



FINAL REVIEW MEMORANDUM

Date Received: May 12, 2015
Amendments: May 19, 2015
Jun 12, 2015
Jul 03, 2015
Aug 25, 2016
Sep 16, 2016
Dec 14, 2016
Mar 07, 2017
Mar 23, 2017
Apr 13, 2017
Apr 17, 2017
May 03, 2017
May 05, 2017
May 18, 2017
May 23, 2017
Jun 05, 2017
Jun 13, 2017
Oct 10, 2017
Oct 26, 2017
Nov 20, 2017
Dec 01, 2017
Jan 09, 2018
Jan 29, 2018
Feb 06, 2018
Feb 14, 2018

Reviewer: Babita Mahajan, Ph.D., PRB/DETDD

Through: David A. Leiby, Ph.D., Chief, PRB/DETDD
Pradip N. Akolkar, Ph.D., PRB/DETDD

To: Iliana Valencia, OBRR/IO
RPM: Iliana Valencia, OBRR/IO

Product: Imugen *Babesia microti* Nuclei Acid Test (NAT)
Sponsor/ Applicant: Oxford Immunotec Ltd.
STN: BL125588

Scientific Disciplines Reviewed: Whole submission

Recommendation: The Review Committee recommends approval of this product

Purpose

IMUGEN, Inc. (Oxford Immunotec Ltd. following ownership transfer), located in Norwood, MA, submitted an original Biologics License Application (BLA) for licensure of the *Babesia microti* Nucleic acid test. This is a first blood donor screening assay intended for the specific detection of *B. microti* DNA. The Imugen *Babesia microti* Nucleic Acid Test is an “in-house” test performed only by the sponsor and no kits are sold.

Intended Use/ Indication for Use

Imugen *Babesia microti* NAT is a nucleic acid screening assay for the detection of *Babesia microti* DNA in human whole blood samples (with EDTA as anti-coagulant). This test is intended for use as a donor screening test to detect *B. microti* DNA in whole blood samples from individual human donors, including volunteer donors of whole blood and blood components, as well as other living donors. It is also intended for use as 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.

The test is not intended for use on samples of cord blood.

This test is not intended for a use as an aid to diagnosis of *Babesia microti* infection.

Past and Concurrent Submissions

- IND 14532 (and its related amendments): Submitted for clinical studies to support the *Babesia* NAT and AFIA assays – received 09/10/2010
- BL125589: Imugen *Babesia microti* Arrayed Fluorescence Immunoassay (AFIA) – received 05/12/2015
- BQ 170068: Submission Issue Meeting Request July 6, 2017 for 483 inspection issues
- BQ 170083: Submission Issue Meeting Request August 4, 2017 for software issues

General Description of the Assay and System

Imugen *Babesia* NAT as described in this BLA submission is an *in vitro* blood donor screening test intended for the detection of specific DNA to *Babesia microti*. The NAT assay can be used as a standalone blood screening application to provide testing of blood donations for evidence of *B. microti* infection. The clinical and analytical studies to support this intended use were conducted under the IND 14532 and its related amendments. The testing using the investigational *Babesia* NAT was performed within IMUGEN’s clinical laboratory by trained staff using dedicated, qualified equipment and instrumentation in assigned, dedicated areas.

The *Babesia* NAT is based on (b) (4) and utilizes the (b) (4) instrument in combination with the (b) (4) for the (b) (4) detection of *B. microti* DNA in EDTA anti-coagulated whole blood samples. The assay employs an internal endogenous human 18S rRNA control (to confirm amplification of a known RNA source in human samples) and *B. microti*-specific assay controls (high positive, low positive, negative, and no template). Custom software called the (b) (4) is used to collect and report data for blood donor sample testing within the Oxford facility.

