



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993

### FINAL COMMITTEE MEMORANDUM

**From:** Robert Duncan, Ph.D., Scientific Lead, LEP/DETTD  
**Date:** February 26, 2018  
**Through:** Sanjai Kumar, Ph.D., Chief, LEP/DETTD  
**To:** File  
**RPM:** Iliana Valencia, MS, MCPM, Chief, RPMS, FDA/CBER/OBRR/IO  
**Product:** Imugen *Babesia microti* Arrayed Fluorescence ImmunoAssay (AFIA)  
**Sponsor:** Oxford Immunotec Ltd.  
**STN:** 125589

**Submission type:** Biologics License Application

**Documents reviewed:** Whole submission

**Recommendation:** Approval

Imugen, Inc. submitted a Biologics License Application for a *Babesia microti* AFIA. The '*Babesia* AFIA Assay' is an in vitro blood screening test intended for the detection of specific antibodies to *Babesia microti*. The BLA was transferred to Oxford Immunotec Ltd. July 16, 2016.

#### Intended Use

The Imugen *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA) is intended for qualitative detection of antibodies to *Babesia microti* in human plasma (EDTA anti-coagulated) samples. This test is intended for use as a donor screening test to detect antibodies to *B. microti* in 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.

## General Description of the Assay and System

The *Babesia* AFIA is based upon a conventional indirect immunofluorescent assay (IFA) and is used for detecting the presence of specific antibodies to *B. microti* in (b) (4) plasma specimens. The test employs *B. microti* infected (b) (4) erythrocytes, as an antigen source, fixed to glass slide wells and a (b) (4) F(ab')<sub>2</sub> anti-human IgG H+L chain specific (b) (4) conjugated antibody as a detector of bound *B. microti*-specific antibody. The fluorescence is detected in the wells of the slide employing a microscope equipped with an episcopic fluorescence illumination system.

Positive and negative control plasma are employed on each slide. The positive control is expected to produce a visible fluorescence pattern, while the fluorescence pattern will not be observed with the negative control plasma.

The *Babesia* AFIA was studied clinically to support this intended use pursuant to IND 14532 and its related amendments. AFIA tests are performed within IMUGEN's Clinical Laboratory Improvement Amendments ("CLIA") accredited clinical laboratory (Accreditation #22D0650196) by trained staff using dedicated, qualified equipment and instrumentation in assigned, dedicated areas.

The sponsor states that IMUGEN's *Babesia* AFIA (as described in this BLA submission - BL125589) and IMUGEN's *Babesia* NAT assay (as described in its separate BLA submission - BL125588) also were evaluated clinically (under an FDA-approved IND) for concurrent use for additional indications. Specifically, based on the clinical data, IMUGEN proposes to (b) (4) in assessing blood donors and blood donations to monitor disease prevalence in endemic and non-endemic areas, and as a tool to prevent or significantly reduce the incidence of transfusion transmitted Babesiosis (TTB), especially in endemic areas.

## Review Summary

This BLA from IMUGEN, Inc. was received by the Agency on May 12, 2015 as a paper submission with electronic content (DCC login 607593). The BLA was granted priority review status; therefore, it was reviewed under the 6 month review timeframe. This submission was filed July 10, 2015 and mid-cycle meeting was held on August 17, 2015. At the mid-cycle meeting, the following issues were identified during the review of the submission and sent to IMUGEN as a Complete Response (CR) Letter on September 29, 2015.

## CR Letter Items

### 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.

*Oxford Immunotec 12/13/2016 Response: Sensitivity and specificity calculations for the AFIA are based only on a 1/128 cut-off. All results were tabulated for study 2 and studies 3A, 3B and 4 based on this cutoff. This question is resolved.*

- 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.

*Oxford Immunotec 12/13/2016 Response: A complete spreadsheet with corrected values was provided. The data were analyzed by the statistician and FDA results concurred with the sponsor submitted results. This question is resolved.*

- 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”, though a “gray zone negative” interpretation may be permitted if defined in the IND. Please correct these interpretations.

*Oxford Immunotec 12/13/2016 Response: This sample was evaluated at the 1/128 cut-off for the specificity analysis included in Clinical Study 2. A follow-up sample from this donor was evaluated at a 1/64 cut-off as part of the ARC research study that is mentioned in the FDA question. The cutoff study concluded that 1/128 is the correct cut-off. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: Imugen has performed the AFIA sensitivity study with a 1/128 cut-off. A testing protocol was attached describing the AFIA testing of 72 blood smear positive clinical samples. The samples were detected 100% reactive resulting in a 95% confidence interval for the sensitivity of 95.01% - 100.00%. The line listing of all 72 samples was provided demonstrating that the samples were well distributed among parasitemia levels ranging from 0.005 % to 5.51 %. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: The claim will be sought for plasma only. This response resolves this question.*

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.

*Oxford Immunotec 12/13/2016 Response: A detailed description of the method of the Western blot and its validation was provided. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: A table of lots used during clinical studies was provided and batch records were examined during the pre-license inspection. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: Summary tables were provided for all studies as well as spreadsheet line listings of all results. Statisticians derived their own tables from the line listings and compared them to the tables provided by the sponsor. The tabulated results agreed and appear in the Summary Basis of Regulatory Action document. This question is resolved.*

## 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.

*Oxford Immunotec 12/13/2016 Response: The pre-clinical studies were performed at a 1:128 cut-off. Other mentions of lower cut-offs in previous documents were for research purposes only. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: A new precision study was designed and implemented. The study was performed near the cut-off with multiple operators on multiple days as described in a protocol submitted with the CR response. Pre-clinical and statistical reviewers found the study and results to be adequate. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: The precision study described in answer to question #8 also included reproducibility studies. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: Tables of lots used in pre-clinical studies were provided. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: Tables of component stability were provided. However, actual test results were not. See further review below following a February 24, 2017 IR letter.*

- b. Some of the stability testing results were given (DOC-STB-RPT-6); however the results seem to be from one slide. Please clarify.

*Oxford Immunotec 12/13/2016 Response: the sponsor clarified that DOC-STB-RPT-6 was not a full stability report but an in-process (b) (4) to determine the adequacy of (b) (4) of slides. DOC-STB-RPT-6 was performed with a single lot of slides. This portion of question #11 is resolved.*

- 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.

*Oxford Immunotec 12/13/2016 Response: details were provided including lot numbers of slides and conjugates. This portion of question #11 is resolved.*

Review of the stability of this device continued in an Information Request Letter sent February 24, 2017. The questions in the IR letter refer to the question numbers in the CR letter of 9/29/2015.

