



June 13, 2017

Our STN: BL 125588/0

BLA COMPLETE RESPONSE

Oxford Immunotec, Inc.
Attention: Wolfgang Pieken, PhD
315 Norwood Park South
Norwood, MA 02062

Dear Dr. Pieken:

This letter is in regard to your Biologics License Application (BLA) for *Babesia microti* Nuclei Acid Test (NAT) manufactured at your Norwood, Massachusetts location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated May 18, 2017, and June 5, 2017, as noted below. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

INSPECTIONAL ISSUES:

1. CBER conducted a Pre-License Inspection (PLI) of the Imugen, Inc. facility from March 6 through 10, 2017, and noted significant deviations at the end of the inspection. We received the response to the FDA Form 483 on April 17, 2017, and find that it does not sufficiently address the concerns noted during the inspection. Your corrective actions do not appear to be fully implemented or comprehensive to address the underlying issues. Examples include, but not limited to:
 - Deviation investigations do not include an evaluation to determine if false positives or false negatives, which would adversely impact patient safety, could have resulted from the deviation.
 - Your manufacturing procedures are not sufficiently detailed to provide consistent lot-to-lot reproducibility of your finished device lots for the NAT assay.
 - Changes to the device design are not verified or validated in accordance with your design change procedures.

- Segregation between operations for blood donor screening and clinical testing is inadequate to prevent mix-up of equipment and test samples.
- The cleaning procedures and processes are insufficient to maintain a sanitary environment.
- Insufficient personnel are available to perform and oversee all aspects related to manufacturing of finished device lots and testing of donated blood samples.
- Investigations of exceptions are inadequate and do not determine root cause of events and initiate further corrective actions to prevent re-occurrence of issues.
- Operator training and instructions are not sufficient to manage the entry of the results of the blood donor samples to prevent vulnerabilities related to data integrity and traceability.
- The equipment maintenance and calibration program does not include the management of all pieces of equipment used for manufacturing and testing of blood donor samples.
- The amount of critical pieces of equipment is insufficient to continuously perform blood donor screening activities at the suggested throughput level.

The deficiencies described in the FDA Form 483 issued at the close of the inspection referenced above are an indication that your Quality system is not effective.

Approval of a Biologics License Application or issuance of a biologics license constitutes a determination that the establishment and the product meets applicable requirements to ensure the continued safety, purity, and potency of such products; whereas, for your situation, this also applies to the continued accuracy of the test results. Applicable requirements for the maintenance of establishments for the manufacture of a product, or test result provider, include, but are not limited to, the good manufacturing practice requirements.

- a. Your corrective actions need to be more comprehensive with respect to addressing the underlying quality oversight issues, and,
- b. A second PLI will be necessary to verify the corrective actions once they have been fully implemented, validated, and established.

Your response will need to demonstrate that the corrective actions to the inspectional observations as listed on FDA Form 483 have been fully

implemented and you will need to provide the supporting evidence of implementation including any related studies or verification/validation reports, as applicable. The unsolicited amendments received on May 18, 2017 and June 5, 2017 did not include implementation of all corrective actions to each inspectional observation.

REVIEW ISSUES:

Pre-Clinical

2. In your response document “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016, to FDA CR Question 8, you have submitted the data from updated precision studies. The results of the PCR precision study were analyzed in two ways, qualitatively (agreement) and quantitatively (Ct). For the quantitative analysis based on the exact Ct value, there were (b) (4) undetected results eliminated from the analysis for panels (b) (4) LOD, (b) (4) LOD and (b) (4) LOD respectively. This would underestimate the variability. However, if they were included, there were no appropriate values to impute the Ct. We recommend that you remove the variability analysis conducted on the Ct values from these table (results) since the estimated variability for Ct values is not accurate. Reporting percent agreement would be sufficient for this product.
3. In your response document “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016, to FDA CR Question 9 on cross-reactivity studies, the data for Chagas cross-reactivity are presented with potentially interfering substances in DOC-RPT-31. It is stated that all samples were of plasma samples. Please clarify if these plasma samples are positive for Chagas antibody or parasite nucleic acid.
4. In your response document “Imugen Response to STN 125588 *Babesia microti* Nucleic Acid Test (NAT) - Information Request” dated March 23, 2017, to FDA IR Question 11 on stability studies, you have provided the updated protocols and data. Please provide the updated stability report with additional time points.

