



Our STN: BL 125589/0

**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* Arrayed Fluorescence Immunoassay 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. Clinical sensitivity and specificity must be calculated from all studies using the same cutoff, testing algorithm, and interpretation of results.
  - a. A cutoff of 1/128 for positive detection was determined in the analytical study presented in “4-1 AFIA CMC Overview”, Section 4.3.1.1, page 140. However, numerous other cut-offs were used in other studies. Briefly, in Clinical Study 1, Pedigreed Clinical Samples, results of (b) (4) were interpreted as positive, Study 2, Retrospective Donor Testing, results of 1/64 were interpreted as positive and the Prospective Studies, 3A, 3B and 4, results of 1/128 were interpreted as positive. These studies cannot be used to calculate a single sensitivity and specificity with different cutoffs. Results from Study 1 and Study 2 can only be used in evaluation of clinical performance if they are available at a 1/128 dilution; otherwise they could be used to evaluate the clinical significance of different cutoff values.
  - b. The testing algorithm is described in LAB-SER-BIFA-1. Donor specimens are tested at an initial dilution (1/64 for retrospective, 1/128 for prospective). “All specimens reactive at a (b) (4) degree of fluorescence are repeated at the initial dilution twice and titered out to endpoint” (page 666). A donor result is reported positive if one or more of the repeat tests is positive. If both repeat tests are negative, the result is reported as negative (Table 8.4.3.5, CSR 3A, page 2849). The sponsor has not included the retest data in the spreadsheets provided. Only those samples that were positive by NAT but negative by AFIA show retest data by AFIA (CS 3A: 7 samples and CS 3B: 2 samples). In study 4, seven samples were reported positive by AFIA,

- but no repeat testing was recorded as required by the protocol. Please provide all retest data.
- c. In another example of protocol deviation, the donor sample, (b) (6), in prospective study 3A was positive on index at a titer of 1/128. In 4 of the 6 follow-up samples, even though the titer was 1/64 the sample was reported as *Babesia* positive. A similar result was reported in study 2 for donor (b) (6). The sponsor must show that the testing algorithm was followed and correct interpretation was made of each test result. Alternate cutoff interpretations are not appropriate for a blood donor screening intended use. A 1/64 result should not be interpreted as “positive”. Please correct these interpretations.
2. In the FDA Clinical Hold Letter dated December 10 2010, FDA requested that IMUGEN “Please demonstrate the clinical sensitivity of this test in human samples that are blood-film positive for *Babesia microti*.” From the data provided it appears that there are approximately (b) (4) blood-film tested specimens reported in Study 1 that could possibly be used in this calculation, if they are tested at the assay cutoff of 1/128. If this is not the case then there is no calculation of clinical sensitivity presented in the submission. Please describe how clinical sensitivity will be calculated for the AFIA and any data that are included in the calculation; please submit the data as line listings in a spreadsheet.
  3. To enable a claim for plasma (b) (4) specimens, data must be presented with sufficient testing of each specimen type. Please provide these data or a plan for a study. Previous submissions for blood donor screening assays have tested at least 50 sets of paired specimens with (b) (4) plasma drawn from the same donor. In addition, a sufficient number of the prospective specimens, at least 1/3 of the clinical study, should be collected as one of the sample types.
  4. The AFIA reactive donors in the clinical studies were retested with a research western blot as agreed in the IND. Please submit the complete description and validation of the western blot method including images of positive and negative test results.
  5. Please provide a summary table showing the lots of *B. microti* AFIA manufactured by IMUGEN that were used in the clinical studies described in your BLA. For each lot (including conjugate, 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) in which each lot was used.
  6. Please submit a data summary for each clinical study, 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 3 outcomes (positive, negative, inconclusive), the data may be displayed in 2X3 or 3X3 tables.

#### Pre-clinical Studies:

7. In the submission document, “4-1 AFIA CMC Overview,” Section 4.3.1.1, you present an analytical sensitivity/cutoff study with (b) (4) blood smear positive or PCR positive diagnostic patient samples. In your conclusion you state, “The data indicate that an AFIA

cutoff at a dilution of 1:128 is sufficient for detecting exposure to *Babesia microti*.” Based on this analysis, 1:128 should be used as the cutoff in all the studies presented. Among the pre-clinical and clinical studies, (b) (4) and 1:64 were also used as cutoffs. Please perform the analysis of all studies with the 1:128 cut off.