1. In the response to question #11 in the CR letter of Sep. 29, 2015, the Imugen response (pages 16&17) as well as the Attachments 11.1 and 11.2, a stability protocol (DOC-STB-24) and a stability report (DOC-STB-RPT-24) refer to other stability reports: DOC-STB-RPT-6, DOC-STB-RPT-22, DOC-STB-RPT-23 and DOC-STB-RPT-20 (page 3 of 15). Please confirm that all the data reported in these individual reports have been included in the result section of DOC-STB-RPT-24 (pages 6-10). Please provide any additional stability data that have not been included in DOC-STB-RPT-24. This data is necessary to evaluate the stability of *Babesia* AFIA kit components.
  - a. The real time stability studies only include (b) (4) DOC-STB-24, page 6 of 13). The data provided for the other (b) (4) are derived from stability testing of kit components which are supportive but not sufficient to establish the shelf life of an assembled finished device at the time of licensure. In order to generate additional stability data that could be considered for establishing a shelf life of the finished device, FDA recommends testing of 2 additional finished

devices among the conformance lots (b) (4) described in Attachment 19.2, Table.1, before their current assigned expiration dates. Please provide results for additional finished devices obtained according to protocol DOC-STB-24. Initial stability results can provide interim expiration dating at the time of licensure. Expiration dating of the Finished Device Lot can be extended by amendments to the BLA as data accumulate.

*Oxford Immunotec Amendment #13, 3/17/2017, Response: the sponsor confirmed that DOC-STB-RPT-24 contains all real-time stability data for the B. microti AFIA components stored in the appropriate state and designated condition for use in the B. microti AFIA system.*

*The reports DOC-STB-RPT-6, DOC-STB-RPT-22, DOC-STB-RPT-23 and DOC-STB-RPT-20 may contain additional data that was either collected not on real-time stability (DOC-STB-RPT-6, Attachment 1.1), was collected on a precursor component (DOC-STB-RPT-23, Attachment 1.2), or included an investigational stability study (DOC-STB-RPT-20, Attachment 1.3).*

*The sponsor further described a finished device lot stability study with results up to (b) (4) months for one lot and 6 months for two lots.*

The review of kit lot or Finished Device Lot (FDL) stability was pursued further in a second CR letter issued June 13, 2017. (item numbering according to CR letter #2)

2. The change proposed by Imugen to their real-time stability study is acceptable. Please provide an updated finished device stability protocol (DOC-STB-24) and updated report to date (DOC-STB-RPT-24) to reflect these changes.

*Oxford Immunotec 10/10/2017 Response: DOC-STB-RPT-24 has been updated reflecting the last testing time point, see Attachment 2.1. For the current protocol please see Attachment 2.2, DOC-STB-24.*

| Time Point | (b) (4) |
|------------|---------|
| T=0        |         |
| Month 3    |         |
| Month 6    |         |

*Legend: N/A: not applicable. Italicized dates are pending.*

*Subsequent communication from Oxford Immunotec confirmed that all test results through Dec. 20, 2017 were consistent with the acceptance criteria. This issue is resolved with an expiration date of (b) (4) months, which may be extended as further stability testing results are reported.*



12. At the conclusion of the Microbial Cross-Reactivity study (4-1 AFIA CMC Overview, page 141-145) you propose repeating the study. Please provide the results of the repeat study.

*Oxford Immunotec 12/13/2016 Response: A microbial cross-reactivity study was performed and the results submitted. FDA's review led to an Information Request letter (Feb. 24, 2017) question: "In the response to question #12 in the CR letter, you have provided data to demonstrate the absence of microbial cross reactivity and interference in the B. microti AFIA (DOC-RPT-35; Attachment 12.1). The data provided shows that there was no interference of bacteria in the B. microti AFIA. However, the conclusion that there was no cross reactivity is inappropriate. To demonstrate cross reactivity, please test plasma from individuals with antibody reactivity to bacterial infections on the Babesia AFIA.*

*Oxford Immunotec Amendment #13, 3/17/2017, Response: we agree that the data submitted demonstrate no interference. Lack of cross-reactivity was demonstrated in the original submission of antibodies to species and substance of concern except 2. For all except those dealt with in the next two questions, this issue is resolved.*

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 and the results submitted for review.

*Oxford Immunotec 12/13/2016 Response: A new Plasmodium falciparum cross-reactivity study was written and performed. All 20 specimens tested negative in this new study. FDA responded that the new results were an improvement, but that the potential cross-reactivity should be reported as 4/24. In a Dec. 1, 2017 response to an Information Request, Oxford Immunotec agreed with this presentation. This question is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: A new study plan for Anti-nuclear antibody (ANA) specimens was written and performed. All 20 specimens tested negative in this study.*

*In the second CR letter (June 13, 2017), the FDA asked: "In the ANA interference study, (DOC-PRO-49 and DOC-RPT-71), please indicate if the 3 ANA positive samples that were AFIA positive at a 1:64 cut off remained positive at a 1:128 cut off. Based on the number of ANA positive samples that are positive at the AFIA cut off of 1:128, please recalculate the percent interference over a denominator of 40 (I.e., the total number of ANA positive samples tested using the AFIA). Alternatively, provide a justification why the 20 ANA samples in the initial study should not be reported as part of the performance evaluation for the AFIA."*



*Oxford Immunotec 10/10/2017 Response: In the ANA interference study for AFIA the initial ANA study samples should be excluded as part of the performance of the AFIA because the original sample data cannot be confirmed. These samples were not purchased through a vendor and did not have a COA to confirm testing and results data. The original study did not include end point titer which cannot be repeated because those samples are no longer available. The FDA did not accept this argument as satisfactory and its position that ANA reactivity should be stated as 5/40 carried through to final resolution when Oxford Immunotec agreed to presenting all the ANA data though not highlighting the reactivity in a Dec. 1, 2017 response to an Information Request. This question is resolved.*

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) 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.

*Oxford Immunotec 12/13/2016 Response: “The statement included in the submission regarding the microbiological control of the AFIA *B. microti* device was inaccurate as the device is not specifically controlled for microorganisms. However, there are a number of controls and specifications in place for the purpose of limiting microbiological contamination.”* This response is partially adequate; however, these issues are dealt with in greater detail to a point of resolution in the Pre-license Inspection documents, EIR and 483memo cited in the introduction to item #41 below.

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.

*Oxford Immunotec 12/13/2016 Response: “We have documented our manufacturing process to create a finished device lot. This is captured in the master validation plan (LAB-VAL-5,*

Attachment 16.1) which also provides an overview of process flow and specifications. This plan is implemented in LAB-VAL-11 (Attachment 16.2) which describes the overall validation protocol.”

The FDA further questioned the Master Validation Plan in an Information Request letter (Feb. 24, 2017) Question #5, asking, “In response to question #16 in the CR letter, you present a comprehensive Master Validation Plan and describe results that seem to be reported in DOC-RPT-46. Please provide this document. Please provide DOC-RPT-60 so that we may evaluate the Validation Study and establish the date on which the manufacturing processes and assay procedures were validated and locked. We expect this information is found in DOC-RPT-60.”

Oxford Immunotec Amendment #13, 3/17/2017, Response: “The manufacturing processes and assay procedures were validated for each component individually in the validation reports.” A detailed table was provided describing the validation process for each manufacturing step, the associated document identification and the date at which the specifications were locked. This question is **resolved**.

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).

