

**Review Memorandum Final****STN: BL125588****Date:** 12/05/2017**From:** Ranadhir Dey, Ph.D. LEP, DETTD**To:** Babita Mahajan, Ph.D., DETTD (Scientific Lead)**RPM:** Iliana Valencia, CBER**Through:** Sanjai Kumar, Ph.D. DETTD, Chief of LEP**Sponsor / Product:** Imugen, Inc. *Babesia microti* Nucleic Acid Test**Purpose of the Submission:** BLA submission

**Documents Reviewed:** FDA communicated Complete Response (CR) letter (1<sup>st</sup>) to the sponsor on September 29, 2015. On December 14<sup>th</sup>, 2016 the sponsor submitted a complete response to CR the letter. This response was reviewed by the CMC reviewers and communicated with the sponsor by IRs. As the answer was not adequate FDA sent another CR letter (2<sup>nd</sup>) on June 13<sup>th</sup> 2017, and the sponsor has submitted response to this CR letter on Oct 10<sup>th</sup> 2017. The comments document my review of the CMC sections of the sponsor's complete response to the both CR letter and their response to the IRs.

**Intended Use and test principal:** IMUGEN Inc.'s ("IMUGEN" or the "company") Nucleic Acid Test ("NAT" or *Babesia* NAT assay") is a blood screening (b) (4) test for the detection of specific DNA to *Babesia microti* ("*Babesia*" or "*B. microti*"). The *Babesia* NAT assay can be used as a stand-alone blood screening application to provide testing of blood donors and blood donations for evidence of *B. microti* infection. IMUGEN's *Babesia* NAT assay (as described in this BLA submission) and IMUGEN's *Babesia* AFIA assay (as described in its separate BLA submission) also were evaluated clinically (under an FDA-approved IND) for concurrent use for additional indications. Specifically, based on the clinical data, IMUGEN proposes to (b) (4) the two assays for exclusive, concurrent use in assessing blood donors and blood

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donations to monitor disease prevalence in endemic and non-endemic areas, and as to a tool to prevent or significantly reduce the incidence of transfusion transmitted Babesiosis (TTB), especially in endemic areas.

**Components of the Assay:**

**List substances purchased from outside vendors provided in the BLA:**

Materials	Supplier/ Manufacturer
Babesia microti sequence detection primers	(b) (4)
(b) (4) Babesia Probe (b) (4)	
Human 18S Sequence Detection Primers	
(b) (4) Human 18S Probe	
(b) (4)	
(b) (4) DNA Mini Kit	
(b) (4)	
(b) (4)	
(b) (4)	

**Immugen, manufactured components for the B. microti NAT assay:**

**Babesia positive NAT controls:**

- A. High and low positive *Babesia* NAT controls are prepared at IMUGEN. The positive controls consist of characterized *Babesia* infected (b) (4) whole blood diluted in *Babesia* negative human whole blood. The controls are aliquot into vials and release tested.
- B. Babesia negative NAT control is prepared at Imungen. The negative control consists of characterized Babesia negative human whole blood.

**Recommendation:** During interactive review process the sponsor has addressed the major issues raised by agency reviewers of CMC section. I do not have any further

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question regarding the CMC section. If reviewers of other sections find satisfactory resolution of all issues, I recommend the approval of the BLA.

**Comments:**

1. As this submission is related to only Blood Donor test, FDA requested the sponsor to remove the claim for (b) (4) test from intended use and sponsor agreed. FDA also suggested to be very specific about the use of (b) (4) and the sponsor agreed to change the claim in intended use. The intended use statement should be reflects in Package Insert or "Instruction for use" before the license of this application get approved.
  
2. *Question 15 of 1<sup>st</sup> CR letter: In your submission, you indicated that the B. microti NAT device is microbiologically controlled; however, no details in regards to the control of organisms in the process (i.e., bioburden testing) or in the facility were provided. Please provide specifics in regards to microbiological control of your process and indicate where in the process bioburden testing is performed. If bioburden testing is not performed, please provide a justification. For example, (b) (4) blood represents the primary source material for making the positive controls; a rigorous microbiological examination of the source material is desirable. Fungal contamination also may occur in (b) (4) derived preparations. The procedures are designed only to capture bacterial contamination. The testing is done on (b) (4) according to LAB-MFG-25 which may not reveal non-bacterial contamination. Please propose a modified microbiological screening procedure or explain why it is not needed.*

*Comment: The sponsor mentioned that there are controls in place for the purpose of limiting microbiological contamination. Raw material acceptance testing of (b) (4) blood is performed by evaluation of (b) (4) made from all (b) (4) blood tubes (LAB-AQC-MOL-106 and LAB-MFG-1; Attachments 15.1 and 23.1, respectively). While LAB-MFG-1 and LAB-MFG-25 refer to the (b) (4) setting on the (b) (4) instrument, this setting produces a (b) (4). Acceptance criteria of the visual verification are the absence of any microorganism other than Babesia parasites. In addition the sponsor has validated the lack of interference by a number of pathogens (DOC-RPT-35, Attachment 9.1). This is acceptable.*

3. *Question 17 of 1<sup>st</sup> CR Letter. A 'kit' is defined.as a set of reagents qualified to be used together to perform an assay. As described in the*

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*original BLA submission, the B. microti NAT is not assembled into a formal kit for commercial distribution, but specific reagent lots that form a finished device will be used to perform in-house donor testing for B. microti by NAT. Extraction kits, a set of PCR reagents, B. microti primers, probes and positive and negative controls belonging to a lot should be assembled and tested together to comprise a test kit lot with the expiration date set by the shortest expiration date of a component of the assemblage.*

*You have submitted lot release documents for individual components as primers, probes, extraction kits (LAB\_AQC\_MOL-32, 33, 34, 35, 36, and 51) etc., rather than the defined kit with a batch of Babesia positive and negative controls according to LAB-AQC-MOL-32. This process of matching should continue until a batch comprised of all components are assembled into a finished device and subjected to final release testing. Please define the composition and size of the lot for the B. microti NAT finished device.*

Comment: The sponsor has now documented manufacturing process to create a finished device lot, they have provided the proper documentation. This is acceptable.