8. The document, “Attachment 4-3-2-14\_DOC-RPT-3\_Analytical Precision Report,” describes the only precision study found in the submission. A precision study in a BLA submission is expected to be based on Clinical Laboratory Standard Institute (CLSI) EP05-A3. Your study should include more repeated measures of the same sample. The analysis of the results you presented is not adequate compared to the statistical analysis that is suggested in the CLSI document. Please provide a plan for a precision study with a statistical analysis plan based on the guidance provided in EP05-A3.
9. The 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) document, EP05-A3 for designing and performing reproducibility studies.
10. Please provide a summary table showing the lots of *B. microti* AFIA manufactured by IMUGEN that were used in the pre-clinical studies described in your BLA. For each lot (including conjugate, 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) in which each lot was used.
11. The document (LAB-QA-59) describes a plan for testing the stability of the components of the AFIA assay.
  - a. Please provide the actual test results (not summary) for each component (multiple lots) at the storage conditions referred to in the SOPs.
  - b. Some of the stability testing results were given (DOC-STB-RPT-6); however the results seem to be from one slide. Please clarify.
  - c. A report of stability testing of the negative and positive controls for the IFA was given in Attachment 4-3-2-20\_LAB-MEM-15. Please provide sufficient information about slides and conjugate used in the testing and how many replicates were tested from each lot at each time point.
12. At the conclusion of the Microbial Cross-Reactivity study (4-1 AFIA CMC Overview, pages 141-145) you propose repeating the study. Please provide the results of the repeat study.
13. In the pre-clinical studies, you showed that plasma from *Plasmodium falciparum* infected individuals reacts 100% (4 of 4) in the *B. microti* AFIA. Given that this is a significant cross reactivity that will likely be included in the labeling of this test; we recommend that at least 20 more *P. falciparum* infected specimens be tested to determine the specificity of the *Babesia* assay and the results submitted for review.

14. In the 4-1 AFIA CMC Overview, Table 4.3.13, the study describing endogenous potentially interfering substances, the AFIA assay produced a positive reaction in 3 out of 20 (15%) of the Anti-nuclear antibody (ANA) specimens. This appears to be high since ANA antibodies can exist in a broad range of conditions including autoimmune disorders and has a prevalence of 5% in normal individuals. Therefore, this could represent a potential confounding factor on the AFIA results. The potential reactivity with ANA antibodies will be listed as a limitation of the assay unless you can provide additional results or interpretation

**Process/Product:**

15. In your submission, you indicated that the AFIA *B. microti* 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 (i.e., cleaning validation, room classifications, etc.) were provided. Please provide specifics in regards to microbiological control of your process and indicate if bioburden testing is performed. For example, since (b) (4) blood represents the primary source material for making the AFIA slides, a more rigorous microbiological examination of the source material is desirable. Fungal contamination also may occur in (b) (4) derived preparations. The procedures, as currently designed, only capture bacterial contamination. Moreover, the testing is done on (b) (4) (b) (4) according to LAB-MFG-25 which may not reveal non-bacterial contamination. Please propose a modified microbiological screening procedure or provide a rationale as to why it is not needed.
16. Though you have submitted numerous documents, such as, Attachment 4-9-2-27 LAB-QA-86, which describe the guidelines for process validation, we could find no implementation of these guidelines in reports of activities specific to the manufacturing or quality systems related to the AFIA. From your submission, it does not appear that adequate process validation was performed as no process validation procedures/protocols and the corresponding reports for specific processes were provided. Please provide process validation report summaries for your manufacturing process. These validation reports should clearly outline how the validation was performed (including statement of the objective, scope, methods of data collection and analysis), description of defined acceptance criteria, results, and deviations and resolution of deviations.
17. In the CMC section of your BLA, you state that both the *B. microti* positive and negative human plasma which are used in the manufacture of the AFIA controls are (b) (4) to remove impurities in the plasma (LAB-MFG-31, p378 and LAB-MFG-5, p388). You also state that you (b) (4).
- Please clarify which impurities you are removing during the (b) (4) of the plasma and (b) (4).
  - Please clarify if you have completed a pathogen reduction study and if not, provide justification.