- a. Please clarify which impurities you are removing during the (b) (4) of the plasma and (b) (4).

Oxford Immunotec 12/13/2016 Response: “The purpose of the (b) (4) and the plasma samples is for the removal of any potential (b) (4) material from the sample, and not for the purpose of (b) (4) sterility. There is not a specification for sterility of the (b) (4)” **Resolved**.

- b. Please clarify if you have completed a pathogen reduction study and if not, provide justification.

Oxford Immunotec 12/13/2016 Response: “As the (b) (4) of the samples is not designed for pathogen removal, this study has not been performed.” **Resolved**.

- 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).

Oxford Immunotec 12/13/2016 Response: “The (b) (4) are used according to the manufacturer’s instructions and no additional validation was performed since their purpose is not related to sterility.” **Resolved**.

#### 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.

*Oxford Immunotec 12/13/2016 Response: "A finished device lot has been defined for sets of AFIA test components. A manufacturing document has been prepared to document the strategy for assembling device lots, release testing and expiration date definition." Detailed protocols and worksheets were included in the submission that indicated the sponsor had conformed to FDA's request. Further observations during the pre-license inspection confirmed that the standard operating procedures in use ensured the integrity of Finished Device Lots. This issue is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: The answer given referred mainly to the answer given to question #18, which is relevant. However, the details of CBER Lot Release testing were resolved in subsequent communications. FDA sent a generic Lot Release Template (LRT) to the sponsor on April 5, 2017 with a request, "Please submit a LRP template which lists tests performed on the final product including specifications and results." The sponsor submitted the completed LRT on May 5, 2017, which was edited slightly in an Oct. 26, 2017 amendment. Blinded CBER panels for testing the three conformance lots were sent to the sponsor, results returned for decoding by the FDA Division of Biologics Standards and Quality Control. All three lots were cleared. This issue is resolved.*

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:

- a. Data on the genetic and antigenic characterization of the *B. microti* isolate including results of genotyping assays performed by (b) (4) (AFIA CMC Overview, Pg. 106).

*Oxford Immunotec 12/13/2016 Response: the sponsor provided a report describing the genetic analysis performed to characterize B. microti isolates. This issue is resolved.*

- b. 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).

*Oxford Immunotec 12/13/2016 Response: the sponsor provided a table listing the items requested and further explained that master cell banks were located at the Norwood facility and at a backup location in (b) (4) to assure a constant supply of the essential parasites. This issue is resolved.*

- c. Acceptance criteria and data for antigenic consistency from lot to lot such as reproducibility of a (b) (4).

*Oxford Immunotec 12/13/2016 Response: "Acceptance criteria are based on results from testing against a release panel. The release panel consists of (b) (4) controls. Lots are tested by the (b) (4) method and the (b) (4) must be within the specification documented in LAB-AQC-SER-97, Section 11.1 (Attachment 20.4). Release testing files and all accompanying raw data is available for onsite review. The (b) (4) is not amenable for testing of antigenic consistency because excessive volumes of blood are required." This response is acceptable recognizing that the consistency of the (b) (4) to the Babesia antigens is the essential criterion.*

- d. 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 (p 8, 10-11) are applicable to maintaining *B. microti* parasites used in manufacturing of the infected red blood cells.

*Oxford Immunotec 12/13/2016 Response: A detailed laboratory standard operating procedure (SOP) was provided that satisfactorily describes master and working cell bank establishment and quality control including (b) (4) confirmation of the identity of the Babesia cells. Babesia infected (b) (4) red blood cells are allowed to be passaged (b) (4) a new vial from the working cell bank. This issue is resolved.*

21. The production of infected (b) (4) red blood cells is performed at the (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.

*Oxford Immunotec 12/13/2016 Response: the sponsor provided additional information including the IACUC document and stated that a contract was being negotiated.*

*The FDA continued the review of this issue with a question in an IR letter, Mar. 17, 2017:*

*“Please provide a signed contract. Also, in the (b) (4), the sponsor is proposing (b) (4) / year) to be used. Please provide a projection of how the sponsor will handle enough (b) (4) to scale up the manufacturing process, if needed, in the future for licensed blood donor testing.*

*Oxford Immunotec Amendment #13, 3/17/2017, Response: “Current projections suggest that utilizing (b) (4) to perform (b) (4) AFIA slide batch manufacturing would yield enough material for greater than (b) (4) blood donor tests per year. (b) (4) typically orders (b) (4) at a time.”*

*The FDA issued a second CR letter on June 13, 2017 which contained the question, “The formal agreement with (b) (4) for housing (b) (4), production and delivery of Babesia infected (b) (4) blood should be signed by the (b) (4) and Oxford Immunotec, Inc. before the pre-license inspection.”*

*Oxford Immunotec 10/10/2017 Response: “The formal agreement between Imugen and (b) (4) was executed on August 16, 2017 and is available for onsite review.” This issue is resolved.*

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:

- a. Each new production of (b) (4) infected blood should start with an inoculum of parasites from the working cell bank.

*Oxford Immunotec 12/13/2016 Response: “We have adapted our procedures such that each production cycle of infected (b) (4) blood is initiated from the (b) (4) working cell bank as described in LAB-MFG-8 (Attachment 21.2). Each production cycle may include up to (b) (4) passages.” FDA further questioned in an IR letter of Feb. 24, 2017, “[a document] should show a record of the infection passage, with a criterion that passage number be less than or equal to (b) (4) or specify how the number of passages in (b) (4) will be tracked and documented for each lot of infected red blood cells.*

*Oxford Immunotec Amendment #13, 3/17/2017, Response: “Imugen agrees that the incoming paperwork should clearly demonstrate that the parasite has had (b) (4)*



passages. The appropriate document for implementing this change is LAB-AQC-SER-85. The Certificate of Analysis worksheet (Page 8) has been updated to include a check box confirming that there are (b) (4). This is acceptable.

- b. Define the total number of parasites that will be used to inoculate the (b) (4)

*Oxford Immunotec 12/13/2016 Response: the operative quantity is (b) (4).* This is acceptable.

- c. 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. *Oxford Immunotec 12/13/2016 Response: modification made. This is acceptable.*

- d. 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.

*Oxford Immunotec 12/13/2016 Response: (b) (4) passages as stated above. This is acceptable.*

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.

*Oxford Immunotec 12/13/2016 Response: A thorough description of the panel, system for maintaining continuity and the testing for B. burgdorferi were presented. This is acceptable.*

24. The document "Titration of Reagents for Indirect Fluorescent Assay, LAB-SER-BIFA-6" cannot be found in the CMC Section. Please provide the document or indicate its location in the BLA File.

*Oxford Immunotec 12/13/2016 Response: "In order to improve the workflow, the procedure originally described in LAB-SER-BIFA-6 is now contained within LAB-MFG-22 (Attachment 24.1). These changes do not have any impact on the manufacturing process other than improving the workflow efficiency. LAB-SER-BIFA-6 is now obsolete." This is acceptable.*

25. In the acceptance criteria for *B. microti* infected red blood cells (LAB-MFG-1, pg 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.