*4. Question 19 of 1<sup>st</sup> CR letter. The process of manufacturing B. microti infected (b) (4) red blood cells, the essential antigen component required to prepare high and low positive controls, is not sufficiently controlled nor is it fully described (NAT CMC overview part 1, Page 108.15). Please provide the following information:*

*a. Detailed genetic and antigenic characterization of the B. microti isolate used to prepare positive controls for the NAT assay along with the results of genotyping assays performed by (b) (4) (NAT CMC overview part 1, Page 108.14).*

*b. Location, storage conditions and composition (i.e., number of vials, volumes, date of preparation, temperature, etc.) of the current stock of B. microti parasites (NAT CMC overview part 1, Page 108.14) used as starting material in the manufacture of the B. microti high and low positive controls for the NAT assay.*

Comment: The sponsor has provided the genetic analysis report as an attachment 19.2

The sponsor has provided the detailed information regarding the B. microti stock and cell banks for working stock. This is acceptable.

*5. Question 20 of 1<sup>st</sup> CR letter. The production of the infected (b) (4) red blood cells is performed at the (b) (4) under*

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*contract. As the license holder for manufacturing the Babesia NAT, IMUGEN must demonstrate sufficient control over all manufacturing processes. Please provide additional information on the content of the contract with (b) (4). Please provide a copy of the IACUC protocol (#A98-04-003) that establishes the animal procedures performed as part of this manufacturing process. Please describe when and how manufacturing is transferred to (b) (4) and the content of contract arrangements and the IACUC protocol for this alternate contractor.*

Comment: Although the sponsor failed to address these issues in response to CR letter, however, by IR letter sponsor has successfully addressed these issues.

*6. Question 21 of 1<sup>st</sup> CR letter. The attachment LAB-MFG-8 describes the procedure for inoculating and harvesting B. microti infected blood from (b) (4) at the (b) (4) animal facility. The protocol is not specific or consistent with regard to the parasite inoculum used to infect (b) (4). In some cases blood from an infected (b) (4) is used to infect a naïve animal and in other cases parasites from a (b) (4) stock are used. It is not clear how many passages in animals have occurred since a (b) (4) stock was used to obtain infected RBCs (IRBCs) for preparation of high and low positive controls described in your BLA. The current process of preparing infected (b) (4) blood is not controlled sufficiently to ensure lot-to-lot consistency of prepared positive controls. In order to improve the consistency of IRBCs and reduce the possibility of antigenic drift over time, we have the following recommendations:*

- a. Each new production of (b) (4) infected blood should start with an inoculum of parasites from the working cell bank.*
- b. Define the inoculum size of the parasite that will be used to infect the (b) (4)*

Comment: The sponsor has adapted the procedures such that each production cycle of infected (b) (4) blood is initiated from the (b) (4) working cell bank and described in LAB-MFG-8 (Attachment 21.1). Each production cycle may include up to (b) (4) passages.

The total number of parasites used to inoculate a (b) (4) is not determined. Rather, the sponsor has determined that the critical parameter to obtain sufficient (b) (4) BiRBCs is the level of parasitemia. This is acceptable.

*7. Question 24 of 1<sup>st</sup> CR letter. For all oligonucleotide primers used in this assay, please provide information to demonstrate their specificity and subtype inclusivity showing sequence alignments among other Babesia species and apicomplexan parasites, and other relevant organisms whose genetic material may be found in donor blood.*

Comment: The sponsor has provided all the relevant information in response to CR letter, and successfully addressed this concern. This is acceptable.

8. *Question 13 of IR letter (Dated 23<sup>rd</sup> March 2017). In your responses to FDA question #25 on physicochemical acceptance criteria for the purchased oligonucleotides, in Table 25.1 and 25.2 you have stated that the purity requirement for oligo is (b) (4) and for (b) (4) is “pass.” Ideally oligos used in NAT screening assays are (b) (4) pure. Please clarify the acceptance criteria for the purity of the oligos. Additionally, the requirement for (b) (4) (b) (4) is a “pass” result from the contract manufacturer (b) (4) of the target calculated (b) (4). In documents submitted in attachment 25.1, the COA doesn't have (b) (4) results (peak) from the contract manufacturer. Please clarify how the physiochemical characteristics of the primers and probes manufactured by contract manufacturer verified.*

Comment: The sponsor has performed an onsite vendor audit and provided the “Supplier Audit Report” in Attachment 13.1. Although, the sponsor failed to provide (b) (4) data of each custom oligoneucleotide at this point of submission, however promise to provide the (b) (4) raw data for each delivered lot of oligos going forward. This is acceptable.