Chemistry Manufacturing and Controls

5. BLA approval requires evaluation and lot release testing of at least three conformance lots that were manufactured using validated manufacturing processes described in the license application, in a lot size that is similar to that proposed for subsequent production. The time required for lot release testing and FDA review of the lot release test results must be considered in the production process. Please provide the batch size information of currently manufactured lots that can sustain uninterrupted supply of test reagents cleared through FDA Lot Release for ongoing testing requirements.

Software and Instrumentation

The following questions were sent to you on April 14, 2017, in response to information received on March 23, 2017, (to the information request sent on February 17, 2017, to “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016). A status update on these questions was provided on May 23, 2017, which generally indicated that work was in progress and that the requested information would be provided.

6. *Performance requirements for (b) (4) hardware and software (sent as FDA Question 1):*

In the NAT amendment received March 23, 2017, in response to FDA IR Question 16, you stated that performance requirements “relevant to IT infrastructure for general lab operation ... is beyond the scope of the (b) (4) software” and were removed. This is not reasonable because the (b) (4) software requires proper operation of the underlying infrastructure to meet its intended use. Your documentation has inconsistently described the components of the system, and it is not clear what hardware supports the (b) (4) software and database functionality. You should include requirements related to the infrastructure that is necessary to support the intended use of the device for both the NAT and AFIA assays. This appears to include the components in the Hardware Network Diagram in section 2.3.2 in your Architectural Design document provided in Attachment 29.4 of your response received December 14, 2016, and any other relevant components not identified in this diagram.

- a. Please clarify all of the required components for your system, including PCs, printers, network connections, etc. Explicitly identify the boundaries of the system with respect to your corporate network.
- b. Please include all requirements related to required capacity for throughput, database capacity and accessibility, connectivity, uptime, etc., in order for the underlying infrastructure system to meet the required needs of the system. These requirements should include testable metrics to ensure that they can be met.
- c. Include all test plans, test results and verification and validation testing for these performance requirements.
- d. Update your traceability matrix to include this information.
- e. Update your risk documentation to include risks associated with the performance needs of the system, and include the mitigations you implemented to reduce those risks to acceptable levels.

7. *Verification and validation testing (sent as FDA Question 2):*

In the NAT amendment received December 14, 2016, in response to FDA CR Question 33, you provided an updated traceability matrix in Attachment 29.3

and referred to IQ and OPQ testing. The testing is incomplete. Note that process validation testing (Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)) testing are not the same as verification and validation testing outlined in part (a). Please refer to FDA's guidance document, "General Principles of Software Validation," with a particular focus on section 5.2.5, located at <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf>. As outlined in the premarket software guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," please ensure that you provide unit, integration and system level test protocols, including pass/fail criteria, test report summary, and tests results. It is difficult to assess the adequacy of a test script by viewing only raw test steps without a description of the test plan and protocol and a summary of results.

8. *User interface error checking (sent as FDA Question 3):*

In the NAT Amendment received March 23, 2017, in response to FDA IR Question 15, you stated that two additional risks were added, but it is not clear if this represents all unexpected conditions. Two conditions were included: R26b "Software must protect against import of corrupt or incomplete source file" and R26c "Software must not allow input of invalid result values." Testing for R26b does not describe what was tested and why; it just illustrates that an uncharacterized file was rejected on import. Testing for R26c is limited to error checking on the IFA Slide screen. R29 describes software error detection functionality but the testing that is included in the traceability matrix (Attachment_15.2-IT-CSV-IMD14-16-TM&DocDetails.pdf refers to IT-CSV-IMD14-07-OPQb, 6.8.11, #11) does not appear to test or detect error conditions.

- a. Please provide a summary description of all user interface requirements and the types of error checking that is performed to identify problems with data interactions with the user via keyboard, barcode scanning, etc., and list the corresponding testing used to ensure proper functionality of the system. Please do not refer to entire design documents, but develop a direct response to this question. This is necessary to assess how the system responds to unexpected conditions and assess the scope of the error checking of the system.
- b. Please provide the corresponding design control documentation for the user interface requirements and error checking in (a).

9. *PCR device interface verification (sent as FDA Question 4):*

In the NAT Amendment received March 23, 2017, in response to FDA IR Question 23, you reported two new risks related to error checking and imported data files and provided relevant design control documents. However, you did not respond to the question. We could not identify explicit information about the file format or interface with the (b) (4) instrument (R27 and R28). We could not confirm that the interface was appropriately tested because the

only documentation for R26b provided was a script 6.8.3 (IT-CSV-IMD14-07-OPQc) with undefined inputs. Please respond to the original questions (a) regarding content and format of the imported data files, and (b) comprehensive testing of the system to ensure that the interface performs as intended.