- c. Regarding the (b) (4), please provide details of the (b) (4) that is used, if the (b) (4) are single-use or disposable, validation of the (b) (4), and if applicable, the cleaning validation of the (b) (4).

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

18. IMUGEN has not made a clear distinction of manufactured lots of the assembled AFIA components. A set of reagents, conjugate, positive and negative controls, and *B. microti* AFIA slides should be assembled and tested together to comprise a lot with the expiration date set by the shortest expiration date of a component of the assemblage to constitute a finished device. Please define the composition and size of a lot of assembled components that will constitute a finished device.
19. Each lot of the assembled components must meet lot release specifications. For example, each batch of conjugated anti-human IgG (b) (4) according to LAB-AQC-SER-97. This process of (b) (4) continues until a batch of slides, conjugate, negative controls and positive controls are assembled into a finished device and subjected to final release testing. BLA approval generally requires evaluation and lot release testing of at least three conformance lots that were manufactured by the protocols in the license application, in lot sizes that are similar to those proposed for subsequent production and that have been used in clinical testing and reviewed by CBER. Please explain how you intend to address these issues. In addition to IMUGEN internal release testing, CBER lot release testing will be performed. Please submit a lot release protocol template for the AFIA. Include the specifications and the name of the method(s) used to perform the analysis.
20. The process of manufacturing *B. microti* infected (b) (4) red blood cells, the essential antigen component required to prepare AFIA slides, is not sufficiently controlled nor fully described. Please provide:
- Data on the genetic and antigenic characterization of the *B. microti* isolate including results of genotyping assays performed by (b) (4) (AFIA CMC Overview, Page 106).
  - Location, storage conditions and composition (i.e., number of vials, volumes, date of preparation, storage temperature, etc.) of the current stock of *B. microti* parasites (LAB-MFG-29) used as starting material to inoculate (b) (4) (LAB-FG-8).
  - Acceptance criteria and data for antigenic consistency from lot to lot such as reproducibility of a (b) (4) (b) (4).
  - 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, 10-11) are applicable to maintaining *B. microti* parasites used in manufacturing of the infected red blood cells.

21. The production of infected (b) (4) red blood cells is performed at the (b) (4) (b) (4) under contract. As the license holder for manufacturing the *Babesia* AFIA, 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.
22. The attachment LAB-MFG-8 describes the procedure for inoculating and harvesting *B. microti* infected blood from (b) (4) at the (b) (4). Based on the information in LAB-MFG-8, 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 are allowed to occur after a (b) (4) stock is used to inoculate a naïve animal. The current process of preparing infected (b) (4) blood is not controlled sufficiently to ensure lot-to-lot consistency of antigen on slides. In order to ensure consistency of iRBCs and reduce the potential antigenic variability between lots, FDA has the following recommendations:
- Each new production of (b) (4) infected blood should start with an inoculum of parasites from the working cell bank.
  - Define the total number of parasites that will be used to inoculate the (b) (4).
  - IMUGEN should modify LAB-MFG-8 to include the added initial steps of (b) (4) a vial from the working cell bank through the collection of blood from infected animals.
  - If passage from (b) (4) is required to establish parasite infection or reach sufficient parasitemia, please clarify how many passages from animal to animal are allowed under the protocol.
23. A QC Panel of human plasma samples is used for release testing of critical assay components, the conjugate and the AFIA slides. Please provide a detailed description of the CAP internal reference standard panel of *B. microti* reactive plasma samples and *B. microti* negative plasma samples (the certificates of analysis found on page 548 of CMC,

“Attachment 4-2-3-34\_ *Babesia* CAP Reference Standard Certificate of Analyses” are not sufficient). Please describe the source of the plasma samples, how they were characterized, and if appropriate titers were achieved by dilution? Please include a validated method for assuring continuity of release testing as panel members are depleted and refreshed with new plasma samples. Some negative and positive panel members are also reactive with *Borrelia burgdorferi*. Please provide data that shows reactivity to *B. burgdorferi* did not interfere with the *B. microti* AFIA. Please provide complete characterization of the function and stability of this essential component of in-process testing.