*Oxford Immunotec 12/13/2016 Response:* “We have revised our documentation to consistently specify a (b) (4) (b) (4) range.” This is acceptable.

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) 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.

*Oxford Immunotec 12/13/2016 Response:* The SOP, LAB-MFG-1, was modified to provide (b) (4) examples of (b) (4) and a procedure for reporting them. Of (b) (4) batches of AFIA slides manufactured, none have been rejected due to (b) (4). This is acceptable.

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.

*Oxford Immunotec 12/13/2016 Response:* The appropriate SOP, LAB-MFG-15, has been updated to clarify the specification for well coverage and how this is determined. The coverage is determined (b) (4). Direct observation of this procedure during the prelicense inspection confirmed that the process is adequately controlled. The FDA pursued this question in an IR letter, Feb. 24, 2017, with a question about how many slides can be rejected before a batch would be failed. Oxford Immunotec responded in Amendment #13, 3/17/2017, that they would implement a (b) (4) threshold for acceptance of a batch of slides. An examination of the records of the (b) (4) prior batches showed none were below (b) (4) accepted. This issue is resolved.

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.

*Oxford Immunotec 12/13/2016 Response:* “LAB-AQC-SER-97 (Attachment 20.4) has been modified to delete references to the (b) (4) well slide format.” This issue is resolved.

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).

*Oxford Immunotec 12/13/2016 Response: "The rationale for using the (b) (4) was for informational purposes during development. This (b) (4) testing is not performed to qualify bulk positive and bulk negative plasmas. The appropriate manufacturing SOP has been modified accordingly. This is acceptable.*

- b. The preparation of the Bulk PC and Bulk NC involve (b) (4)

*Oxford Immunotec 12/13/2016 Response: "The plasma is (b) (4) to remove any potential (b) (4) in the sample, and not to (b) (4) the sample. A step to verify the integrity of the (b) (4), has been added to the appropriate manufacturing SOP. This is acceptable.*

- 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).

*Oxford Immunotec 12/13/2016 Response: "The source material of Positive Control lot# (b) (6) was High Positive Control lot# (b) (6) and Negative Control (b) (6) " This is acceptable.*

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.

*Oxford Immunotec 12/13/2016 Response: The hold time of (b) (4) is specified in these SOP documents. This is acceptable.*

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.

*Oxford Immunotec 12/13/2016 Response: “The fluorescence intensity is not included in the final result reporting.” The information in the grading scale is used 1) to qualify the positive control, 2) to aid in assessment of scoring consistency and 3) to identify reactive results. A table of (b) (4) initially reactive samples out of (b) (4) total were compared between their initial score and subsequent scores. (b) (4) were scored the same in all 3 tests.*

*FDA responded in and IR letter on Feb. 24, 2017 that there has not been sufficient control of operator-to-operator variability and asked about microscopist training.*

*Oxford Immunotec Amendment #13, 3/17/2017, Response: “Training is performed according to LAB-SER-BIFA-16, “Hands-On Evaluation for AFIA Test System” and typically takes (b) (4) days. Competent operators undergo routine proficiency testing in (b) (4) month intervals. Direct observation of the operator to operator scoring of blood donor samples and quality control panels was further convincing that this operation is sufficiently controlled.*

*In the Feb. 24, 2017 IR letter, the FDA inquired further into the procedure for result scoring asking the question, ““A sample which scores (b) (4) is considered reactive...a reactive sample must be retested in duplicate.” However, page 22/28, step I. of that SOP, says that “additional retests (N=2 or 3) may be required at the discretion of the supervisor to further evaluate any inconclusive findings in order to yield interpretable results.” If multiple retests of the same samples are required, what is the algorithm to make the final interpretation from the 5 or 6 results and how are these results captured in the (b) (4)? Please revise LAB-SER-BIFA-1 accordingly. Oxford Immunotec responded in Amendment #13, 3/17/2017, that appropriate changes had been made in the Instructions for Use document, LAB-SER-BIFA-1. However, FDA review of that document led to the addition of the following question in the second CR letter sent June 13, 2017: “The FDA expects that a clear finite number of tests are performed to make an interpretation of non-reactive or repeatedly reactive in a serological test. Therefore, the wording in [the IFU document] is acceptable. Remove the additional retests in [the subsequent section]. Please revise LAB-SER-BIFA-1 to indicate how many retests are allowed and how the final interpretation of the results is reached. Oxford Immunotec responded 10/10/2017 with a revised LAB-SER-BIFA-1 that was acceptable. This issue is resolved.*

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).

*Oxford Immunotec 12/13/2016 Response: A Device Master Record unique to the AFIA was provided. This issue is resolved.*

#### 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.

*Oxford Immunotec 12/13/2016 Response: A revised Design Plan was submitted that included the required elements for Design Verification, Design Validation, Design Transfer, Design Changes and for a Design History File. In addition, Design Review requirements are covered in the document.*

*FDA continued the review of this issue in an IR letter (Feb. 24, 2017) with the question: How are the version changes mentioned in the response to the CR letter approved, recorded and tracked? There was reference to the (b) (4) system as the means by which Imugen documents are controlled. Please provide some description of the documentation of changes to such documents.*

*Oxford Immunotec Amendment #13, 3/17/2017, Response: The documents mentioned in the IR letter were provided along with attached pages from the (b) (4) system that documented each change, the date of each change and the individual initiating the change. This (b) (4) attachment was made to every document provided by the sponsor continuing to the last amendment submitted. The FDA reviewers were well satisfied by this improvement in the clarity of the document control process. This issue is resolved.*

- 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.

*Oxford Immunotec 12/13/2016 Response: LAB-QA-70 and LAB-QA-71 are obsolete, a new document, LAB-DSGN-3, was provided along with LAB-QA-67 which take the place of the obsolete documents. This response is acceptable.*

- 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.

*Oxford Immunotec 12/13/2016 Response: Most of the documents listed in FDA's question are obsolete and have been replaced with a number of new documents covering these Design Review procedures. The new documents were attached to the response, examined by FDA reviewers and found acceptable. This issue is resolved.*

- 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.

*Oxford Immunotec 12/13/2016 Response: The Design History File has been reworked as described in the previous parts of this question.*

*FDA: The procedures for design change and verification/validation of a device change were assessed during the PLI; reference EIR section "Design Controls: AFIA Design Controls".*

This issue is resolved.

#### Instruments and Software:

The expert reviewer for software and instrumentation, Lisa Simone, PhD, PRB/DETDD, reviewed the software submissions and amendments interactively between May12, 2015 and December 19, 2017. She has provided a final review memo recommending that the software and instrumentation is approvable. Dr. Simone's memo,

(b) (4), is available to provide complete details. Excerpts from The Appendix 1 of her final memo, which specifically addresses the resolution of the questions in the September 29, 2015 Complete Response letter are inserted below.

- 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>. Please also consult a possible example of a FMEA table available at: <http://asq.org/learn-about-quality/process-analysis-tools/overview/fmea.html>.

