



## MEMORANDUM

**From:** Alain Debrabant, Ph.D.,  
Laboratory of Emerging Pathogens (LEP)  
DETTD, OBRR, CBER

**Thru:** Sanjai Kumar, Ph.D.,  
Chief, LEP  
DETTD, OBRR, CBER

**To:** Robert Duncan, Ph.D.,  
Principal Investigator  
LEP/DETTD/OBRR/CBER  
Scientific Lead

**To:** Iliana Valencia, MS, MCPM  
Chief, Regulatory Project Management Staff  
OBRR/CBER

**Subject:** Review Memo

**Sponsor:** Imugen/Oxford Immunotec, Inc.

**Biologic Product Name:** *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA)

**STN:** 125589

**Document reviewed:** STN 125589\0\27: Imugen's responses to questions 2 and 5 of the FDA CR Letter dated June 13, 2017  
STN 125589\0\30: Imugen's response to Information request dated November 29, 2017

### **Recommendation:**

Imugen responses to questions #2 and #5 of the FDA CR Letter dated June 13, 2017 are acceptable. I recommend approval of the *B. microti* AFIA pending resolution of the remaining issues identified by the other reviewers assigned to this BLA.

## SUMMARY AND REVIEW COMMENTS

### Abbreviated timeline:

- May 12, 2015: FDA received a BLA from Imugen, Inc., now Oxford Immunotec, for a *Babesia microti* Arrayed Fluorescence Immunoassay.
- September 29, 2015: FDA sent a Complete Response (CR) Letter to the company following review of the BLA.
- December 13, 2016: FDA received a Complete Response to the FDA CR Letter.
- June 13, 2017: FDA sent a second CR Letter to Imugen following review of Imugen's complete response including review of subsequent amendments. FDA concluded that significant issues remained to be resolved.
- October 10, 2017: Imugen responded to FDA second CR Letter.

**In this review memo, I evaluate whether Imugen satisfactory answered FDA questions #2 and #5 in the second FDA CR Letter as they pertain to the issues I raised during my review of the stability and CMC sections of the BLA.**

### Principle of *Babesia microti* AFIA:

The *Babesia microti* Arrayed Fluorescence Immunoassay 'Babesia AFIA' is based upon a conventional indirect immunofluorescent assay (IFA) and is used for detecting the presence of specific antibodies to *B. microti* in blood donor specimens. The test uses *B. microti* infected (b) (4) erythrocytes, as an antigen source, fixed to glass slide wells and a (b) (4) F(ab')<sub>2</sub> anti-human IgG H+L chain specific (b) (4) conjugated antibody as a detector of bound *B. microti*-specific antibody. The fluorescence is detected by manual observation of the wells of the slide employing a microscope equipped for epi-fluorescence. Positive and negative controls (human (b) (4)/plasma containing or not *B. microti* antibodies) are used on each slide. The positive control is expected to produce a visible fluorescence pattern, while the fluorescence pattern will not be observed with the negative control plasma.

### Proposed intended use:

The Imugen *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA) is intended for qualitative detection of antibodies to *Babesia microti* in human plasma (EDTA anticoagulated) samples. This test is intended for use as a donor screening test to detect antibodies to *B. microti* in plasma samples from individual human donors, including volunteer donors of whole blood and blood components, as well as other living donors. It is also intended for use to screen organ and tissue donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on specimens from cadaveric (non-heart beating) donors. This test is not intended for use on samples of cord blood. This test is not intended for use as an aid to diagnosis of *Babesia microti* infection.

Note that this assay is proposed as a service and is performed by Imugen. It is not assembled as a test kit nor distributed.

### Review of Imugen's responses to FDA questions #2 and #5 in the June 13, 2017 FDA CR Letter:

Note: The questions included in the FDA Complete Response letter are repeated in italics below for clarity.

**FDA Question#2:** *The change proposed by Imugen to their real-time stability study is acceptable. Please provide an updated finished device stability protocol (DOC-STB-24) and updated report to date (DOC-STB-RPT-24) to reflect these changes.*

Imugen Response: Imugen provided updated finished device stability protocol (DOC-STB-24) and updated report to date (DOC-STB-RPT-24) as requested (Attachment 2.1. and 2.2.). Based on the Table 5.1. in the report, the real-time stability data will support a (b) (4)-month expiration dating for the *B. microti* AFIA finished device by the action due date of April 18, 2018.

Reviewer Comment: **Imugen's response is acceptable.**

**FDA Question#5:** *Your response to IR question#11 is not acceptable. The revised LAB-SER-BIFA-1 procedure does not clearly specify how many additional retests of a clinical specimen are allowed to reach a final result: Section 9.2.1. says that an initial reactive sample is retested twice at 1:128 and titrated out to endpoint (1:1024) and Section 9.2.2.6. says that additional re-tests may be required at the discretion of the supervisor to further evaluate any inconclusive findings. The FDA expects that a clear finite number of tests are performed to make an interpretation of non-reactive or repeatedly reactive in a serological test. Therefore the wording in Section 9.2.1 is acceptable. Remove the additional retests in Section 9.2.2.6. Please revise LAB-SER-BIFA-1 to indicate how many retests are allowed and how the final interpretation of the results is reached.*

**Imugen Response:** Imugen provided a revised LAB-SER-BIFA-1, "Arrayed Fluorescence Immunoassay (AFIA) for Anti-Babesia microti Antibody for use in Blood Donor Screening." (Attachment 5.1.). Section 9.2.2.6. has been removed as requested.

**Reviewer Comment:** This response is not complete. Imugen was requested, in an information request sent November 27, 2017, to clarify how the final interpretation is made after the initial and repeat testing results are obtained is obtained and reported for a sample tested in this assay. This interpretation should also be included in LAB-SER-BIFA-1.

Imugen responded December 1, 2017 by providing table showing how a final interpretation is reached for every possible testing result combination (table below). This table and corresponding description will be added in Section 9.5. of LAB-SER-BIFA-1.

**Imugen's response is acceptable**

Initial Result	Replicate (1)	Replicate (2)	Interpretation	Reported Result
Negative	N/A	N/A	No <i>B.microti</i> antibody detected	Negative
NSF	Negative	Negative	No <i>B.microti</i> antibody detected	Negative
NSF	1 or more NSF replicates		<i>B. microti</i> antibody status cannot be determined	Inconclusive
NSF	Negative	Positive	<i>B. microti</i> antibody status cannot be determined	Inconclusive
NSF	Positive	Positive	<i>B. microti</i> antibody detected	Positive
Positive	Negative	Negative	No <i>B.microti</i> antibody detected	Negative
Positive	Negative	NSF	<i>B. microti</i> antibody status cannot be determined	Inconclusive
Positive	NSF	NSF	<i>B. microti</i> antibody status cannot be determined	Inconclusive
Positive	1 or more Positive replicates		<i>B. microti</i> antibody detected	Positive