

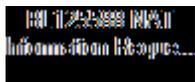
Valencia, Iliana

From: Valencia, Iliana
Sent: Friday, February 17, 2017 4:11 PM
To: Wolfgang Pieken (WPieken@oxfordimmunotec.com)
Cc: Jan Pullen (JPullen@oxfordimmunotec.com)
Subject: STN 125588 Babesia microti Nuclei Acid Test (NAT)- Information Request

Dear Dr. Pieken,

We are reviewing your December 14, 2016 resubmission to your biologics license application BL125588 for *Babesia microti* Nucleic Acid Test. We are providing the attached comments and request for additional information to continue our review.

Please provide the responses to questions **1 to 8** marked ** by February 27, 2017, and to the remaining questions by March 17, 2017.



Sincerely,

Iliana Valencia, MS, MCPM
Chief, Regulatory Project Management Staff
FDA/CBER/OBRR/IO
240-402-8444
iliana.valencia@fda.hhs.gov



"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender by e-mail or phone."

"At the intersection of differences lies the opportunity for innovation" Joel Barker

We are reviewing your December 14, 2016 resubmission to your biologics license application BL125588 for *Babesia microti* Nucleic Acid Test. We are providing the following comments and request for additional information to continue our review. Please provide the responses to questions **1 to 8** marked ** by February 27, 2017 and to the remaining questions by March 17, 2017.

1. **In your NAT Amendment response received December 14, 2016 to FDA question #1 (CR dated September 29, 2015) regarding clinical sensitivity, you have provided the summary of the data generated to demonstrate the clinical sensitivity of your NAT assay along with the line data. Additionally in your document 001_NAT response to AI_1 to 297 (page 37) you have provided the “lot numbers of the components” used in clinical sensitivity study.
 - a. Please clarify if the lots (or individual components) used for this study were released as “finished device lots” before they were used in this study. Please provide the finished device lot numbers and the release dates.
 - b. Please clarify if the low positive controls used in this study were at **(b) (4)** LOD.
2. **The document LAB-MOLBPCR-10 submitted in the original submission (received May 12, 2015) was reported as version 1.12; the version submitted with complete response letter (received Dec 14, 2016) is version 1.17. The SOP is neither dated nor signed. It is not clear what changes were made in the SOP from version 1.12 to 1.17. The SOP should reflect the legacy document numbers, along with description and justification of the changes and should identify the individual responsible for making the changes to the SOP. This individual also needs to sign and date the documents. Please submit the updated document. As a part of quality system, all your protocols and SOPs should follow the guidelines of document control.
3. **In your NAT Amendment response received December 14, 2016 to FDA question #8 (CR dated September 29, 2015) regarding the precision study, you have submitted the new precision study. Please clarify the following regarding this study:

STN 125588 Babesia microti Nuclei Acid Test (NAT)- Information Request

- a. The document “Protocol for Estimating Precision of the *Babesia microti* (DOC-PRO-26)” is not dated. Please clarify when the protocol was implemented and when the study was conducted.
 - b. Please clarify if the “component lots” used for this study were released as “finished device lots” before they were used in this study. Please provide the finished device lot numbers and the release dates.
4. **In your NAT Amendment response received December 14, 2016 to FDA question #9 (CR dated September 29, 2015) regarding cross reactivity studies and question # 10 (CR dated September 29, 2015) regarding interference studies, you have submitted the new cross-reactivity and interference studies. Please clarify the following regarding these studies:
- a. When the protocols were approved (implemented) and when these studies were conducted?
 - b. Please clarify if the “component lots” used for these studies were released as “finished device lots” before they were used in these studies.
5. **In your NAT Amendment response received December 14, 2016 to FDA question #12 (CR dated September 29, 2015) regarding incorporating a low positive control of (b) (4) LOD, you have stated that a low positive of (b) (4) LOD was introduced effective 03/26/16. Please provide the design, verification and validation documents that describe how this change was incorporated in the finished device.
6. **In your NAT Amendment response received December 14, 2016 to FDA question #15 (CR dated September 29, 2015), you have provided the information on different lots used in pre-clinical studies. You have submitted studies that were conducted in response to the complete response letter.
- a. Please clarify which studies were carried out with finished device lots (following the definition of finished device lot). Please provide the lot numbers of finished device lots used in this study.