Response: *In the amendment received December 13, 2016 in response to FDA Question 34, the applicant provided risk analysis information including reference to the risk analysis, (b) (4) Risk Analysis IT-CSV-PDF-41.*  
The response was inadequate.

Comments: *The following was included in the February 17, 2017 communication for the NAT submission (BL 125588) as FDA Question 17. The resolution to this issue has been copied from the NAT memo and provided below, as it is applicable to this submission.*

*In your NAT Amendment response received December 14, 2016 in response to FDA Question 29 and in your AFIA Amendment received December 13, 2016 in response to FDA Question 34, you provided risk analysis information including reference to the risk analysis, (b) (4) Risk Analysis IT-CSV-PDF-41.*

*a. In your response, you stated that the risk management document “[r]eferences mitigation plan, documented in SRS.” The file includes mitigations, but no numerical traceability from the risk ID to the SRS. Please provide this traceability. The Traceability Matrix “IT-CSV-IMD14-16-TM” embedded in your response document references Risk IDs that appear to be the Risk IDs in this document, but this is not explicitly stated. Please clarify this and provide updated documentation.*

*b. This file does a better job of identifying individual risks than the document “B. microti AFIA Device Risk Analysis” (Attachment- 33.5\_LAB-DSGN-5.xlsx) and nicely allows the reader to use filtering to explore the effects of different causes and the scope of different mitigations. However, harm is not explicitly stated and too many “Potential Effects” are listed for each Risk ID. Some “Hazards” include cause information. Similar to the Device Risk Analysis, please update and provide this analysis to align better with ISO 14971 to leverage its benefits.*

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



Note: this was resolved in the NAT submission, and the resolution cut-and-pasted below. All file references are to NAT documentation.

Response a: In the amendment received March 23, 2017 in response to FDA Question 17, the applicant provided an updated Traceability Matrix IT-CSV-IMD14-16-TM, (b) (4) Traceability Matrix” (Attachment 15.2) with the requested traceability information.

This is adequate.

Response b: In the amendment received March 23, 2017 in response to FDA Question 17, the applicant provided an updated FMEA risk analysis (Attachment\_15.1-IT-CSV-PDF- 41.xlsx) to better align with ISO 14971. The applicant refers to this as an “FMEA,” which it is not. It is table with some FMEA columns and some ISO 14971 columns but lacking sufficient information for either.

There continues to be misunderstandings, as described in the Comments section below.

Response c: In the amendment received March 23, 2017 in response to FDA Question 17, the applicant stated that other mitigations requested are included in LAB-DSGN-11, “NAT Device Risk Analysis” and LAB-DSGN-5, “AFIA Device Risk Analysis”. The software specific risks are addressed in Attachment 15.1, IT-CSV-PDF-41, (b) (4) Risk Analysis”. These updated documents were also referenced in the AFIA submission (BL125589) and the same concerns exist.

Additional questions on content and harmonization are described in the Comments section below.

Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 9, and was included in the Complete Response letter sent June 13, 2017 as FDA Question 15:

Risk processes: In the NAT amendment received March 23, 2017 in response to FDA 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-LABDSGN- 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.*

*Response: In the complete response (001\_BLI25588-NAT Complete Response.pdf) received October 10, 2017 in the response to FDA Question 11 on PDF page 25, the applicant provided updated risk management information.*

*(a) The applicant stated that they revised their risk assessment processes to comply with ISO 14971 in LAB-MEM-38, “Memo on Risk Management” (Attachment 6.9). Several changes in their processes were made, such as ensuring potential causes related to a specific hazard and foreseeable events are documented with specific links to outcome malfunctions. Hazardous situations are clarified and assessed according to ISO 14971, probability of harm from hazardous situations has been added, a “risk probability number” is added, and mitigations are assessed individually to determine effects on risks separately. Risks to harm from both manufacturing process failure and assay process failure are included.*

*The risk processes are significantly improved from previous submissions. A note about a conflict with the term, “Risk Probability Number” should be sent to clarify any confusion – see the Comments section.*

*(b) Methods to determine the new probability level are included in the memo, with examples in Section 3. This is adequate.*

*(c) The applicant stated that the risk formats were harmonized as requested. This is adequate.*

*Comments: The following was emailed to the applicant on November 9, 2017 as new FDA Question 4:*

*In the complete response, in your Memo on Risk Management (029\_Attachment-6.9\_LABMEM- 38& Doc Details.pdf) you described updates to your risk assessment methods to comply with ISO 14971 and provided clear instructions and examples. As a minor note, you defined “Risk Probability Number (RPN)” as the product of Severity, P1 and P2.*

*Calculating risk this way is acceptable. However, please be aware that the acronym “RPN” is used heavily in industry as “Risk Priority Number” and refers to a different concept. To avoid confusion, you should refer to your risk calculation differently (perhaps “Risk Number (RN)” ), or simply call it what it is: Risk.*



Response: *In the amendment (001\_Response to IR Received 9Nov2017\_NAT.pdf) received November 20, 2017 in response to FDA Question 4, the applicant stated that the terminology has been modified and documents will refer to “Risk Number” and “RN”.*

Comments: The response is acceptable. **Resolved.**

35. You provided Software Requirements Specifications (SRS) in the document (b) (4) 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.

Response: *In the amendment received December 13, 2016 in response to FDA Question 35, the applicant provided an updated SRS where information has been inexplicably removed. The response was inadequate.*

Comments: *The following was included in the February 17, 2017 communication for the NAT submission (BL 125588) as FDA Question 16. The resolution BL 125589/0 Software and Instrumentation Review to this issue has been copied from the NAT memo and provided below, as it is applicable to this submission.*

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

Note: *this was resolved in the NAT submission, and the resolution cut-and-pasted below. All file references are to NAT documentation.*

Response: *In the amendment received March 23, 2017 in response to FDA Question 16, the applicant stated that requirements “relevant to IT infrastructure for general lab operation ... is beyond the scope of the (b) (4) software” and were removed. Unfortunately, performance requirements are very relevant for their throughput and capacity claims, which don’t appear in the requirements. These should be added back, with testable criteria, and corresponding test results to show that the underlying infrastructure can support the device intended use. The sponsor’s response was inadequate.*

Comments: *The following was sent to the applicant on April 14, 2017 as new FDA Question 1, and was included in the Complete Response letter sent June 13, 2017 as FDA Question 6:*

*Performance requirements for (b) (4) hardware and software: In the NAT amendment received March 23, 2017 in response to FDA Question 16, you stated that 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 BL 125589/0 Software and Instrumentation Review 30 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.*

Response: *In the complete response (001\_BLI25588-NAT Complete Response.pdf) received October 10, 2017 in the response to FDA Question 6 on PDF page 7, the applicant provided additional information.*

- (a) Architectural design information and updated components of the system were provided to illustrate system boundaries and facilitate development of the applicant’s risk documentation.*
- (b) Requirements were updated and untestable requirements were changed to address the issues. Untestable specifications were corrected and retested. Additional requirements were added to ensure the infrastructure can support (b) (4) performance needs.*
- (c) An FDA consultant was hired who reviewed testing of performance requirements; updated test plans and results were provided.*
- (d) Updated traceability was provided.*
- (e) Risk documentation was updated with performance-related risks and countermeasures implemented to reduce risk to acceptable levels.*

Comments: The response is acceptable. **Resolved**.

