



Our STN: BL 125588/0

**BLA COMPLETE RESPONSE**

IMUGEN, Inc.  
Attention: Mr. Victor Berardi  
315 Norwood Park South  
Norwood, MA 02062

Dear Mr. Berardi:

This letter is in regard to your biologics license application (BLA) for *Babesia microti* Nucleic Acid Test manufactured at your Norwood, MA, 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. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

**Clinical:**

1. You have not provided the data for the clinical sensitivity of the *Babesia* NAT. In the clinical hold letter to IND 14532 dated December 10, 2010, we requested that you demonstrate the clinical sensitivity of this test in human samples that are blood-film positive for *B. microti*. Please provide data to demonstrate the clinical sensitivity of your assay in confirmed clinical *Babesia* positive samples.
2. In the clinical section, analysis of the data submitted in BAFSBLA.xlsx and MSTDONOR.xlsx, identified significant protocol deviations. The protocol for human 18S internal control testing (Page 259.17, document 021\_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states, "*Ct values for the human 18S internal control should be (b) (4) at a threshold setting of (b) (4) for all negative samples and controls. Any Babesia negative sample with a Hu18S Ct value of (b) (4) will be repeated from amplification. If the Ct value on the repeat sample is (b) (4) repeat from extraction. If the Ct value does not meet specifications after repeat testing, consult a supervisor.*" There are a total of 327 samples where the internal Hu18S PCR Ct ranged from (b) (4) . Repeat testing was not performed on these samples as per the protocol.
  - a. Please clarify why the SOP of repeat testing was not followed when Ct values for Hu18S were (b) (4) for several of these specimens.
  - b. Please exclude these samples from data analysis and instead report them as protocol deviations and provide a separate excel worksheet with all excluded data.

Alternatively, please perform new testing on samples where the SOP was not followed and submit the results for review to FDA.

- c. Please clarify what steps are taken by the supervisor to resolve out of specification results and how such test results are resolved and reported to the end users (i.e., blood establishments).
3. Similar to what is described above for Hu18S Ct Value, the protocol is not followed for *Babesia* specific amplification. For the *Babesia* NAT, the protocol (Page 259.17, document 021\_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states that “*Samples with Babesia-specific Ct values (b) (4) will be repeated. The original sample will be (b) (4) to the PCR plate.*” Further, the Figure 8.4.1.2: Testing Flow Chart, 002\_8-4-1 CSR study 1, Page 1595, indicated *Babesia* NAT will be (b) (4) if Ct (b) (4).
  - a. Please clarify at what *Babesia*-specific 18S Ct value the repeat testing is done (i.e., (b) (4)).
  - b. Please reanalyze the data using a consistent measure to determine positivity of the sample. Please clarify what controls are in place to confirm that protocols are followed for *Babesia* NAT and protocol deviations are reported accurately.
4. In the data provided in document MSTDONOR.xls, there are 707 samples where line item data for the *Babesia* 18S Ct and the Hu18S Ct value columns are blank. However, the donor test results are interpreted as “negative” (i.e., no *Babesia* DNA was detected for these 707 samples). This is a significant deviation from the IND protocol for these prospective blood donations. Please clarify why these specimens were not classified as invalid and why the testing was not repeated for these specimens rather than classifying them as *Babesia* negative. Please report these samples as invalid results and exclude them from analysis.
5. In the document 002\_8-4-1CSR study 1 (Page 15) it is stated that “*The NAT method used in this study differs in 2 respects from the NAT method used in the NAT assay that will be licensed: 1. The extraction method used in this study is less sensitive than the current NAT method. 2. The NAT testing in use at the time of this study did not incorporate Human 18S RNA as an endogenous internal control.*”
  - a. Please clarify why the investigational NAT assay was not used to conduct this study.
  - b. Please provide an excel document for the CS1 data used to generate attachments 8.4.1.1, 8.4.1.2 and 8.4.1.3.
6. Please provide a summary table showing the lots of *Babesia* NAT manufactured by IMUGEN that were used in the clinical studies described in the BLA. For each lot (including positive and negative controls), please provide the lot number, the size of the

lot (i.e., number of tests that a lot can perform), production and expiration dates, and also indicate the corresponding study(ies) that each lot was used in.