Review Summary

This BLA application from IMUGEN, Inc. was received on May 12, 2015. This submission was filed on July 10, 2015 and the mid-cycle meeting was held on August 17, 2015. A Complete Response (CR) Letter was issued on September 29, 2015. On July 1, 2016, FDA was informed of an ownership change for BLA 125588 from IMUGEN, Inc. to Oxford Immunotec Ltd. On September 16, 2016, FDA received an amendment from the sponsor requesting an extension of 6 months for its response to FDA's CR Letter dated September 29, 2015. The response to the CR Letter was submitted on December 14, 2016 and the amendment was classified as Class 2 resubmission. An Information Request (IR) Letter was sent on February 17, 2017. CBER conducted an establishment Pre-License Inspection (PLI) of the Oxford Immunotec Inc., d/b/a Imugen (hereinafter referred to as "Imugen") facility from March 6 through 10, 2017. FDA noted serious concerns at the end of the inspection that were conveyed to the sponsor in the form of observations on FDA Form 483. The sponsor responded to the FDA Form 483 observations on April 17, 2017, and it was concluded that the sponsor didn't sufficiently address the concerns noted during the inspection. Additionally, the sponsor had not responded and resolved the software and instrumentation deficiencies. A second CR Letter was issued on June 13, 2017. Two submission issue meetings were requested to discuss 483 inspection issues (BQ170068) and software issues (BQ170083), however, the sponsor was satisfied with the written responses provided by the review committee and the meetings were cancelled. The response to the CR Letter was submitted on October 10, 2017 and the amendment was classified as a Class 2 resubmission.

The review of the analytical and clinical performance of the Imugen *Babesia microti* NAT device is documented in the Summary Basis of Regulatory Action document (available in EDR). It also documents the major review issues identified and their resolution. The first CR letter was issued on September 29, 2015. The details of the deficiencies; their resolution and/or further questions raised are documented in Appendix I. The second CR letter was issued on June 13, 2017; with major focus on inspectional 483, and software and instrumentation issues. The details of the deficiencies; interactive review, and traceability to their resolution is documented in Appendix II.

For each donor screening test a lot release by CBER/FDA is required. Typically, for each donor screening test a lot release testing plan is developed by the sponsor, approved by CBER, and used for routine lot release testing/FDA panels developed for that purpose. For testing services,

however, CBER conducts lot release testing of each “finished device lot,” which in this case is defined as a set of independent lots of matched critical reagents including primers, probes, master mix, assay controls and other components that form a functional in-house assay system. Each time any critical reagent is changed, this results in a new lot that is subject to the lot release process. Imugen performed testing of 3 lots of the *B. microti* NAT kit as defined above on the blinded CBER *B. microti* NAT Lot Release Panel and submitted data in an approved Lot Release Protocol. The results of testing of three conformance lots of the Imugen *Babesia microti* Nucleic Acid Test were evaluated and found to be acceptable by CBER.

Results of Conformance Lot Release Testing

Batch ID	Expiration Date	Kit Lot Pass/Fail
(b) (4)		Pass
		Pass
		Pass

Appendix I

Interactive Review

The following questions were provided in the CR letter of September 29, 2015. The response to the CR letter was submitted on December 14, 2016. An IR letter was sent on February 17, 2017 and the responses were received on March 1, 2017 and March 23, 2017. A follow-up IR was sent on April 14, 2017 to software and instrumentation questions. The responses to those questions were not received and were part of second CR letter.

Clinical:

1. **FDA CR#1 Question 1:** *You have not provided data for the clinical sensitivity of the Babesia NAT. In the clinical hold letter to IND 14532 dated December 10, 2010, we requested that you demonstrate the clinical sensitivity of this test in human samples that are blood-film positive for B. microti. Please provide data to demonstrate the clinical sensitivity of your assay in confirmed clinical Babesia positive samples.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has stated that they have conducted the study to determine the clinical sensitivity of the *Babesia* NAT by testing 72 human samples that were blood-film-positive for *B. microti*. They have provided the study protocol and summary of the data as attachments 1 and 2. As the part of interactive review they also submitted the line data for the 72 samples (Pages 1-3 of 85).

Comments: The responses are acceptable. Resolved.