10. *Documentation package for Build 1.0.5.5 (sent as FDA Question 5):*

In the NAT Amendment received March 23, 2017, in response to FDA IR Question 14, you stated that the (b) (4) software will no longer be compiled for commercial release, but that the final version will be Build 1.0.5.5. Please review the documentation provided, and ensure that all design documentation including appropriate verification and validation testing corresponding to version Build 1.0.5.5 has been provided.

11. *Risk processes (sent as FDA Question 9):*

In the NAT amendment received March 23, 2017, in response to FDA IR Question 17, you included updated risk documentation. There is some better alignment with ISO 14971 “Medical device – application of risk management to medical devices,” but the table in the (b) (4) Hazard Analysis (Attachment_15.1-IT-CSV-PDF-41.xlsx) is not an FMEA and does not align with terminology used in ISO 14971. Consider the following:

- a. What does your “Probability” correspond to in ISO 14971? It is not clear what your “Probability” refers to so it is difficult to assess the risk table. The “Scoring System” tab refers to Likelihood, not Probability. For example, Risk 2 “password hacked” has a Probability of 4 which is high, so it is unclear if this refers to P1 or P2 or the combination. In the “Front page” tab of the NAT Risk Analysis (Attachment_22.1-LAB-DSGN-11.xlsm), the Likelihood definitions specifically refer to failures. This suggests that your probability is still focused only on P1 and does not include probability of a hazardous situation leading to harm. Please revisit your risk management processes and provide a clear description of your processes and how they align with ISO 14971. State explicit the scope of “probability” in your documentation and ensure your risk documentation includes all aspects of probability. As a start, we suggest removing the notion of “failure” from your definitions.
- b. What is your process to determine the new level of Probability as the result of the identified mitigation(s)? Please provide your risk documentation that describes how this is determined.
- c. Please refer to comments made regarding the “Babesia microti AFIA device risk analysis” (Attachment_13.1-LAB-DSGN-5.xlsm) and its alignment with ISO 14971, and ensure that you make the same changes to both risk documents for consistency regarding clear traceability with hazards, hazardous situations, causes, traceability to mitigations in manuals and SOPs, etc. We recommend that you should harmonize the format you are using to capture risk information so that all use the same

terminology and methods, or you should provide a clear description and process for each that allows independent review.

12. *Cybersecurity considerations (sent as FDA Question 10):*

In the NAT Amendment received March 23, 2017, in response to FDA IR Question 20, you provided several documents including an updated (b) (4) Risk Analysis” (Attachment_15.1-IT-CSV-PDF-41.xlsx). Please note that we assess the adequacy of your cybersecurity features based on the threats and vulnerabilities you identify in your risk assessment. Without your analysis and identification, it is difficult for us to determine if the mitigations you implement are adequate. We do not have a clear picture of the client server and database components and connectivity to other systems. We see mention of some mitigations and some evidence of threats in several documents, but you have not provided a comprehensive view of the security risks to your system. The following suggest that the analysis activities we requested and described in the cybersecurity premarket guidance have not occurred.

- a. Your system is networked but you have no requirements or specifications related to connectivity or use of a firewall. You included a firewall in the Hardware Network Diagram in your Architectural Design document in Attachment 29.4 of your response received December 14, 2016, but it is not referenced in your risk documentation. You have not identified which risks might be addressed by use of a firewall, and the residual risks. You have not identified vulnerabilities related to this architecture.
- b. You reference antivirus updates in your “Information Technology Security Policy” (Attachment_20.2-IT-SEC-POL-01&DocDetails.pdf) but you have not identified the vulnerabilities for which this mitigation would be effective. It also mentions physical security, but it is not clear if or how this applies to access to the software or hardware.
- c. Some features that represent suggest security vulnerabilities were not included; for example you mention USBs in the “Information Technology Security Policy” but you have not discussed the risks of allowing an open USB port.
- d. You have not identified functionality on the computer that should be restricted to limit exposure (e.g., disabling access to various unnecessary programs, unauthorized access through unattended workstation availability, etc.). Can users access the internet on the computer used to access the (b) (4) software? Can a user boot from a USB and alter the system? Can a user replace the (b) (4) software with an altered copy? Many scenarios related to misuse have not been explored.

