	Team Biologics May 2016 VAI

Team Biologics performed a surveillance inspection of the Edinburgh, Scotland, UK facility May 12, 13, 16-20, 2016. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

No pre-approval inspection was performed as there were no changes to the approved application that would require such an inspection.

d) Environmental assessment

The supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 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

The *in vitro* Product is filled into 5mL (b) (4) glass vial with 18mm screw neck and (b) (4) plastic red cap 8mm/400 with liner, which are provided by (b) (4) Alba conducted the container closure integrity testing at the Edinburgh, UK facility, employing (b) (4) all acceptance criteria were met.

4. Analytical Studies

Analytical studies included stability, anticoagulant, and precision studies.

Stability Studies

All three conformance lots of ORTHO™ Sera Anti-Fy^{b} for ID-MTS™ Gel Card were included in the real-time stability studies. Vials were opened briefly at the start of the study and then stored at 2-8 °C until testing at the following time points: day zero, and 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, (b) (4) Months.

Specificity was performed using (b) (4)

Microbiology testing was performed at day zero (post-fill), 12 , 24, and (b) (4) time points to demonstrate integrity of the closure system and verify effectiveness of the preservative included in the formulation of the IVP.

In addition to the real time stability study on the IVP, Alba also performed a simulated transport stability study to determine the impact of extreme

temperature conditions which could potentially occur during transportation of the product between Alba and the end user. Vialled reagent underwent the following simulated worst case conditions:

- (b) (4)

The data provided in the submission met the acceptance criteria and support the shelf life of 24 months.

Anticoagulant Studies

The package insert includes the following sample limitations:

- Samples collected in EDTA should be tested within seven days from collection.
- Donor blood collected in ACD, CPD, CP2D, CP2D with AS-3 and CPDA-1may be tested until the expiration date of the donation.

The following is a list of the anticoagulants and corresponding testing dates included in the validation study:

EDTA Potassium (b) (4)
CPD (b) (4)
ACD (b) (4)
CPDA-1 (b) (4)
CP2D (b) (4)
CP2D with AS-3 (b) (4)

The donor red blood cell samples were immediately transferred into glass vials which contained a pre-determined volume of each of the anticoagulants. All samples were stored at 2 to 8^{o}C for the duration of the study. Specificity testing was performed in accordance with the test method listed in the package insert

and included four homozygote positive cells, two heterozygote positive cells, and four negative cells. The data from the anticoagulant study support the specimen collection claims described in the package insert.

Precision Studies

The Reproducibility and Repeatability study was performed to demonstrate that the test reagent generates reproducible and accurate results using a panel of well-characterized samples across different sites, using different operators, and on different days. The acceptance criterion stated that there should be 100% agreement between the test outcomes and the expected results.

The external study was performed at three sites, using (b) (4) lots of test reagent against a panel of three reagent red blood cells. The testing was performed by three operators over (b) (4) non-consecutive days, with (b) (4) testing performed by each operator within each run. There were no discordant results; all expected positive tests generated unequivocal positive reactions and all expected negative tests generated unequivocal negative reactions.

5. Clinical Studies

a) Clinical Program

ORTHO™ Sera Anti-Fy^b using the Ortho ID-Micro Typing System™ Anti-IgG Gel Card as the test method was tested in parallel with a currently licensed US product using de-identified leftover clinical samples at multiple clinical locations. The acceptance criterion requires $\geq$ 99% concordance at the lower bound of the one-sided 95% confidence interval for both negative and positive percent agreement. The study was conducted at the following four sites:

- Alba Bioscience Limited (internal site)
- New York Blood Center
- Memorial Blood Center
- Blood Center of Wisconsin

The three US study sites were selected for the diversity of their locations and

donor populations. Three lots of the ORTHO™ Sera Anti-Fy^b reagent were included in the study. Testing was performed in accordance with the Instructions for Use documents for both the trial and the comparator reagents.

The following disease state samples were included in the study (see Table 3 below):

TABLE 3: *(copied from Section 6.5 of the Performance Evaluation Report)*

Disease state	Number of samples tested
Multiple Myeloma	10
Waldenstrom's Macroglobulinemia	2
Pregnant	11
Lymphoma	9
Leukaemia	11
Lipemic	10
Hemolysed	10
DAT positive	18[1]
Weak Antigen	10
WAIH	7
Sickle cell	11
Elderly	11
Cord	10

Using the Clopper-Pearson exact calculation method, the one-sided 95% lower confidence limits for positive and negative percentage agreement are as follows (see Table 4 below):

TABLE 4 *(copied from Section 6.2.5 of the Performance Evaluation Report)*

Anti-Fy^b	Sample size	Agreement	Percentage Agreement	One sided 95% Lower Confidence
Positive Percentage Agreement	782	780	99.7%	0.99
Negative Percentage Agreement	353	330	93.5%	0.91

The study did not meet the acceptance criteria for the negative percent agreement at the one-sided 95% lower confidence limit: 0.91 versus 0.99. There were twenty-three (23) false positive discordant results and two (2) false negative discordant results between

the trial reagent and the comparator. These results are described in detail below:

- Five false positive results were due to positive direct antiglobulin test results
- Four false positive results were due to the Fy^x phenotype which was detected by the trial reagent but was negative with the comparator reagent
- Six false positive results due to cord blood samples
- Two false positive results that may have been due to transfused cells (not verified)
- Five false positive and two false negative (seven in total) initial results due to testing errors; sample results were concordant upon retest.
- One false positive sample (not concordant upon retest or with resolver reagent)

Based on the comparator testing results, the package insert was amended to state that cord blood samples, DAT positive red blood cell samples, and mixed red blood cell populations due to transfusion history or transplant may cause anomalous results.

b) Pediatrics

Cord blood samples were included in the comparator study however six false positive results were attributed to this sample type. Based on these comparator testing results, the package insert was amended to state that cord blood samples may cause anomalous results.

6. Advisory Committee Meeting

This supplement does not include novel technology; therefore, an advisory committee meeting was not required.

7. Other Relevant Regulatory Issues

There are no relevant regulatory issues for this submission. The review committee members reviewed their specific sections of the BLA and resolved any issues through Information Requests and Complete Response letters with Alba. 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 that the licensed Anti-Fy^{b} reagent be approved for use with the Ortho ID-Micro Typing System™ Anti-IgG Gel Card column agglutination test method.

8. Labeling

The Product Office and the Advertising and Promotional Labeling Branch reviewed the container labels, the Instructions For Use (IFU) document, and generic packing labels. All labels met the requirements outlined in 21 CFR Part 610.62, 610.64, 660.28 and 21 CFR Part 809.10. The IFU document also includes the Ortho™ Sera Anti-Fy^{a} (Monoclonal) (IgG) blood grouping reagent which was submitted under BL 125567/0.

As stated above, this reagent will be distributed by Ortho under the trade name Ortho™ Sera; therefore, Ortho will be responsible for providing the end user the IFU document. Alba provided the procedure that addresses control of the implementation of a revised electronic IFU document and the Quality Agreement between Ortho and Alba that delineates the labeling responsibilities between the two companies.

9. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee members representing the necessary review disciplines recommend that the licensed Anti-Fy^{b} reagent be approved for use with the Ortho MTS Anti-IgG Gel Card. These were independent conclusions based on the content of this efficacy supplement 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 clinical benefits using the Ortho MTS Anti-IgG Gel Card as the test method for the Ortho™ Sera Anti-Fy^b Blood Grouping Reagent include reduction in errors associated with subjective interpretation due to manual tube method testing and the capability to review stored test results, if necessary.

c) Recommendation for Post-marketing Activities

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