2. **FDA CR#1 Question 2:** *In the clinical section, analysis of the data submitted in BAFSBLA.xlsx and MSTDONOR.xlsx, identified significant protocol deviations. The protocol for human 18S internal control testing (Page 259.17, document 021_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states, “Ct values for the human 18S internal control should be (b) (4) at a threshold setting of (b) (4) for all negative samples and controls. Any Babesia negative sample with a Hu18S Ct value of (b) (4) will be repeated from amplification. If the Ct value does not meet specifications after repeat testing, consult a supervisor.” There are a total of 327 samples where the internal Hu18S PCR Ct ranged from (b) (4) . Repeat testing was not performed on these samples as per the protocol.*
 - a. *Please clarify why the SOP of repeat testing was not followed when Ct values for Hu18S were (b) (4) for several of these specimens.*
 - b. *Please exclude these samples from data analysis and instead report them as protocol deviations and provide a separate excel worksheet with all excluded data. Alternatively, please perform new testing on samples where the SOP was not followed and submit the results for review to FDA.*

- c. *Please clarify what steps are taken by the supervisor to resolve out of specification results and how such test results are resolved and reported to the end user (i.e., blood establishments).*

Response a: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor stated that they have re-reviewed the Human 18S data for all the clinical studies and have made adjustment to the data sets; and have included the information on pages 3-5 of 85.

b: The sponsor has updated the MSTDONOR.xlsx database and to ensure a consistent evaluation at the current cut-off specification for Ct value of (b) (4), all samples with Human 18S values (b) (4) that were not repeat-tested have been excluded. They have provided the updated data.

c: The sponsor has clarified the steps to resolve out of specification results and how such test results are resolved and reported to the end user (Page 5-6 of 85).

Comments: The responses are acceptable. Resolved.

3. **FDA CR#1 Question 3:** *Similar to what is described above for Hu18S Ct Values, the protocol is not followed for Babesia specific amplification. For the Babesia NAT, the protocol (Page 259, 17, document 021_Attachment 4-2-3-17 LAB-MOL-BPCR-10) states that “Samples with Babesia-specific Ct values (b) (4) will be repeated. The original sample will be (b) (4).” Further, the Figure 8.4.1.2: “Testing Flow Chart, 002_8-4-1 CSR study 1, Page 1595, indicated Babesia NAT will be repeated if Ct (b) (4).*

- a. *Please clarify at what Babesia-specific 18S Ct value the repeat testing is done (i.e., (b) (4))*
- b. *Please reanalyse the data using a consistent measure to determine positivity of the sample.*

Response a: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has clarified that Clinical Study 1 was exploratory and no data from that study were intended to be used to establish clinical sensitivity for the final assays. They further stated that “*For the clinical studies used to establish sensitivity and specificity (Studies 2 and 3a), blood donor specimens tested for Babesia using the investigational NAT assay follow protocol LAB-MOL-BPCR- 10: “Babesia microti Detection by Nucleic Acid Test for Use on Blood Donor Screening,” provided as Attachment 4. Per this SOP, all Babesia positive NAT specimens are repeated. Section 8.2.1-b-v., on page 24, states, “Blood Donor Samples with Babesia-specific Ct values due to an exponential curve (b) (4) will be repeated.”*”

b: The sponsor clarified that as the cut-off of ^{(b) (4)} was consistently used to determine positivity in Clinical Studies 2, 3a, 3b, and 4; therefore no re-analysis was needed.

Comments: The responses are acceptable. Resolved.

4. **FDA CR#1 Question 4:** *In the data provided in document MSTDONOR.xls, there are 707 samples where line item data for the Babesia 18S Ct and the Hu18S Ct value columns are blank. However, the donor test results are interpreted as “negative” (i.e., no Babesia DNA was detected for these 707 samples). This is a significant deviation from the IND protocol for these prospective blood donations. Please clarify why these specimens were not classified as invalid and why the testing was not repeated for these specimens rather than classifying them as Babesia negative. Please report these samples as invalid results and exclude them from analysis.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has stated that these values were excluded from the MSTDONOR.xlsx due to result transcription error and not to a protocol deviation. They have reexamined the records and have provided an updated MSTDONOR.xlsx spreadsheet containing the corrected data (Attachment 6).

Comments: The response is acceptable. Resolved.

5. **FDA CR#1 Question 5:** *In the document 002_8-4-1 CSR study 1 (Page 15) it is stated that “The NAT method used in this study differs in 2 respects from the NAT method used in the NAT assay that will be licensed: 1. The extraction method used in this study is less sensitive than the current NAT method. 2. The NAT testing in use at the time of this study did not incorporate Human 18S RNA as an endogenous internal control.”*

- a. *Please clarify why the investigational NAT assay was not used to conduct this study.*
- b. *Please provide an excel document for the CSI data used to generate attachments 8.4.1.1, 8.4.1.2 and 8.4.1.3.*

Response a, b: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has clarified again (as in earlier response) that Clinical Study 1 was exploratory and no data from that study were intended to be used to establish clinical sensitivity for the final assays.