24. The document “Titration of Reagents for Indirect Fluorescent Assay, LAB-SER-BIFA-6” was not provided in the CMC Section. Please provide the document or indicate its location in the BLA File.
25. In the acceptance criteria for *B. microti* infected red blood cells (LAB-MFG-1, page 563), you indicate that the red blood cell must have (b) (4) (b) (4). However, for processed (b) (4) red blood cells the specifications call for a (b) (4) (b) (4). Please explain this difference in the specifications.
26. As described in the document, 4-1 AFIA CMC Overview, on page 95: one of the specifications to accept infected blood from (b) (4) (b) (4) in the blood samples received and tested by IMUGEN with a reference to Attachment 4.2.3.6 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.
27. The Attachment 4-2-3-30, LAB-SER-SPF-1, specifies that antigen coverage per well of *B. microti* coated AFIA slides should be (b) (4). The methods document referred to (LAB-MFG-15) does not mention any coverage other than (b) (4). Please explain the discrepancy and how the (b) (4) coverage will be determined.
28. LAB-AQC-SER-97: “*Babesia microti* IFA slide batch release testing” needs to be updated to contain only the product that is under evaluation (i.e., the (b) (4)-well AFIA slide format). All information related to a (b) (4)-well slide AFIA format should be deleted from this document for clarity.
29. Please provide the following information regarding the manufacturing of the positive and negative controls.
  - a. In LAB-MFG-31, the Bulk Positive and Bulk Negative plasmas are evaluated (b) (4) (LAB-SER-BWB-2). Please explain the rationale for performing an (b) (4). Please provide the results of this testing and explain how the results are used during the manufacture of the *Babesia* AFIA positive and negative controls (PC and NC, respectively).

- b. The preparation of the Bulk PC and Bulk NC involve (b) (4)
- c. Please provide information about the source material used in the manufacture of the Positive Control Lot# (b) (6) ; this information is not found in the Batch record 4-7-2-3 AFIA Low Positive Control lot (b) (6) (p1464).
30. LAB-MFG-5 and LAB-MFG-31 do not specify the maximum length of time the Bulk PC or Bulk NC can be (b) (4) until they are aliquoted according to LAB-MFG-20 and LAB-MFG-21. Please include this information in these documents and provide documentation of how that hold time was validated.
31. LAB-SER-BIFA-1, Section 8.3 (p663) explains that the degree of fluorescence of a test result is recorded using a numerical grading system (b) (4) with (b) (4) being (b) (4) fluorescence seen, (b) (4) being the highest degree of fluorescence, and (b) (4) being a (b) (4) fluorescence. The titer that is reported as the result is determined by the (b) (4) dilution with a (b) (4) signal. In what way is the information of the grading scale used in this assay? Please comment on the accuracy of this grading system (i.e. how have you assessed the operator-to-operator variability and how the variability is controlled). Please clarify how fluorescence intensity will be taken into account in final results reporting.
32. 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:

33. Please address the following deficiencies regarding Design Control information:
- a. 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.
- b. 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 182; however the text is very general and does not describe any specific inputs to the AFIA device. Documents LAB-QA-70 and LAB-QA-71 are titled Design Inputs and Design Outputs respectively, however, there is no indication that these documents provide specific inputs and outputs of the AFIA 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 and 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 on page 178 and page 182, suggesting that a complete description is found in Attachment 4.9.2.6 LAB-DSGN-6. The list of documents that is the sole content of LAB-DSGN-6 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 that 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, page 183 including important types of items to be discussed at a design review meeting. However, the document elaborating on this, LAB-QA-72 Design Reviews was not found in the submission and should be provided. In addition, the following documents were not found in the submission and should be provided: 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 187 of the CMC Overview document and in LAB-QA-69 should be provided. This will be reviewed during the pre-license inspection and FDA expects to find all the documents listed in the table shown on page 187 and 188 completed, signed and dated with information about the design of the AFIA specifically.

#### **Instruments and Software:**

- 34. In your BLA, you provided a Hazard Analysis (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 verification that the method of control was implemented correctly are 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 FMEA table accordingly. Therefore, please provide an updated table based on FMEA and ISO 14971 methodologies. For further information, please refer to the FDA software guidance document, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>. Also, please consult a possible example of a FMEA table

available at: <http://asq.org/learn-about-quality/process-analysis-tools/overview/fmea.html>.