7. For each study's data summary, please display the data as a 2X2 table with results for the test under review in rows and the results of the comparator test in columns. In cases where there are three outcomes (i.e., positive, negative, inconclusive) the data may be displayed in 2X3 or 3X3 tables.

### Pre-clinical Studies:

8. The precision and reproducibility studies submitted fail to capture intra- and inter-assay variability, intra- and inter-lot variability, inter-operator variability, and inter-instrument variability. Please follow Clinical Laboratory Standard Institute (CLSI) documents EP05-A3 for designing and performing precision and reproducibility studies. Please provide a plan for a proper precision and reproducibility studies with a statistical analysis plan or statistically justify the study presented.
9. The analytical specificity/cross reactivity study has been conducted using seven bacteria species and one yeast species. Please expand the cross-reactivity studies to include the following pathogens (*Plasmodium* sp., *Leishmania* sp., *Trypanosoma cruzi*, and *Borrelia burgdorferi*) as agreed upon in the IND study protocols (IND # 14532).
10. In response to non-clinical hold issue #12 in our IND Hold letter (IND 14532) dated December 10, 2010, you have submitted interference studies using (b) (4) samples only. In document Lab-DSGN-9 it is stated that "Assay was evaluated for performance with the following endogenous substances: Elevated total proteins, Elevated bilirubin, Lipemic, Elevated triglycerides, Elevated Cholesterol, Alkaline Phosphatase, Anti-nuclear Antibodies (ANA), and Rheumatoid Antibody (RA)." The results from these studies could not be located in the submission. Please identify where this information is located in the submission or submit the results of these studies.
11. You have submitted cross reactivity studies with bacteria (NAT CMC Overview Part 2, Pages 108.65 and 108.66) and interference studies using (b) (4) samples (043\_Attachment 4-3-2-7 DOC RPT-13), respectively. In both studies, your assay failed to detect *Babesia* DNA in several samples spiked with *Babesia* parasites although the presence of *Babesia* was demonstrated using a digital PCR. You have attributed this to an improperly stored *Babesia* positive stock sample used for spiking (stock sample stored for (b) (4) or a change in the concentration of the *Babesia* positive stock sample. The results from both of these studies are not acceptable. Please perform the interference and cross reactivity studies with a well characterized stock sample stored at appropriate storage conditions and submit the results for review to FDA. In addition, please ensure that the calibration curve is run in parallel with the samples using the same PCR assay to determine the amount of target/ml during the re-testing if needed.
12. In SOP LAB-MFG-10, it is indicated that (b) (4) *Babesia* parasites/ml were used as low positive control in the NAT assay. The 95% detection limit of NAT is (b) (4) *Babesia* parasites/ml. The low positive is almost (b) (4) times the limit of detection (LOD). The use of low positive control that is (b) (4) LOD fails the purpose of the low positive control (i.e.,

to determine if the assay is working as per specifications). FDA recommends that you add an appropriate low positive control to your panel that is close to LOD (b) (4) and submit the results to FDA for review.

13. The document (LAB-MOL-BPCR-7) reports testing results to determine the stability of primers, probes and controls.
  - a. Please date the SOPs used to generate this report.
  - b. Please provide the actual test results (not summary) for each component (multiple lots) at the storage conditions referred to in the SOPs.
14. Please provide a summary table showing the lots of *Babesia* NAT manufactured by IMUGEN that were used in the pre-clinical studies described in the BLA. For each lot (including positive and negative controls), please provide the lot number, the size of the lot (i.e., number of tests that a lot can perform), production and expiration dates, and also indicate the corresponding study(ies) that each lot was used in.