Comments: The response is acceptable. Resolved.

6. **FDA CR#1 Question 6:** *Please provide a summary table showing the lots of Babesia NAT manufactured by IMUGEN that were used in the clinical studies described in the BLA. For each lot (including positive and negative controls), please provide the lot*

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

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided spreadsheets (Attachment 10) with the information for the lots of the NAT assay components used for Clinical Studies 2, 3a, 3b and 4.

Comments: The response is acceptable. Resolved.

7. **FDA CR#1 Question 7:** *For each study’s data summary, please display the data as a 2X2 table with results for the test under review in rows and the results of the comparator in columns. In cases where there are three outcomes (i.e., positive, negative, inconclusive) the data may be displayed in 2X3 or 3X3 tables.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the summary of the data supporting sensitivity and specificity of the clinical studies in 2/1, 2/2 or 2/3 table format, as appropriate (Pages 8-11 of 85).

Comments: The response is acceptable. Resolved.

8. **FDA Additional question** dated Nov 11, 2016: *The following comments apply to the data contained in the document MSTDONOR_PROSPECTIVE, Attachment-6_BCR-PCR-ATT-6”*

- a. *The line data for samples (b) (6) have only (b) (4) PCR repeat testing result instead of (b) (4) results. Please clarify this deviation.*
- b. *The line data for two samples (b) (6) have similar initial and repeat PCR test results; but their final interpretations are different: one is inconclusive and the other one was negative (see the table below). Please clarify.*

(b) (6) (b) (4)
(b) (6) (b) (4)

(b) (4)

- c. *The line data for two samples (b) (6) has the initial Hu18S Ct result as “Undet,” but the SOP for retesting was not followed. Please clarify this deviation.*
- d. *There is data entry errors observed regarding the PCR repeat testing results for the two samples (b) (6) Please update the data sheet.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided Table 8A clarifying the data associated with identified donor IDs in MSTDONOR_PROSPECTIVE on pages 12-14 of 85 and during interactive review.

- a. For samples (b) (6), the initial *Babesia* Ct value was noted on the test run as a nonexponential curve. Per testing SOP, LAB-MOLBPCR-10, Section 8.2, a non-exponential curve is considered negative and does not require repeat testing.
- b. For samples (b) (6), the initial curve was noted as a real, exponential curve. This result could not be repeated, resulting in the specimen report being “Inconclusive.” For sample (b) (6), the initial *Babesia* Ct value was noted on the test run as a nonexponential curve, but was repeated by error.
- c. For samples (b) (6), the sponsor acknowledges that the samples were retested to produce HU18s result. Missing data was a transcription error that has since been corrected in the STDNR_PROSPECTIVE Spreadsheet.
- d. For samples (b) (6), the sponsor acknowledges that miscellaneous entry was a transcription error that has since been corrected.

Comments: The responses are acceptable. Resolved.

Pre-clinical Studies:

- 9. **FDA CR#1 Question 8:** *The precision and reproducibility studies submitted fail to capture intra- and inter-assay variability, intra- and inter-lot variability, inter-operator variability, and inter-instrument variability. Please follow Clinical Laboratory Standard Institute (CLSI) documents EP05-A3 for designing and performing precision and*

reproducibility studies. Please provide a plan for a proper precision and reproducibility studies with a statistical analysis plan or statistically justify the study presented.

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the protocol (DOC-PRO-26; Attachment 8.1) and data (DOC-RPT-26; Attachment 8.2) of the repeat precision studies.

Comments: The study is acceptable. Minor comment from statistician “In your Table 3 page 6 of 10, Attachment 8.2 (NAT), the overall result of precision study showed that there was one negative result observed with 99.7% agreement in panel of (b) (4) LOD. The acceptance criterion (100%) was not met.” The question was communicated in 2nd CR letter.

