



Review Memorandum

BLA: BL12558

Date: 2/15/2018

Reviewer: Sreenivas Gannavaram, Ph.D., OBRR/DETTD/LEP

APPROVED

By Sreenivas Gannavaram at 4:44 pm, Feb 15, 2018

Through: Sanjai Kumar, Ph.D., Lab Chief, OBRR/DETTD/LEP

For Sanjai Kumar

RPM: Alisha Miller

APPROVED

By Alain Debrabant at 4:51 pm, Feb 15, 2018

Sponsor: Oxford Immunotec Ltd. (Formerly Imugen)

Product: Babesia microti Nucleic Acid Test

Recommendation: Approval

Intended Use: The *Babesia* nucleic acid test (NAT) blood screening assay is an (b) (4) test intended to detect DNA specific to *Babesia microti* in blood donor specimens. The blood donor specimens are collected using EDTA tubes and delivered to Imugen's CLIA certified laboratory. Imugen will perform the analysis of these samples using a (b) (4) based method to detect the presence of *Babesia* nucleic acids in the donated blood samples using *B. microti* specific primers. Detection of the *B. microti* specific DNA by using nucleic acid probes will indicate a positive blood donor specimen. A negative result indicates the absence of *Babesia* DNA in the specimen.

Documents Reviewed:

Chemistry manufacturing and controls including device description and back ground, attachments describing high and low positive PCR assay control preparation, isolation of nucleic acids using (b) (4), detection of *Babesia microti* by real time polymerase chain reaction, analytical performance characterization for *Babesia microti* NAT, stability studies, Analytical sensitivity and Limit of Detection study.

Comments:

Device Description and background Part I:

1) The source material for the production of glass slides containing *Babesia* infected red blood

cells is obtained from the *Babesia* infected (b) (4). Infection of the (b) (4) and collection of source material is performed at the (b) (4)

(b) (4). The material obtained from the infected (b) (4) is analyzed by Genotyping to ascertain the molecular identify of the *Babesia microti* by analyzing (b) (4) different loci on the genome.

It is not clear from the submission how often the genotyping of the source material performed. Is the *Babesia microti* organisms in the starting material (infected (b) (4) blood) obtained in the field by the (b) (4)

Is the material obtained from (b) (4) (b) (4) similarly genotyped?

How the genetic identify of the *Babesia microti* organisms used in preparing the AFIA slides used in the donor blood screening assay ascertained?

In the Figure 4.2.3 flow chart that describes the processing and testing *Babesia microti* infected red blood cells at IMUGEN, only the percentage (b) (4), absence of bacterial contamination are tested for but no further testing on the genetic identity of the *Babesia microti* deposited on the slides.

Please explain what steps are taken to ascertain the genetic stability of the *Babesia microti* organisms in infected RBC used in preparing the test material for blood screening assay.

.2. *B. microti* NAT low positive assay control preparation: Fig 4.9.7. Page 108.137.

The flow diagram describing the manufacturing process for *B. microti* NAT assay low positive positive control (Fig 4.9.7) states that the approved *Babesia* infected (b) (4) whole blood stock will be (b) (4) into *Babesia* (b) (4) to obtain a final concentration of (b) (4) *Babesia*/ml. This (b) (4) preparation will be tested by a protocol

involving (b) (4) extractions and (b) (4) PCR reactions per extraction. After a PASS result is obtained, this bulk stock will be aliquoted as (b) (4) stocks.

Since the (b) (4) to detect *B. microti* NAT assay has a sensitivity of (b) (4) Babesia/ml of whole blood, a preparation containing (b) (4) parasites/ml could represent a low positive sample. Please explain if this assumption is valid for the purpose of optimizing low positive controls.

3. Human 18S rRNA-gene specific probe (b) (4) release testing for the *B. microti* PCR assay.

(LAB-AQC-MOL-35). The document describes testing consideration for the 18S rRNA specific probe to be used in the *B. microti* NAT assay. The probe is manufactured by (b) (4) [REDACTED]. Testing of this probe at Imugen involves reviewing the certificate of analysis, assign raw material part number, assign an expiration date and testing with negative and low positive and high positive Babesia controls.

The reports describing the release testing results are not included in the submission. Further, the SOP LAB-AQC-MOL-35 describes conditions where the shelf life of the probes could be extended based on the stability data. In the absence of reports describing these tests of stability of the probes, it is not possible to verify if the testing met the conditions described in the SOP.

4. Babesia 18S rRNA-gene specific probe release testing for the *B. microti* PCR assay.

(LAB-AQC-MOL-32). The document describes testing consideration for the 18S rRNA specific probe to be used in the *B. microti* NAT assay. The probe is manufactured by (b) (4) [REDACTED]. Testing of this probe at Imugen involves reviewing the certificate of analysis, assign raw material part number, assign an expiration date and testing with negative and low positive and high positive Babesia controls. The reports describing the release testing results are not included in the submission. In the absence of reports describing these tests of stability of the probes, it is not possible to verify if the testing met the conditions described in the SOP. Please explain what steps are taken for a more rigorous assessment of the probes before use in the blood screening assay.

Comments following the complete response from the sponsor:

Following the complete response provided by the sponsor, the issues raised in my initial review have been resolved.