As requested previously, please perform the analysis described in the guidance, “Content for Premarket Submissions for Management of Cybersecurity in Medical Devices” and updated your design documentation accordingly.

13. In the (b) (4) status update received May 23, 2017, in response to FDA Question 1(a), you provided (b) (4) infrastructure details (b) (4) Infrastructure Details.docx).
- a. The (b) (4) database server appears to be running on an unsupported operating system, Windows (b) (4) . As of July 14, 2015, Microsoft no longer provides automatic fixes, updates or security updates for this product to protect against harmful viruses, spyware and other malicious software. Your Information Technology Security Policy (Attachment_20.2-IT-SEC-POL-01&DocDetails.pdf) does not provide a process for supporting an operating system when patches are no longer available. Please provide your plan for migrating to a supported operating system. If you do not intend to upgrade, please discuss the additional security risks, how you will identify vulnerabilities and manage the risks of this increased exposure.
 - b. Please identify the cybersecurity product(s), including version number(s), running on each of the servers and computers identified in the (b) (4) specific infrastructure. Your Information Technology Security Policy (Attachment_20.2-IT-SEC-POL-01&DocDetails.pdf) references two generic product lines but does not indicate how the individual systems are protected.

Facility

14. In your response document “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016, to FDA CR Question 44 on categorical exclusion, your justification from a categorical exclusion for preparation of an environmental assessment for the NAT assay is not satisfactory. Please revise your justification to indicate how your finished device lots for the NAT assay meets the exclusion criteria.

Equipment Qualification

15. The equipment qualification reports you provided for the NAT Extraction Systems in your Complete Response Letter dated December 14, 2016, response to question #47 do not appear to be performed in accordance with a protocol with defined acceptance criteria. In addition, the reports do not appear to include a sign-off review by Quality. Based on your performance qualification protocol for the new NAT extraction systems, please perform an evaluation of the results of the performance qualifications for the legacy NAT extraction systems and determine if the systems were adequately qualified and meet the criteria outlined in the protocol. Please provide a copy of the evaluation(s).
16. In the September 29, 2015, Complete Response Letter, question #47C, you were asked to provide the performance qualification report summaries for all data collected from all machines used on all shifts, however, you only provided the performance qualification data for (b) (4) (units (b) (4) of the (b) (4) NAT extraction units. Please provide the performance qualification reports for the remaining

legacy NAT Extraction systems (units (b) (4) in use for blood donor screening operations.

17. Please provide a summary and a copy of the procedure related to the performance verification activities that are performed on the current NAT extraction systems to ensure the systems are functioning correctly and not resulting in a false positive or false negative test result. Please ensure your response describes the frequency of performing the verification activities.
18. We acknowledge that you intend to qualify additional pieces of NAT equipment to perform manufacturing and blood donor screening activities for licensure of your BLA. For each new piece of equipment, please provide the applicable equipment performance qualification (PQ) protocol and the executed report. The protocols shall include defined tests to be performed, representative number of samples to be tested, and the acceptance criteria.
19. The cleaning of the NAT equipment used for manufacture of assay components and to perform blood donor screening shall be documented in procedures to ensure consistent cleaning between operators. Please provide a copy of the cleaning procedures.
20. Please perform an evaluation of the cleaning agents and cleaning process (indicated to include (b) (4) you utilize to determine if the cleaning is effective at removing contaminating material from your NAT equipment including the extractors, PCR set-up system, and thermocyclers. Please provide a copy of the applicable equipment cleaning reports demonstrating the removal of contaminants.

Labeling

21. Please submit the updated summary of application.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For MDUFA products, please submit the Submission Issue Q-Sub with a valid eCopy. Your submission should reference this BLA, identify the specific deficiencies you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting, or

teleconference). For additional information regarding Q-Subs, please refer to the *Final Guidance for Industry and FDA Staff on Medical Devices: Request for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff* at

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>, or you may request this document from the Office of Communication, Outreach, and Development, at (240) 402-8020.

We acknowledge receipt of your amendments dated May 18, 2017, and June 5, 2017. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendments dated May 18, 2017, and June 5, 2017, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Iliana Valencia, at (240) 447-4377.

Sincerely,

Hira L. Nakhasi, PhD
Director
Division of Emerging and
Transfusion Transmitted Diseases
Office of Blood Research and Review
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