- b. Please clarify when the first finished device was released/manufactured. Please provide the list of finished device lots that have been released/manufactured since defining the finished device.

7. **In your NAT Amendment response received December 14, 2016 to FDA question #16 (CR dated September 29, 2015) on process validation, you have provided the validation plan along with process validation report summarizing the results. Please provide the following information:
 - a. Please provide a list of critical lab SOPs/Protocols (including version number) that have been locked (no major modification) following process validation.
 - b. Please clarify since when (specific date) NAT manufacturing and testing are being conducted following implementation of process validation (i.e., locked down, with no major changes).
 - c. Please clarify when the document LAB-VAL-19 was implemented.
 - d. Please provide the following documents: LAB-RPT-54, 55, 58 and 62; LAB-VAL-20 and 24. Please ensure that these documents are signed and dated.

8. **In your NAT Amendment response received December 14, 2016 to FDA question #17 (CR dated September 29, 2015) on the finished device, you have provided an SOP (LAB-ACQ-MOL-102) “*Babesia microti* NAT Finished Device Lot Final Release Testing”. Please clarify the following regarding this SOP:
 - a. Please clarify when this SOP was approved and implemented.
 - b. On Page 3 of 15 (P385) of this document the column 1 of the table has “finished device lot components” and column 4 refers to “previously approved.” While the first seven components (that includes primers, probes and master mix) have a selection option of “Yes/No”; the last three rows (that include negative, high and low positive controls) the selection option is “n/a.” Please clarify why the last three rows are different.

- c. On Page 7 of 15 (P393), under procedure assay controls it is stated, “*Babesia positive (High: (b) (4) and Low: (b) (4) and negative (b) (4) controls will be extracted both test and reference extraction kits, as detailed in the finished device lots. Babesia high positive control eluate (b) (4) will be amplified and detected for inclusion as a component in the finished device lot.*” Throughout the submission *Babesia* high positive control has part (b) (4). Please clarify which high positive control with part (b) (4) is referred to here. Is high positive control (b) (4) a panel member for finished device release?
9. In your NAT Amendment response received December 14, 2016 to FDA question 8a (IR dated November 11, 2016) for samples (b) (6) (that have only (b) (4) PCR repeat testing result instead of (b) (4) results), you have stated that “*The initial Babesia Ct value was noted on the test run as a non-exponential curve. Per testing SOP, LAB-MOLBPCR-10, Section 8.2, a non-exponential curve is considered negative and does not require repeat testing.*” However in the document MSTDONOR_PROSPECTIVE (Attachment-2.2_ MSTDONOR_BCR-NAT-ATT-6) under PCR Repeat testing column the result is reported as “Undet/26.8 and Undet/23.4”.
- a. Please clarify if the final result designating the samples as negative was based on initial testing and amplification plot review or if repeat testing was done. If no repeat testing was done, why are two Ct values reported for Hu18S Ct (b) (4) for sample (b) (6) and (b) (4) for sample (b) (6))?
- b. Please clarify if for each donor sample along with Ct value, the amplification curve is analyzed by the analyst irrespective of negative or positive result.
10. In your NAT Amendment response received December 14, 2016 to FDA question 8b (IR dated Nov 11, 2016) for the sample (b) (6), you have stated that “*The initial curve was noted as a real, exponential curve. This result could not be repeated, resulting in the specimen report being “Inconclusive”.* You stated that the result could not be repeated, but still repeat testing results are reported in the document (MSTDONOR_PROSPECTIVE (Attachment-2.2_ MSTDONOR_BCR-NAT-ATT-6)). Please clarify this discrepancy.