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.

Response: *In the amendment received December 13, 2016 in response to FDA Question 36, the applicant provided an updated architecture diagram in Attachment 34.4.*

Comments: This response is acceptable. **Resolved**.

37. You provided a software design specification document (Attachment 4-5-6 SDS(b) (4) IMUGEN.pdf) for the (b) (4). The document includes the modules of the (b) (4) 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.

Response #1: *In the amendment received December 13, 2016 in response to FDA Question 37, the applicant provided an updated SDS in Attachment 34.5 that is missing testable details and test case information. The response was inadequate.*

Response #2: *In the amendment received December 13, 2016 in response to FDA Question 37, the applicant provided an updated SDS in Attachment 34.5 that does not contain explicit design specification information traceable to requirements. The response was inadequate.*

Comments #1: *To resolve the issue of testable details, the following was included in the February 17, 2017 communication for the NAT submission (BL 125588) as FDA Question 18. The resolution to this issue has been copied from the NAT memo and provided below, as it is applicable to this submission.*

*In your NAT Amendment response received December 14, 2016 in response to FDA Question 32 and in your AFIA Amendment received December 13, 2016 in response to FDA Question 37, you stated that for the (b) (4) software, you included an updated Software Design Specification and Traceability Matrix that "contain measurable and*

testable values.” Thank you for providing these updates and the detailed information. Several Risk ID/SRS entries in your traceability table do not trace to software design specifications, and some trace to testing that does not appear to relate to the corresponding risk/requirement. This makes it difficult to assess the adequacy of your proposed mitigations. Note that necessary testing at the unit, integration and system level is often different and more comprehensive than qualification testing.

a. For example, Risk ID 24/SRS 24 addresses a risk that PCR results might be modified. No design information was provided on how this would be performed, and the referenced V&V test cases don't appear to test any attempts to modify PCR results to ensure the risk is properly mitigated. The tests are

"Script (b) (4)  
" and "Script (b) (4)  
." Step (b) (4)

How do these tests verify that software prevents any modification of the PCR results? Please provide the correct documentation.

b. Risk ID 34/SRS34 involves risk of loss of sample origin, but has no associated SDS. The requirement itself is vague and the corresponding testing refers to step (b) (4) of a test script. However, the test script ends after (b) (4) steps.

Please clarify the risk and requirement, and provide corrected documentation.  
c. Risk ID 39/SRS 39 refers to a test script that was not provided. This portion of the testing documentation is blank. Please provide the correct documentation.

d. Risk ID 49/SRS 49 does not include testable information and is not traceable to an SDS. Some of the relevant information appears in the test case; however, specifics of the device design should be captured in the requirements and specification documentation, and not documented solely in testing documentation. Please update your SRS and/or SDS with the appropriate design information accordingly, and provide the correct documentation.

e. Risk ID 51/SRS 51 and Risk ID 52/SRS 52 specify software by version number “or later.” Your requirements should apply to a specific version or versions with testing corresponding to those versions. Please remove reference to “or later” for any software used in the system, including in any labeling, and ensure explicit versions are referenced. This is not a complete list of issues, but a representative sample of concerns. Please review and update the remainder of the document for traceability and accuracy issues. For requirements that have no corresponding design specification, clarify why an SDS is not necessary.

Note: this was resolved in the NAT submission, and the resolution cut-and-pasted below. All file references are to NAT documentation.

Response #1 for CR Question 37: In the Amendment received March 23, 2017 in response to FDA Question 18, the applicant addressed each of the Risk/SRS pairs enumerated in the FDA Question: (a) was clarified, (b) has been corrected with correct validation, (c) supplemental testing was provided. For (d), testing details were augmented, (e) references to “or later” were removed, and traceability and SRS documents were updated accordingly.

Comments #1: The response is acceptable. **Resolved.**

Comments #2: *To resolve the issue of explicit design specification information traceable to requirements the following was included in the February 17, 2017 communication for the NAT submission (BL 125588). The resolution to this issue has been copied from the NAT memo and provided below, as it is applicable to this submission.*

*In your NAT Amendment response document received December 14, 2016 in response to FDA Question 32 and in your AFIA Amendment response received December 13, 2016 in response to FDA Question 37, you provided a Software Design Specification document. This version 1.1 of the document does not appear to be substantially changed over version 1.0 provided in your original submission. Many screen shots are presented but it is not always apparent what has changed from one screen to the next, what is expected to appear on the screen, what information the user entered, and what are the system responses when the user does something unexpected. Each of these specifications should include explicit text about what should appear on the screen and what the device and/or user is expected to do. It is not sufficient to collect screen shots of a completed system and state that these encompass a software design specification without additional information. It is not reasonable to expect a designer/tester/reader to compare successive screen shots to determine for themselves what has changed between the two screen shots. This increases the opportunity for misunderstanding, inadequate design and testing.*

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

*Note: this was resolved in the NAT submission, and the resolution cut-and-pasted below. All file references are to NAT documentation.*

*Response #2: In the Amendment received March 23, 2017 in response to FDA Question 19, the applicant provided updated versions of the Risk Analysis, Traceability Matrix, SRS and SDS referred to above (Attachments 15.1, 15.2, 15.3 and 18.1, respectively). The Software Design Specification contains significantly more detailed and testable information to accompany the previous screen shots, and the corresponding testing is provided and included in the other design documentation.*

Comments #2: The response is acceptable. **Resolved.**

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.

*Response: In the amendment received December 13, 2016 in response to FDA Question 38, the applicant provided an updated traceability matrix in Attachment 34.3. The applicant enumerated each of 58 Risk IDs and corresponding requirements, and stated that testing information appears in relevant IQ and OPQ reports. IQ and OPQ testing are not the same as verification and validation testing outlined in part (a); the applicant did not provide adequate testing documentation.*

The response was inadequate.