35. You provided Software Requirements Specifications (SRS) in the document “(b) (4) [REDACTED] Software Requirements Specification” (Attachment 4-5-5 SRS (b) (4) IMUGEN.pdf) that describes the client/servicer application. The document includes 20 requirements for hardware, interface, software, performance, regulatory, system backup and restore. 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 a modified version of the Software Requirements Specification document, which should clearly document the functional, performance, interface, design and development requirements.
36. You did not provide an Architectural Diagram that shows a description of the software system partitioned into its functional subsystems, including 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.
37. You provided a software design specification document (Attachment 4-5-6 SDS (b) (4) IMUGEN.pdf) for the (b) (4) [REDACTED]. The document includes the modules of the (b) (4) [REDACTED] for Process Role, IFA 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 886-888, definitions are included in Section 2.4 starting on page 889 and all components are described by Field with included Notes and Type. However, none of the fields have specified measurable or testable values. There is no traceability from the requirements enumerated in document “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 requirements specifications, including all step-by-step workflow requirements, for both AFIA and NAT, and provide all updated design control documentation that is affected.
38. You provided a traceability document (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 the associated hazards are identified. 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 which 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, including the 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.
39. 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.
40. You stated that “laboratory managers will use the software to produce reports of sample results which are electronically transmitted to the submitting entity” (page 867, Attachment 4-5-5 SRS(b) (4)\_IMUGEN-20150324). 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:**

41. 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.
42. 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.

43. 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).
44. Please provide the cleaning qualification data and disinfectant effectiveness studies for cleaning agents used in your facility and the Biological Safety Cabinets (BSC). Demonstration of facility cleaning should include but is not limited to: bench top workstations, walls, floor, and any other facility surface material.
45. Please provide the qualification summary of the HVAC system, details of the room classifications and justification for the classification, room 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.
46. Your environmental monitoring program was not described in sufficient detail.
  - a. Please provide details of your environmental monitoring program and system used for the monitoring.
  - b. Please indicate your monitoring sites throughout the facility and in the BSCs and describe the criticality of these monitoring sites.
  - c. Please include the results of your environmental monitoring that is performed during the manufacture of your conformance lots.
47. In your BLA, you identify (b) (4) sources of water, (b) (4), which are used in the manufacture of the components of the AFIA assay. Please identify which components of the assay are manufactured with each specific water type.
48. 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).
49. Please note that a pre-license inspection is required for your Norwood, MA facility prior to approval of your biologic license application.

**Equipment:**

50. In reference to the major pieces of equipment including the incubator and (b) (4) used in the manufacturing/testing process of the AFIA system, there were no details in regards

to the status of this equipment as shared or dedicated, if this equipment has product contact, or how many pieces of equipment are used in the manufacturing process. Additionally, it is not clear if this equipment is also used for other manufacturing campaigns not associated with *B. microti* AFIA manufacturing. Please provide a listing of all critical pieces of equipment (including the number of each) and indicate if the equipment is shared or dedicated, has product contact, and identify the room location in your facility.

51. There was no assurance that equipment qualification was completed for major pieces of equipment including the incubator, (b) (4), and BSCs as summaries of these reports were not provided. For equipment that requires qualification, please provide a copy of the performance qualification in which you demonstrate the equipment's operation during process manufacturing. Information provided should include the following:
- a. Certification that IQ was performed for each machine.
  - b. OQ report summary for at least one machine of the same model.
  - c. PQ report summaries for data collected from all machines used on all shifts.
52. It is not clear if cleaning validation was performed for the major pieces of equipment including the incubator and (b) (4) as cleaning validation studies were not provided. Please provide the cleaning validation reports performed for all major pieces of equipment used in the manufacture and testing of the AFIA system components.

### **Labeling:**

53. The intended use statement as provided is not correctly worded. FDA offers the following suggestion for the intended use statement for the AFIA:

The IMUGEN *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA) is intended for qualitative detection of antibodies to *Babesia microti* in human (b) (4) plasma (EDTA anti-coagulated) samples. This test is intended for use as a donor screening test to detect antibodies to *B. microti* in (b) (4) plasma 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  
Transfusion Transmitted Diseases  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research