11. In your NAT Amendment response received December 14, 2016 to FDA question #13 (CR dated September 29, 2015) regarding stability studies, you have submitted overview of stability studies. Please clarify the following regarding these studies:
 - a. You have stated that “*LAB-MOL-BPCR-7 has been obsoleted and replaced with more robust and complete documents*”. Please submit the current SOP that is in compliance with your quality systems (dated, signed, version # etc.)
 - b. Please provide the results obtained for stability analysis after November 2016, if available.
 - c. Please clarify which “finished device lots” were used in these studies.
 - d. Please submit the following documents: DOC-RPT-63; DOC-STB-RPT-25; DOC-STB-25. Please ensure that these documents are signed and dated.
12. In your NAT Amendment response received December 14, 2016 to FDA question #18 (CR dated September 29, 2015) on finished device and lot, you have clarified the components of a lot; please provide further clarification regarding which components of the finished device are the critical components.
13. 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) 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.
14. In your original submission, in the Software Description document (Attachment 4-5-3 Imugen (b) (4) software description) on the second page, you stated that a version of (b) (4) will be compiled for commercial release which eliminates the Repository study option. Please provide the following:

- a. Describe the software architecture to convey the magnitude of this change; for example, is the Repository study option selected with a compile flag or is a more invasive method required to remove this functionality?
- b. Provide the test plan and test results illustrating that this recompile does not affect the functionality of the commercial release.
- c. Confirm that this will be the only change to the software between the version used to perform the testing thus far, and the final commercial version. Update and provide your revision history documentation to reflect this and any other changes made since 8/28/2013.

15. In your original submission in the document “Life Cycle Development Plan” (Attachment 4-5-8 Imugen (b) (4) Life Cycle Development), you stated on the first page that “[a]ll of the functions of the software, (i.e., the functions described in Section 5.0) were tested. All of the variations of the user inputs were also tested to detect unexpected conditions.” In your NAT Amendment response received December 14, 2016 in response to FDA Question #33 (and in your AFIA Amendment response received December 13, 2016 in response to FDA Question #38) you provided an updated traceability matrix. From the traceability information provided, it is not clear that comprehensive testing involving unexpected conditions was performed. Much of the testing appears to be testing to verify normal operation and does not explicitly specify test steps related to unexpected conditions or the corresponding identified risks. Note that necessary testing at the unit, integration and system level is often different and more comprehensive than qualification testing.

- a. Please provide testing documentation that supports this claim.
- b. Please update your traceability matrix and testing documentation to explicitly include testing of the mitigations you identified in your risk analyses documents, including testing of the mitigations related to labeling and information for safety. References to

testing of risk control measures can also be included in your risk documentation if this is easier. This is necessary to review how you determined that your mitigations appropriately reduce the risk to acceptable levels.

16. In your original submission in the software requirements document (Attachment 4-5-5 SRS-(b) (4) IMUGEN) in Section 2.5 you provided Performance Requirements. In your NAT Amendment response received December 14, 2016 in response to FDA Question #30 (and in your AFIA Amendment response received December 13, 2016 in response to FDA Question #35) you provided an updated Software Requirements Specification document where all performance requirements were removed. Please clarify why entire sections of requirements have been removed, and update and provide your requirements documentation to ensure all requirements including functional, performance, interface, design, and other requirements necessary to capture what the device is supposed to do are correctly captured in the requirements documentation.

17. In your NAT Amendment response received December 14, 2016 in response to FDA Question #29 (and in your AFIA Amendment received December 13, 2016 in response to FDA Question #34), you provided risk analysis information including reference to the risk analysis, (b) (4) Risk Analysis IT-CSV-PDF-41.”
 - a. In your response, you stated that the risk management document “[r]eferences mitigation plan, documented in SRS.” The file includes mitigations, but no numerical traceability from the risk ID to the SRS. Please provide this traceability. The Traceability Matrix “IT-CSV-IMD14-16-TM” embedded in your response document references Risk IDs that appear to be the Risk IDs in this document, but this is not explicitly stated. Please clarify this and provide updated documentation.
 - b. This file, (b) (4) Risk Analysis IT-CSV-PDF-41, does a better job of identifying individual risks than the document “*B. microti* AFIA Device Risk Analysis” (Attachment- 33.5_LAB-DSGN-5 .xlsx) and nicely allows the reader to use filtering to explore the effects of different causes and the scope of different mitigations.