*Comments: The following question was included in the AFIA Complete Response letter sent June 13, 2017 as FDA Question 9. The applicant was informed that some AFIA questions contained NAT references, but applied to both.*

*In the NAT amendment received December 14, 2016, in response to FDA 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) of Question 33. 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.*

*Response: Identical information was provided for the NAT and AFIA responses, although an additional follow-up question was sent for the NAT that also applies here. Therefore, what appears below is the NAT resolution of this common deficiency:*



*In the NAT complete response (001\_BLI25588-NAT Complete Response.pdf) received October 10, 2017 in the response to FDA Question 7 on PDF page 12, the applicant provided Attachment 13.3, “(b) (4) Submissions Table” that indicates all documents sent to the FDA with their date of submission, the relevant attachment number, the relevant software version, and whether the document is now obsolete. This is extremely helpful because multiple versions of documents have been sent over the last two years. Table 7.1 on page 14 lists all the individual types of tests performed, an explanation of the test, justification, and test activity (with file name).*

*The testing plan and strategy for v1.0.5.5 was provided, and was revised to include unit, integration, and system level testing. The updated test plan and test report were provided for version Build 1.0.5.5 (024\_Attachment-6.4\_IT(b) (4)-1 &Doc Details.pdf, 025\_Attachment-6.5\_IT(b) (4)-2 &Doc Details.pdf) and includes the testing types and computers involved. All requirements were met.*

*Comments: The following was emailed to the applicant on November 9, 2017 as new FDA Question 1:*

*In the complete response (001\_BLI25588-NAT Complete Response.pdf) received October 10, 2017 in the response to FDA Question 7 on PDF page 12, you provided a table of testing activities. We were unable to locate the test protocol results that correspond to IT(b) (4) SPT- 24 (b) (4) CyberSecurity Test Protocol” and IT-(b) (4)-SPT-17 (b) (4) System Uptime Test Protocol.” Please provide these test case results. This is necessary to confirm the claim that all requirements have been correctly implemented.*

*Response: In the amendment (001\_Response to IR Received 9Nov2017\_NAT.pdf) received November 20, 2017 in response to FDA Question 1, the applicant stated that the test results were inadvertently omitted, and provided the requested information.*

*The testing is adequate.*

*Comments: The response is acceptable. Resolved.*

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.



Response: *In the amendment received December 13, 2016 in response to FDA Question 39, the applicant provided an Information Technology Security Policy in Attachment 34.6 that is not related to security concerns during device operation.*

The response was inadequate.

Comments: *The following was included in the February 17, 2017 communication for the NAT submission (BL 125588) as FDA Question 20. The resolution to this issue has been copied from the NAT memo and provided below, as it is applicable to this submission.*

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

*a. Please refer to the FDA guidance and provide updated cybersecurity information for your device to address the elements listed in the guidance: "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" located at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356190.pdf>. This should include, in part, the following: hazard analysis, mitigations, and design considerations pertaining to intentional and unintentional cybersecurity risks associated with your device, and a traceability matrix that links your actual cybersecurity controls to the cybersecurity risks that were considered.*

*b. Please describe your process for identifying and evaluating new operating system patches and other updates to off-the-shelf software and integrating patches and updates into your device.*

Note: *this was resolved in the NAT submission, and the resolution cut-and-pasted below. All file references are to NAT documentation.*

Response: *In the Amendment received March 23, 2017 in response to FDA Question 20, the applicant stated the referenced information was reviewed. In response, the applicant created a "Business Continuity and Disaster Recovery Plan" (Attachment 20.1 Attachment\_20.1- DOC-POL-1.pdf) that focuses on business risk and includes data backup and recovery plans. The*

*applicant also provided a substantial update to the “Information Technology Security Policy” (Attachment\_20.2-IT-SEC-POL-01&DocDetails.pdf) that includes policies for accounts management, password management, encryption, data security, and software patches and updated, including antivirus updates. The applicant also pointed to the updated “(b) (4) Risk Analysis” (Attachment\_15.1-IT-CSV-PDF-41.xlsx). These are not adequate to answer the questions posed.*

*The applicant has not provided documentation aligned with the FDA guidance document. The risk management should include entries for all identified cybersecurity related risks to link these risks to the mitigations implemented, but this has not been done.*

*Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 10, and was included in the Complete Response letter sent June 13, 2017 as FDA Question 16:*

*Cybersecurity considerations: In the NAT Amendment received March 23, 2017 in response to FDA 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.*

- 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.*
- 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.*
- 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.*
- 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.

Response: In the complete response (001\_BLI25588-NAT Complete Response.pdf) received October 10, 2017 in the response to FDA Question 12 on PDF page 27, the applicant provided requested information and stated that their design documentation was updated to align with the analysis described in the premarket cybersecurity guidance document, as outlined on page 32.

(a) The applicant stated that a full review of security risks was conducted using the new risk management procedure (Attachment 6.9) and documented in the cybersecurity risk analysis DOC-RSK-9, “Cybersecurity Risk Analysis” (Attachment 12.1). Traceability to associated design control documentation was provided. The response document provides a good overview of the analysis.

(b) The applicant clarified the vulnerabilities and relevance of the document in Tables 12.4 and 12.5 on page 30.

(c) The applicant stated risks of unsecured USBs and other external device ports is included in the Cybersecurity Risk document, DOC-RSK-9 (Attachment 12.1) and enumerated in Table 12.6 on page 31.

(d) The applicant provided the Cybersecurity Risk Assessment (DOC-RSK-9, Attachment 12.1) that includes risks and appropriate mitigations for potential computer misuse. (b) (4) vulnerabilities were identified and discussed in Table 12.7 on page 32.

Comments: The response is acceptable. **Resolved**.

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.

Response: In the amendment received December 13, 2016 in response to FDA Question 40, the applicant stated that reports are sent manually by email in PDF format or as .csv file via secure FTP.

The response is acceptable.

Comments: The response is acceptable. **Resolved**

#### Facility:

The following questions are dealing with the disciplines reviewed by committee members from the Office of Compliance and Biologics Quality/Division of Manufacturers and Product

Quality. Lori Peters, the lead Facility Reviewer, provided a memo covering the first CR letter (DMPQ Memo 1) available at

(b) (4) and a final memo (DMPQ Memo 2) that can be accessed at

(b) (4) which provide complete details including a final recommendation for approval. Excerpts from these memos, which specifically address the resolution of the questions in the September 29, 2015 Complete Response letter are inserted below. Some of the facilities issues were dealt with in the Pre-license Inspection (PLI) as 483 items. The PLI issues are covered in a separate Establishment Inspection Report (EIR), (b) (4) and 483 Response Memo (483Memo),

(b) (4) Each of these documents will be cited where appropriate below.

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.

*Oxford Immunotec 12/13/2016 Response:*

- a. More details were provided and the facility layout was assessed during the inspection, reference EIR section "Facility Design".
- b. Security access and restrictions were reviewed during the PLI; reference EIR section "Security" for additional details.
- c. The PLI was scheduled to occur after the sponsor responded to the first CR letter. See EIR and 483Memo for details. This issue is resolved.

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. Include in your narrative a complete description of all manufacturing activities or donor testing that occurs in each room and the facility controls you have in-place to prevent cross-contamination.

*Oxford Immunotec 12/13/2016 Response:* The response included two figures, one figure for each of the (b) (4) lab areas; each figure was labeled with additional details regarding the activities that occur in each room.

*FDA: The evaluation of the flow paths of materials and personnel was observed during the PLI, reference EIR sections “Facility Walk-Thru”, “Production Systems”, and “Donor Screening Systems”. This issue is resolved.*

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).