10. **FDA CR#1 Question 9:** *The analytical specificity/cross reactivity study has been conducted using seven bacteria species and one yeast species. Please expand the cross-reactivity studies to include the following pathogens (*Plasmodium* sp., *Leishmania* sp., *Trypanosoma cruzi*, and *Borrelia burgdorferi*) as agreed upon in the IND study protocols (IND # 14532).*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the data (DOC-RPT-35; Attachment 9.1) for expanded the cross-reactivity studies for *Trypanosoma cruzi* and *Borrelia burgdorferi*. It is further stated that data for *Plasmodium falciparum* is presented in DOC-RPT-31 (Attachment 9.2), which followed protocol DOC-PRO-31. The sponsor also states that suitable *Leishmania* blood samples were not available for testing.

Comments: The study for *B. burgdorferi* and *P. falciparum* is acceptable. The data for *T. cruzi* in presented in DOC-RPT-31 which states that all samples were plasma samples; it is not clear if these are Chagas antibody positive or Chagas parasite positive plasma. Comment to sponsor “In your response to FDA question #9 on cross-reactivity studies, the data for Chagas cross-reactivity is presented with potentially interfering substances in DOC-RPT-31. It is stated that all samples were plasma samples. Please clarify if these plasma samples are Chagas antibody or parasite positive. The question was communicated in 2nd CR letter.

11. **FDA CR#1 Question 10:** In response to non-clinical hold issue #12 in our IND Hold letter (IND 14532) dated December 10, 2010, you have submitted interference studies using (b) (4) samples only. In document Lab-DSGN-9 it is stated that “Assay was evaluated for performance with the following endogenous substances: Elevated total proteins, Elevated bilirubin, Lipemic, Elevated triglycerides, Elevated Cholesterol, Alkaline Phosphatase, Anti-nuclear Antibodies (ANA), and Rheumatoid Antibody (RA).” The results from these studies could not be located in the submission. Please identify where this information is located in the submission or submit the results of these studies.

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the data (DOC-RPT-31; Attachment 9.2) for potentially interfering substances.

Comments: The studies are acceptable. Resolved.

12. **FDA CR#1 Question 11:** *You have submitted cross reactivity studies with bacteria (NAT CMC Overview Part 2, Pages 108.65 and 108.66) and interference studies using (b) (4) samples (043_Attachment 4-3-2-7 DOC RPT-13), respectively. In both studies, your assay failed to detect Babesia DNA in several samples spiked with Babesia parasites although the presence of Babesia was demonstrated using a digital PCR. You have attributed this to an improperly stored Babesia positive stock sample used for spiking (stock sample stored for (b) (4) or a change in the concentration of the Babesia positive stock sample. The results from both of these studies are not acceptable. Please perform the interference and cross reactivity studies with a well characterized stock sample stored at appropriate storage conditions and submit the results for review to FDA. In addition, please ensure that the calibration curve is run in parallel with the samples using the same PCR assay to determine the amount of target/ml during the re-testing if needed.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor states that they have repeated the interference and cross reactivity studies (DOC-RPT-35 - Attachment 9.1; DOC-RPT-31 - Attachment 9.2).

Comments: The studies are acceptable. Resolved.

13. **FDA CR#1 Question 12:** *In SOP LAB-MFG-10, it is indicated that (b) (4) Babesia parasites/ml were used as low positive control in the NAT assay. The 95% detection limit of NAT is (b) (4) Babesia parasites/ml. The low positive is almost (b) (4) times the limit of detection (LOD). The use of low positive control that is (b) (4) LOD fails the purpose of the low positive control (i.e., to determine if the assay is working as per specifications). FDA recommends that you add an appropriate low positive control to your panel that is close to LOD (b) (4) and submit the results to FDA for review.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor states that “a new low positive control was prepared with a concentration of approximately (b) (4) Babesia parasites/ml reflecting a value of approximately (b) (4) above the limit of detection of (b) (4) Babesia parasites/ml. This preparation was prepared following LAB-MFG-10 and instituted as the new low positive control effective (b) (4) as described in, SOP LAB-MOL-BPCR-10 (Attachment 2.5). Between (b) (4) this control has been used in (b) (4) extraction runs. Of these runs, there were 4 occasions where the low positive control was out of range (failure rate of (b) (4) and the test run had to be repeated and subsequently passed.