However, harm is not explicitly stated and too many “Potential Effects” are listed for each Risk ID. Some “Hazards” include cause information. Similar to the Device Risk Analysis, please update and provide this analysis to align better with ISO 14971 to leverage its benefits.

- c. This file, (b) (4) Risk Analysis IT-CSV-PDF-41, only references mitigations by “design.” Where have you documented the mitigations using other means; for example, in labeling that includes hazards or instructions? Please provide this information, including traceability from the individual mitigations to the corresponding user documentation where appropriate. This is necessary to review your proposed mitigations for risks that you have controlled through means other than by design.

18. In your NAT Amendment response received December 14, 2016 in response to FDA Question #32 (and in your AFIA Amendment received December 13, 2016 in response to FDA Question 37), you stated that for the (b) (4) software, you included an updated Software Design Specification and Traceability Matrix that “contain measurable and testable values.” Thank you for providing these updates and the detailed information. Several Risk ID/SRS entries in your traceability table do not trace to software design specifications, and some trace to testing that does not appear to relate to the corresponding risk/requirement. This makes it difficult to assess the adequacy of your proposed mitigations. Note that necessary testing at the unit, integration and system level is often different and more comprehensive than qualification testing.

- a. For example, Risk ID 24/SRS 24 addresses a risk that PCR results might be modified. No design information was provided on how this would be performed, and the referenced V&V test cases don't appear to test any attempts to modify PCR results to ensure the risk is properly mitigated. The tests are "Script #15 Create NEW PCR plate template and import results from multiple submitters" and "Script #9: Create slide(s), and add specimen to slide(s) from single submitter." Step #9 is "Click SAVE SLIDE, Close Slide." How do these tests verify that software prevents any

- modification of the PCR results? Please provide the correct documentation.
- b. Risk ID 34/SRS34 involves risk of loss of sample origin, but has no associated SDS. The requirement itself is vague and the corresponding testing refers to step #16 of a test script. However, the test script ends after 13 steps. Please clarify the risk and requirement, and provide corrected documentation.
 - c. Risk ID 39/SRS 39 refers to a test script that was not provided. This portion of the testing documentation is blank. Please provide the correct documentation.
 - d. Risk ID 49/SRS 49 does not include testable information and is not traceable to an SDS. Some of the relevant information appears in the test case; however, specifics of the device design should be captured in the requirements and specification documentation, and not documented solely in testing documentation. Please update your SRS and/or SDS with the appropriate design information accordingly, and provide the correct documentation.

Risk ID 51/SRS 51 and Risk ID 52/SRS 52 specify software by version number “or later.” Your requirements should apply to a specific version or versions with testing corresponding to those versions. Please remove reference to “or later” for any software used in the system, including in any labeling, and ensure explicit versions are referenced.

This is not a complete list of issues, but a representative sample of concerns. Please review and update the remainder of the document for traceability and accuracy issues. For requirements that have no corresponding design specification, clarify why an SDS is not necessary.

19. In your NAT Amendment response document received December 14, 2016 in response to FDA Question #32 (and in your AFIA Amendment response received December 13, 2016 in response to FDA Question #37), you provided a Software Design Specification

document. This version 1.1 of the document does not appear to be substantially changed over version 1.0 provided in your original submission. Many screen shots are presented but it is not always apparent what has changed from one screen to the next, what is expected to appear on the screen, what information the user entered, and what are the system responses when the user does something unexpected. Each of these specifications should include explicit text about what should appear on the screen and what the device and/or user is expected to do. It is not sufficient to collect screen shots of a completed system and state that these encompass a software design specification without additional information. It is not reasonable to expect a designer/tester/reader to compare successive screen shots to determine for themselves what has changed between the two screen shots. This increases the opportunity for misunderstanding, inadequate design and testing.

Please augment the information in your Software Design Specification with explicit testable information. Some of this information appears to exist in various testing documents and SOPs, but you have not provided a comprehensive collection of software design specifications which describes how the requirements in the Software Requirements Specifications (SRS) are implemented in a clear and unambiguous manner. Please provide this updated information.