**Process/Product:**

15. In your submission, you indicated that the *B. microti* NAT device is microbiologically controlled; however, no details in regards to the control of microorganisms 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 that may not reveal non-bacterial contamination. Please propose a modified microbiological screening procedure or explain why it is not needed.
16. You have submitted document 134\_Attachment 4-9-2-29\_LAB-QA-86, which describes the guidelines for process validation. We could not find implementation of these guidelines in reports of activities specific to the manufacturing or quality systems related to the NAT. It is not clear from your submission if an adequate process validation was performed as no process validation procedures/protocols and the corresponding reports for the manufacturing process were provided. Please provide process validation report summaries for your manufacturing process. These reports should indicate how the validation was performed (including statement of the objective, scope, methods of data collection and analysis), defined acceptance criteria, results, and deviations and resolution of deviations.

**Chemistry Manufacturing and Controls (CMC):**

17. A “kit” is defined as a set of reagents qualified to be used together to perform an assay. As described in the 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 all the components identified. For example each new batch of primers is tested 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.

18. BLA approval generally 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 and that have been used in the clinical testing. Please provide the following information with regard to the “lot.”
  - a. Define what constitutes a “lot” for the NAT assay, including all essential and non-essential components.
  - b. Explain how IMUGEN performs final lot release testing.
  - c. Describe how IMUGEN assigns the expiration date of a new manufactured lot.
  - d. Submit a lot release protocol including the release specifications and the name of the method(s) used to perform the analysis.
19. The process of manufacturing *B. microti* infected (b) (4) red blood cells, the essential 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.

- c. A manufacturing plan that includes preparation of a master cell bank and working cell bank for *B. microti* and a method of propagating the *B. microti* in (b) (4) and testing to ensure that each batch of infected red cells has sufficient antigenic similarity to a reference batch. Please refer to the CBER Guidance for Industry “Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product - <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092272.pdf>.” This document refers to manufacturing of vaccines, not in vitro diagnostics. However, the principles that govern use of cultured microbes in manufacturing (Pages 8, 10, and 11) are applicable to *Babesia* infected red blood cells.
20. The production of infected (b) (4) red blood cells is performed at the (b) (4) (source) under contract. As the license holder for the manufacturing of 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 the contract arrangements and the IACUC protocol for this alternate contractor.
  21. 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 batch 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).
    - c. IMUGEN should modify LAB-MFG-8 to include the added initial steps of (b) (4) from the working cell bank through the collection of blood from infected animals.
    - d. If passage from (b) (4) to (b) (4) is required to establish parasite infection, please clarify how many passages from animal to animal are allowed under the protocol.

22. In the acceptance criteria for *B. microti* iRBC (LAB-MFG-1, Page 321.9), you indicate that the red blood cell must have (b) (4). However, for processed (b) (4) red blood cells the specifications call for a (b) (4). Please explain this difference in the specifications.
23. In the document NAT CMC overview part 1 (Page 108.13); one of the specifications to accept infected blood from (b) (4) is: (b) (4) in the blood samples received and tested by IMUGEN with a reference to LAB-MFG-1. LAB-MFG-1 does not provide sufficient instruction to determine evidence of (b) (4) nor instruct the technician to report their presence. The LAB-MFG-1 document should clarify what (b) (4) could be. It should also describe how to report the observation of such (b) (4) with the blood preparation.
24. 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.
25. Please provide the physicochemical acceptance criteria for the purchased oligonucleotides and documentation that the acceptance criteria were met for purity, sequence, and concentration.
26. Please provide a copy of the Device Master Record, LAB-QA-44, which contains a list of all Raw Materials, both Critical and Non-Critical (referred to in LAB-MFG-9).