Comments: On Feb 17, 2017 the following IR was sent to sponsor *“In your NAT Amendment response received December 14, 2016 to FDA question #12 (CR dated September 29, 2015) regarding incorporating a low positive control of (b)(4) to (b)(4) LOD, you have stated that a low positive of (b)(4) LOD was introduced effective 03/26/16. Please provide the design, verification and validation documents that describe how this change was incorporated in the finished device.”* In March 01, 2017 response the sponsor stated that *“adjustment in concentration of the low positive control was made on April 26, 2016 following a notebook study which was conducted to ensure the change would be appropriate for use in Blood Donor Screening.”* They submitted the notebook study as Attachment 5.1(DOC-RPT-88, Report on the Adjustment of the *Babesia microti* NAT Low Positive Control). The report failed to demonstrate if any risk analysis was conducted associated with this change. The review of documents during inspection revealed that the sponsor failed to follow their design change SOP for making this change. This issue became the basis of a 483 observation. The details on issue resolution is available in Lori Peters 483 memo (Feb 12, 2018).

14. **FDA CR#1 Question 13:** *The document (LAB-MOL-BPCR-7) reports testing results to determine the stability of primers, probes and controls.*
- Please date the SOPs used to generate this report.*
 - Please provide the actual test results (not summary) for each component (multiple lots) at the storage conditions referred to in the SOPs.*

Response: In the response document *“BLA Complete Response BL125588/0 Imugen Response”* dated Dec 14, 2016, the sponsor states that LAB-MOL-BPCR-7 has been obsoleted and replaced with more robust and complete documents.

Comments: On Feb 17, 2017 the following IR was sent to sponsor *“In your NAT Amendment response received December 14, 2016 to FDA question #13 (CR dated September 29, 2015) regarding stability studies, you have submitted overview of stability studies. Please clarify the following regarding these studies:*

- You have stated that “LAB-MOL-BPCR-7 has been obsoleted and replaced with more robust and complete documents”. Please submit the current SOP that is in compliance with your quality systems (dated, signed, version # etc.)*
- Please provide the results obtained for stability analysis after November 2016, if available.*
- Please clarify which “finished device lots” were used in these studies.*
- Please submit the following documents: DOC-RPT-63; DOC-STB-RPT-25; DOCSTB- 25. Please ensure that these documents are signed and dated.”*

In their March 23, 2017 response (Question 11 of IR request) the sponsor provided:

- The document IDs for the updated documents (Page 2 of 18; DOC-MEM-38).
- The updated interim stability results (Page 2-9 of 18; DOC-MEM-38).

- c. The real time stability study that utilizes NAT Finished Device Lots is DOC-STB-25 (Attachment 11.1). The Finished Device Lots used in this study are (b) (4)
- d. The documents were submitted as attachment.

The response is acceptable. Comment to sponsor “Please submit the updated stability report while submitting the CR responses.”

15. **FDA CR#1 Question 14:** *Please provide a summary table showing the lots of Babesia NAT manufactured by IMUGEN that were used in the pre-clinical studies described in the BLA. For each lot (including positive and negative controls), please provide the lot number, the size of the lot (i.e., number of tests that a lot can perform), production and expiration dates, and also indicate the corresponding study(ies) that each lot was used in.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has submitted the details lots of *Babesia* NAT manufactured by IMUGEN that were used in the pre-clinical studies (Pages 27- 37 of 85).

Comments: The response is acceptable. Resolved.

Process/Product:

16. **FDA CR#1 Question 15:** *In your submission, you indicated that the B. microti NAT device is microbiologically controlled; however, no details in regards to the control of microorganisms in the process (i.e., bioburden testing) or in the facility were provided. Please provide specifics in regards to microbiological control of your process and indicate where in the process bioburden testing is performed. If bioburden testing is not performed, please provide a justification. For example, (b) (4) blood represents the primary source material for making the positive controls; a rigorous microbiological examination of the source material is desirable. Fungal contamination also may occur in (b) (4) derived preparations. The procedures are designed only to capture bacterial contamination. The testing is done on (b) (4) according to LAB-MFG-25 that may not reveal non-bacterial contamination. Please propose a modified microbiological screening procedure or explain why it is not needed.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor clarified that the statement included in the submission regarding the microbiological control of the NAT *B. microti* device was inaccurate as the device is not specifically controlled for microorganisms. However, there are controls in place for the purpose of limiting microbiological contamination. Raw material acceptance testing of (b) (4) blood is performed by evaluation of Gram and Giemsa stained (b) (4) made from all (b) (4) blood tubes (LAB-AQC-MOL-106 and LAB-MFG-1; Attachments 15.1 and 23.1, respectively).