20. In your NAT Amendment response received December 14, 2016 in response to FDA Question #35 (and in your AFIA Amendment received December 13, 2016 in response to FDA Question #39) with respect to cybersecurity, you provided the document, "Information Technology Security Policy, IT-SEC-POL-1." You stated that this describes "control of confidentiality information and accountabilities." This policy appears to apply to your corporate networks and business policies rather than for the device itself. Please note that you should identify risks associated with not only confidentiality, but integrity and availability, and take steps to reduce risk that device functionality is intentionally or unintentionally compromised by inadequate cybersecurity considerations. The (b) (4) system appears to include at least three types of servers and multiple workstations/clients, at least one of which has established connectivity to the outside world. Your risk documentation appears to contain some mitigations for

potential cybersecurity risks, although you have not identified many of the possible causes to demonstrate that these mitigations would be adequate.

- a. Please refer to the FDA guidance and provide updated cybersecurity information for your device to address the elements listed in the guidance: “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices” located at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356190.pdf>. This should include, in part, the following: hazard analysis, mitigations, and design considerations pertaining to intentional and unintentional cybersecurity risks associated with your device, and a traceability matrix that links your actual cybersecurity controls to the cybersecurity risks that were considered.
- b. Please describe your process for identifying and evaluating new operating system patches and other updates to off-the-shelf software and integrating patches and updates into your device.

21. In your original submission in the Unresolved Anomalies document (082_Attachment 4-5-11 Imugen (b) (4) Unresolved Anomalies_04172015.pdf) you provided one unresolved anomaly: “*PCR Results import - The PCR Results import template to be printed does not currently highlight Ct values which exceed a specified threshold. The laboratory technician performing the experiment cross checks the output of the (b) (4) template with the (b) (4) printout and is trained to identify Ct values over specified threshold which would require the sample to be retested. Accordingly, as there is a manual check of the Ct values performed, this anomaly does not impact the safety or efficacy of the product.*” This anomaly could be associated with a false negative if a sample is not retested when it should be. This anomaly and mitigation information were not included in the hazard analysis, and no requirements were added to address this. Please correct this anomaly, and update and provide the associated design documentation, or provide justification for why the risk is acceptable.

22. In your original submission in the NAT Design Risk Assessment document (Attachment 4-9-2-5 LAB-DSGN-11) in the risk table on page 31, you included an unnumbered risk, “*Sample IDs and results are delinked, and false positive or false negative results are reported.*” You stated that the mitigation includes “[a]greements with customers describe the use of barcode labels for samples.” Please describe the technical requirements that must be identified and met for these agreements with customers. Identify how these requirements are tested to ensure sample IDs and results are not delinked and how this adequately reduces the risk to ‘Low.’”

23. In your NAT Amendment response received December 14, 2016 in response to FDA Question #32 you provided a Software Design Specification. On page 21 in section 3.3 you described use of the (b) (4) Software for creating a sample setup template and for exporting PCR results. This appears to correspond to requirements R27 and R28 on page 7 of the Software Requirements Specification in Attachment 29.2 and to the trace on page 8 of the updated Traceability Matrix in Appendix 29.3. Reference to creating and reading PCR slides appears in your original submission on page 604 in the QA scripts (e.g., “069_Attachment 4-5-8-1 (b) (4) QA Script for January 11 2013.pdf”) where templates are imported, selected, and then results are imported.

- a. Please describe the content and format of the imported data files and any error checking performed to ensure that the import was successful and that the appropriate template and results are matched. This information should be explicitly captured in your requirements and/or specifications documents (or provided separately with explicit traceable references), with traceability to testing captured in your traceability documentation. Please update and provide the relevant documentation accordingly. It appears that document LAB-SFW-1 might be relevant to this discussion.
- b. The V&V Test Cases only illustrated import of a valid file. Please provide testing to illustrate that the software is able to perform correctly when challenged with invalid or out of range data. This is necessary to ensure that the system is robust enough to

STN 125588 Babesia microti Nuclei Acid Test (NAT)- Information Request

protect against potentially corrupted incoming information from external uncontrolled sources.