*Oxford Immunotec 12/13/2016 Response: Manufacturing occurs on a campaign basis. Equipment and lines are cleared and cleaned according to LAB-SAF-MLE-8 and LAB-SAF-MLE-2. These documents were attached.*

*FDA: As Imugen is not solely dedicated to *B. microti* manufacture, the cleaning of the equipment, especially of the biosafety cabinets, is paramount. Imugen will need to show that the cleaning procedure effectively remove (b) (4) antigen in order to prevent cross-contamination. Imugen has not provided a complete description identifying the facility controls that are in-place to control to prevent contamination or mix-up. Additional information was requested in the CR Letter regarding the manufacturing flow and prevention of cross-contamination.*

*FDA’s second CR letter (June 13, 2017) pursued this matter within the Inspectional Issues (question #1 of the CR letter).*

*The issue was resolved in the 483Memo.*

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.

*Oxford Immunotec 12/13/2016 Response: All cleaning/disinfecting is done by wiping surfaces, equipment and treating floors with (b) (4) according to SOP LAB-SAF-MLE-1, LAB-SAF-MLE-2.*

*FDA: The facility cleaning practices were reviewed during the PLI which included the aforementioned SOPs; for further details, please reference the EIR, section “Facility Cleaning”, “Facility Walk-Thru”, and “Production Systems: NAT Process Operations Observed”. Excerpt from 483Memo p 54: “Overall, the cleaning process appears satisfactory for cleaning of the biosafety cabinets and benchtop surfaces given the IVD products manufactured in the facility. No further issues are noted regarding the cleaning process.”*

*This issue is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: All manufacturing occurs in (b) (4) temperature controlled manufacturing rooms or Biosafety Cabinets as appropriate for the particular manufacturing step.*

*FDA: The HVAC system including the filters and maintenance of the system was reviewed during the PLI, reference EIR section "Heating, Ventilation and Air Conditioning (HVAC)". The issue was pursued further in an IR letter, Dec. 15, 2017, to BLA 125588 because these facilities where both manufacturing processes take place apply equally to BLA 125589 as well. The question (#28): "Please provide documentation identifying the preventive maintenance and calibration activities for the facility items."*

*Oxford Immunotec 1/9/2018 Response: A new "Operation and Preventative Maintenance of the HVAC System" document was provided.*

*FDA: Overall, Imugen has provided the procedures identifying the preventive maintenance activities for the facility and has satisfied this observation and request.*

*This issue is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: The manufacturing occurs in an (b) (4) space, monitoring sites were described in response to question 41c and temperature monitoring logs were provided.*

*FDA: The lack of particulate monitoring may be acceptable for an in-vitro assay permitted the results of spiking studies or interference studies are acceptable and demonstrate that the assay will function as intended (i.e. no false positives or false negatives) due to particulate contamination in the facility or BSCs.*

*This issue is resolved.*

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.

*Oxford Immunotec 12/13/2016 Response: A table was provided listing the components manufactured with the specific water type.*

*FDA: The maintenance of the (b) (4) water system and the use of the (b) (4) water were reviewed during the inspection, reference EIR section "Water Systems".*



*EIR Discussion Point #10: “following the discussion with [sponsor personnel] regarding the water quality since the use did not appear to require (b) (4) water, Imugen should evaluate their water requirements and if it is determined that a component requires (b) (4) water, an evaluation regarding the (b) (4) of the water at the (b) (4) is necessary to confirm the (b) (4) is meeting (b) (4) limits for (b) (4) water.*  
This issue is **resolved**.

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).

*Oxford Immunotec 12/13/2016 Response: Imugen is requesting a categorical exclusion of an environmental assessment based on 21 CFR 25.31(c). The justification for this categorical exclusion is that, to Imugen’s knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.*

*FDA: This justification is not satisfactory as Imugen has not explained why their product meets the intent of 21 CFR 25.15(d). Therefore an item was added to the FDA CR letter of June 13, 2017:*

*#18. Your justification for a categorical exclusion from preparation of an environmental assessment for the AFIA assay is not satisfactory as provided in your December 13, 2016, Complete Response Letter to Item #48. Please revise your justification to indicate how your finished device lots for the AFIA assay meets the exclusion criteria.*

*Oxford Immunotec 10/10/2017 Response: Imugen is requesting a categorical exclusion of an environmental assessment based on 21 CFR 25.31(c), which states that, “Action on...a biologic product...for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment,” are categorically excluded from environmental impact considerations and, therefore, ordinarily do not require the preparation of an EA or an EIS.*

*FDA: The justification provided by Imugen is acceptable as they describe the reagents contain constituents which are naturally occurring and that the assay components are used as a laboratory based test and are not consumed or injected in to the body and excreted as waste.*

The request is **acceptable**.

49. Please note that a pre-license inspection is required for your Norwood, MA facility prior to approval of your biologic license application.



*Oxford Immunotec 12/13/2016 Response: Imugen understands the requirement for FDA pre-license inspection.*

*FDA: A pre-license inspection of the Imugen facility in Norwood, MA was performed by representatives from DMPQ, DETTD, and ORA from March 6-10, 2017. Details regarding the inspection can be referenced in the Establishment Inspection Report (EIR).*

This issue is **resolved**.

#### 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.

*Oxford Immunotec 12/13/2016 Response: A table was included in the response which lists the critical pieces of equipment used for B. microti AFIA device manufacture or testing.*

*FDA: The listing is sufficient. However, the cleaning procedures and cleaning agent (b) (4) will be important to understand as most of the equipment is shared (though used on campaign basis). This issue was further reviewed in the Pre-license Inspection. Refer to EIR Section 12, "Equipment" and 483memo Item #26 (p 88 of the 483memo).*

This issue is **resolved**.

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.

*Oxford Immunotec 12/13/2016 Response: Installation qualifications were performed and approved on incubators, (b) (4) and BSCs, new documents were submitted.*

*FDA: DMPQ performed a review of the three documents provided in the response. The results of the IQ/OQ demonstrate the BSCs are operating within the ranges for airflow patterns and air velocities are maintained. Overall, the results appear satisfactory and indicate the BSCs are operating normally (i.e. no performance loss, operation within*

operating airflow ranges). During the PLI, the maintenance procedure was reviewed along with the daily use log and the maintenance log; further details can be referenced in the EIR section "Biosafety Cabinets".

This issue is resolved.

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.

*Oxford Immunotec 12/13/2016 Response: All cleaning/disinfecting is done by wiping with (b) (4) in accordance with SOPs.*

*FDA: During the PLI, the cleaning of the equipment was evaluated. Reference EIR sections "Incubator" (p 47) and (b) (4)" (p 47). The review of this issue continued as 483 Observation #13. As stated in the 483memo (p 61): Overall, the reports demonstrate that the cleaning method ((b) (4)) are satisfactory at removing the B. microti (b) (4) microorganisms from stainless steel and epoxy surfaces in the facility. The issue of cleaning effectiveness has been resolved.*

This issue is resolved.

#### 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.

*Oxford Immunotec 12/13/2016 Response: the sponsor agreed to use the recommended Intended Use Statement.*

This issue is resolved.