### Quality Systems:

27. Please address the following deficiencies regarding the Design Control information:
- Your Design Plan did not include required elements such as design verification, design validation, design transfer, design changes or reference to a design history file. Additionally, your plan does not describe procedures for review, update and approval as the device evolves.
  - Design inputs and outputs were not clearly stated and defined in your application. Both of these terms are mentioned in the CMC Overview on Page 108.103; however the text is very general and does not describe any specific inputs to the NAT device. Documents LAB-QA-70 and LAB-QA-71 are titled Design Inputs and Design Outputs respectively. Please provide these documents. There is no indication that these documents provide specific inputs and outputs of the NAT device. Additionally, design outputs are not clearly linked to design inputs nor are acceptance criteria for outputs clearly indicated. Please note that design inputs are the physical and performance requirements of a device. Design inputs are the basis of the design verification and validation; therefore, design inputs need to be defined and recorded as

formal requirements that allow for confirmation to the design outputs. In addition, design output procedures should contain or make reference to acceptance criteria and shall ensure that those outputs that are essential for the proper functioning of the device are identified.

- c. Design review is mentioned in the CMC Overview Document part 3 on Pages 108.99 and 108.103, suggesting that a complete description is found in Attachment 4-9-2-6 LAB-DSGN-12. The list of documents that is the sole content of LAB-DSGN-12 does not offer sufficient explanation of how formal design reviews are planned or conducted, and it appears that design review was not performed for all phases of your design process. Please note design review should include the review of design verification data to determine whether design outputs met functional and operational requirements. The CMC Overview also suggests that Design planning is described in the document LAB-QA-67 and recorded on LAB-QA-28, the Design and Development Form. Please provide these documents which were not included in the submission. You have provided some description of the design review in the CMC Overview part 3, Page 108.104 including important types of items to be discussed at a design review meeting. Please provide the document LAB-QA-72 (Design Reviews) along with other related documents LAB-QA-62 (Risk Management Program), LAB-QA-76 (Design Verification), LAB-QA-75 (Design Validation), LAB-QA-74 (Design Transfer From), and LAB-QA-68 (Design Change Management).
  - d. The Design History File, described on Page 108.108 of the CMC Overview Document part 3 and in LAB-QA-69 should be provided. These will also be reviewed at the pre-license inspection and FDA expects to find all the documents listed in the table shown on Pages 108.108 and 108.109 to be completed, signed and dated with information about the design of the NAT specifically.
28. Regarding your critical material suppliers, specifically: the [REDACTED] (b) (4) [REDACTED], please provide the following for each supplier:
- a. Details of your supplier qualification that was performed and descriptions of the supplier monitoring program
  - b. Identify the date of the last on-site audit that was performed
  - c. Quality Agreements
  - d. Clarify the component(s) of the NAT assay (e.g., primers, probes, etc.) for which IMUGEN holds proprietary rights.

**Instruments and Software:**

29. In your BLA you have provided Hazard Analysis document (064\_Attachment 4-5-4 (b) (4) Hazard Analysis.pdf.) that includes potential hazards, severity estimation, hazard mitigation and updated severity estimation after hazard mitigation. However, information such as cause(s) of the hazard and/or verification that the method of control was implemented correctly is not included in your table. Your Hazard Analysis document should be in the form of an extract of the software-related items from a comprehensive risk management document, such as the Risk Management Summary described in ISO 14971. For example, Failure Mode and Effects Analysis (FMEA) can be one of the approaches that could be utilized to identify the hazards, their corresponding validation and verification, and construction of the table accordingly. Therefore please provide an updated table based on FMEA and ISO 14971 methodologies. For further information, please refer to FDA software guidance document, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>. Please also consult a possible example of FMEA table available at: <http://asq.org/learn-about-quality/process-analysis-tools/overview/fmea.html>
30. In your BLA submission you provided Software Requirements Specifications (SRS) in document (b) (4) Software Requirements Specification” (065\_Attachment 4-5-5 SRS-(b) (4) IMUGEN.pdf) that describes the client/servicer application. The document includes 22 requirements for hardware, interface, software, performance, regulatory, system backup and restore, etc. Most requirements are too high level and do not include testable information. The requirements for workflow processes, boundary conditions and error recovery are missing. Please provide an updated copy of the Software Requirements Specification document, which should clearly document the functional, performance, interface, design and development requirements.
31. You have not provided an “Architectural Diagram” that should include a description of the software system partitioned into its functional subsystems, incorporating a description of the role that each module plays in fulfilling the software requirements. Please provide an Architectural Diagram of your software. It is recommended that you consult ISO 62304 (Medical device software - Software life cycle processes) to prepare your software documentation and conduct testing.
32. You have provided a software design specification (SDS) document (066 Attachment 4-5-6 SDS-(b) (4) IMUGEN.pdf) for the (b) (4). The document includes the modules for the (b) (4) Process Role, PCR Role, Report Role, Audit Role, and Admin Role. These each illustrate the control flow among the User, the UI, the Data Model and the Data Storage. The database schematic is presented in Figure 1 on Page 566, definitions are included in Section 2.4 starting on Page 569, and all components are described by Field with included Notes and Type. However, none of the fields have specified measureable or testable values. There is no traceability from the requirements enumerated in document “065\_Attachment 4-5-5 SRS-(b) (4) IMUGEN.pdf” to this SDS document to describe how the requirements in the Software