Comments: The response is acceptable. Resolved

17. **FDA CR#1 Question 16:** *You have submitted document 134_Attachment 4-9-2-29_LAB-QA-86, which describes the guidelines for process validation. We could not find implementation of these guidelines in reports of activities specific to the manufacturing or quality systems related to the NAT. It is not clear from your submission if an adequate process validation was performed as no process validation procedures/protocols and the corresponding reports for the manufacturing process were provided. Please provide process validation report summaries for your manufacturing process. These reports should indicate how the validation was performed (including statement of the objective, scope, methods of data collection and analysis), defined acceptance criteria, results, and deviations and resolution of deviations.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has submitted the master validation plan (LAB-VAL-4, Attachment 16.1) which also provides an overview of process flow and specifications. This plan is implemented in LAB-VAL-19 (Attachment 16.2) which describes the overall validation protocol. They also provided DOC-RPT-53 (Attachment 16.3) for the Process validation summary report for the NAT manufacturing process.

Comments: On Feb 17, 2017 the following IR was sent to sponsor “*In your NAT Amendment response received December 14, 2016 to FDA question #16 (CR dated September 29, 2015) on process validation, you have provided the validation plan along with process validation report summarizing the results. Please provide the following information:*

- a. *Please provide a list of critical lab SOPs/Protocols (including version number) that have been locked (no major modification) following process validation.*
- b. *Please clarify since when (specific date) NAT manufacturing and testing are being conducted following implementation of process validation (i.e., locked down, with no major changes).*
- c. *Please clarify when the document LAB-VAL-19 was implemented.*
- d. *Please provide the following documents: LAB-RPT-54, 55, 58 and 62; LAB-VAL-20 and 24. Please ensure that these documents are signed and dated.”*

In their March 01, 2017 response (Question 07 of IR request) the sponsor provided:

- a. List of critical lab SOPs/Protocols (Table 4; Page 6-7 of 9)
- b. The dates are provided in the Table 4
- c. LAB-VAL-19 was approved and activated on 12/8/16
- d. The documents were provided as attachments 7.2-7.7

The submitted documents are acceptable. During inspection deficiencies were observed in document control and became the basis of 483 observations. The issue was resolved in 483 responses (Lori Peters 483 Memo of Feb 12, 2018)

Chemistry Manufacturing and Controls (CMC):

18. **FDA CR#1 Question 17:** A “kit” is defined as a set of reagents qualified to be used together to perform an assay. As described in the original BLA submission, the *B. microti* NAT is not assembled into a formal kit for commercial distribution, but specific reagent lots that form a finished device will be used to perform in-house donor testing for *B. microti* by NAT. Extraction kits, a set of PCR reagents, *B. microti* primers, probes and positive and negative controls belonging to a lot should be assembled and tested together to comprise a test kit lot with the expiration date set by the shortest expiration date of a component of the assemblage. You have submitted lot release documents for individual components as primers, probes, extraction kits (LAB-AQC-MOL-32, 33, 34, 35, 36, and 51) etc., rather than the defined kit with all the components identified. For example each new batch of primers is tested with a batch of *Babesia* positive and negative controls according to LAB-AQC-MOL-32. This process of matching should continue until a batch comprised of all components are assembled into a finished device and subjected to final release testing. Please define the composition and size of the lot for the *B. microti* NAT finished device.

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has defined the finished device lot (LAB-AQC-MOL-102; Attachment 17.1); the batch size, and expiration dating (defined by the shortest expiration date of the lot components that constitute that finished device lot).