Requirements Specifications (SRS) are implemented. Please add the missing requirements to your software requirement specifications, including all step-by-step workflow requirements, for both AFIA and NAT, and provide all updated design control documentation that is affected.

33. You have provided a traceability document (067\_Attachment 4-5-7 IMUGEN (b) (4) Traceability Analysis.pdf) that includes items for each of 22 high level requirements. The “Verification and Validation Tests” in the form of references to Installation Qualification tests or Operational/Performance Qualification tests are included and associated hazards are identified. However, the traceability of requirements and specifications to testing and hazards are not comprehensive. This is due in part to inadequately formulated requirements, which are often vague and untestable as written, and the use of test cases that are mostly limited to using valid values and workflow actions.
- a. Please provide verification and validation information for all software requirements (including missing requirements mentioned in other deficiencies), which should include the unit, integration and system level test protocols with pass/fail criteria, and test report, summary and test results.
  - b. Please provide traceability information described at the detail level of individual software requirements rather than the high level software requirements, R1-R22. This includes traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing in an enumerated manner.
34. In the 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 was not included in the hazard analysis, and no requirements were added to address this. Please correct this anomaly and update the associated design documentation.
35. You did not provide information on Cybersecurity related to all instruments, hardware and software incorporated into the system, including Off-the-Shelf components. The (b) (4) system includes at least (b) (4) types of servers and multiple workstations/clients, at least (b) (4) of which has established connectivity to the outside world. Please provide information on the Cybersecurity aspects of your device, including, but not limited to, the following facets of information security with respect to communication features of your device, associated software and other required components: confidentiality, integrity, availability and accountability. Confidentiality assures that no unauthorized users have

access to the information. Integrity is the assurance that the information is correct - that is, it has not been improperly modified. Availability suggests that the information will be available when needed. Accountability is the application of identification and authentication to assure that the prescribed access process is being done by an authorized user.

36. In the document 065\_ Attachment 4-5-5 SRS-(b) (4)\_IMUGEN, you have stated that “*When testing and data collection is complete, laboratory managers will use the software to produce reports of sample results which are electronically transmitted to the submitting entity (Page 547).*” However, it is not clearly described how these results are transmitted to these facilities. As your service expands in the future, you will be collecting and reporting greater amounts of data. Please explain how these data will be managed and coordinated between your laboratories and blood establishment facilities.

**Facility:**

37. The facility description in your BLA was limited and a determination of the adequacy of the overall facility and facility control could not be determined. Please provide the following information:
- a. Details regarding the overall construction of the facility (i.e., brick and mortar); the location of manufacturing activities, quality labs, office space, warehouse, etc.; and choice of building materials comprising the manufacturing and donor testing areas.
  - b. Security measures of the facility and within your production areas.
  - c. Description of your building monitoring system: identify which elements the system monitors and include a summary of the performance qualification that was performed.
38. Please provide a detailed narrative of the manufacturing flow, in addition to flow diagrams of how personnel, materials (raw materials, in-process materials, finished product), and waste are moved through the facility. In your narrative please include a complete description of all manufacturing activities or donor testing that occur in each room and the facility controls you have in-place to prevent cross-contamination.
39. Please provide a list of all additional products or assays, other than *B. microti*, that are manufactured or manipulated in the same areas used to produce the assay that is the subject of this application. Information provided should include a brief description of the type and developmental status of the additional products or assays and indicate the areas into which these other products or assays will be introduced, whether on an ongoing or campaign basis, and what manufacturing steps will be performed in the multiple-use area(s).
40. Please provide the cleaning qualification data and disinfectant effectiveness studies for cleaning agents used in your facility and the Biosafety Cabinets (BSCs). Demonstration of facility cleaning should include, but is not limited to: bench top workstations, walls, floor, and any other facility surface material.

41. Please provide the qualification summary of the HVAC system, details of the room classifications and justification for the classification, rooms serviced by each HVAC, and airflow patterns and pressure differentials that are used to prevent cross-contamination in your manufacturing area. In addition, please provide facility schematics that indicate the room classifications of your facility.
42. Details of your environmental monitoring program were not described in sufficient detail. Please provide the following information:
  - a. Details of your environmental monitoring program and system used for the monitoring.
  - b. Indicate your monitoring sites throughout the facility and in the BSCs and describe the criticality of these monitoring sites.
  - c. The results of your environmental monitoring that is performed during the manufacture of your conformance lots.
43. In your BLA, you identify <sup>(b) (4)</sup> sources of water, <sup>(b) (4)</sup>, which are used in the manufacture of the components of the assay. Please identify which components of the assay are manufactured with the specific water type. In addition, please provide a validation data summary for the water purification system.
44. In your BLA submission, you claim categorical exclusion of an environmental assessment based on 21 CFR 25.34 (d). This is not appropriate given that your submission is classified as a BLA, thus the class action considerations should be based under 21 CFR 25.31 Human drugs and biologics. Please change the requested action of your claim for categorical exclusion to 21 CFR 25.31(c) and state in your justification specifically, “To IMUGEN’s knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment” as per 21 CFR 25.15(d).
45. Please note that a pre-license inspection is required for your Norwood, MA facility prior to approval of your biologic license application.

**Equipment:**

46. In reference to the major pieces of equipment including the Real Time PCR system and the <sup>(b) (4)</sup> system used in the manufacturing/testing process, there were no details in regards to the status of this equipment as shared or dedicated, if this equipment is product contact or how many machines are used in the process. Additionally, it is not clear if this equipment is also used for other manufacturing campaigns not associated with *B. microti* NAT and testing. Please provide a listing of all critical pieces of equipment (including the number of machines) and indicate if the equipment is shared or dedicated, has product contact, and identify the room location in your facility.

47. Please provide equipment qualification data to support your equipment operating parameters for the Real Time PCR system and the (b) (4). Information provided should include the following:
- Certification that IQ was performed for each machine.
  - OQ report summary for at least one machine of the same model.
  - PQ report summaries for data collected from all machines used on all shifts.
48. It is unclear if a cleaning validation was performed for the major pieces of equipment including the Real Time PCR system and the (b) (4). Please provide cleaning validation summary reports performed for all major pieces of equipment.

**Labeling:**

49. The intended use statement as provided is not correctly worded. FDA offers the following suggestion for the intended use statement for the *Babesia microti* NAT:

IMUGEN Inc.'s *Babesia microti* NAT is a nucleic acid screening assay for the detection of *Babesia microti* DNA in human whole blood samples (with EDTA as anti-coagulant).

This test is intended for use as a donor screening test to detect *B. microti* DNA in whole blood 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 in diagnosis of *Babesia microti* infection.

Should additional information relating to the safety and effectiveness of this drug product become available before our receipt of the final printed labeling, revision of that labeling, may be required.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*,” dated May 2009.

This document is available on the internet at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf> or may be requested from the Office of Communication, Outreach, and

Development, at (240) 402-8020. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER’s *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*.

This document also is available on the internet at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Alisha Miller, at 240-402-8421.

Sincerely yours,

Hira L. Nakhasi, PhD  
Director  
Division of Emerging and  
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