Comments: On Feb 17, 2017 the following IR was sent to sponsor “*In your NAT Amendment response received December 14, 2016 to FDA question #17 (CR dated September 29, 2015) on the finished device, you have provided an SOP (LABACQ-MOL-102) “Babesia microti NAT Finished Device Lot Final Release Testing”. Please clarify the following regarding this SOP:*

- a. Please clarify when this SOP was approved and implemented.
- b. On Page 3 of 15 (P385) of this document the column 1 of the table has “finished device lot components” and column 4 refers to “previously approved.” While the first seven components (that includes primers, probes and master mix) have a selection option of “Yes/No”; the last three rows (that include negative, high and low positive controls) the selection option is “n/a.” Please clarify why the last three rows are different.
- c. On Page 7 of 15 (P393), under procedure assay controls it is stated, “*Babesia* positive (High: (b) (4) and Low: (b) (4) and negative (b) (4) controls will be extracted both test and reference extraction kits, as detailed in the finished device lots. *Babesia* high positive control eluate (b) (4) will be amplified and detected for inclusion as a component in the finished device lot.” Throughout the submission *Babesia* high positive control has part (b) (4). Please clarify which high positive control with part (b) (4) is referred to here. Is high positive control (b) (4) a panel member for finished device release?”

In their March 01, 2017 response (Question 08 of IR request) the sponsor provided the following comments:

- a. LAB-AQC-MOL-102 was not yet approved or implemented. It remained in draft while related documents were modified to reflect the change. All affected documents will be implemented together prior to the next scheduled manufacturing.
- b. The sponsor clarified how the worksheet is completed during final release testing.
- c. The sponsor clarified that (b) (4) is an in-process material utilized in the manufacture of (b) (4), via extraction. (b) (4) is also utilized in finished device lot release testing, in the particular event of testing new lots of (b) (4) extraction kits, following the procedure detailed in LAB-AQC-MOL-102 worksheet 1. (b) (4) is used as a further whole blood control for extraction, ensuring a high positive sample is effectively extracted by incoming extraction kits. Following the aforementioned testing procedure, (b) (4) is also amplified to ensure the completion of a finished device lot.

The responses are acceptable. Resolved

19. **FDA CR#1 Question 18:** *BLA approval generally requires evaluation and lot release testing of at least three conformance lots that were manufactured using validated manufacturing processes described in the license application, in a lot size that is similar to that proposed for subsequent production and that have been used in the clinical testing. Please provide the following information with regard to the “lot.”*

- a. *Define what constitutes a “lot” for the NAT assay, including all essential and non-essential components.*
- b. *Explain how IMUGEN performs final lot release testing.*
- c. *Describe how IMUGEN assigns the expiration date of a new manufactured lot.*
- d. *Submit a lot release protocol including the release specifications and the name of the method(s) used to perform the analysis.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor referred to Q #17 defining the lots.

Comments: On Feb 17, 2017 the following IR was sent to sponsor “*In your NAT Amendment response received December 14, 2016 to FDA question #18 (CR dated September 29, 2015) on finished device and lot, you have clarified the components of a lot; please provide further clarification regarding which components of the finished device are the critical components.*”

In their March 23, 2017 response (Question 12 of IR request) the sponsor stated all components of the NAT Finished Device Lot are critical components.

The response is acceptable. Resolved.

20. **FDA CR#1 Question 19:** *The process of manufacturing *B. microti* infected (b) (4) red blood cells, the essential component required to prepare high and low positive controls is not sufficiently controlled nor is it fully described (NAT CMC overview part 1, Page 108.15). Please provide the following information:*
- a. *Detailed genetic and antigenic characterization of the *B. microti* isolate used to prepare positive controls for the NAT assay along with the results of genotyping assays performed by (b) (4) (NAT CMC overview part 1, Page 108.14).*
 - b. *Location, storage conditions and composition (i.e., number of vials, volumes, date of preparation, temperature, etc.) of the current stock of *B. microti* parasites (NAT CMC overview part 1, Page 108.14) used as starting material in the manufacture of the *B. microti* high and low positive controls for the NAT assay.*
 - c. *A manufacturing plan that includes preparation of a master cell bank and working cell bank for *B. microti* and a method of propagating the *B. microti* in (b) (4) and testing to ensure that each batch of infected red cells has sufficient antigenic similarity to a reference batch. Please refer to the CBER Guidance for Industry “Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product - <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092272.pdf>.” This document refers to manufacturing of vaccines, not in vitro diagnostics. However, the principles that govern use of cultured microbes in manufacturing (Pages 8, 10, and 11) are applicable to *Babesia* infected red blood cells.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the following:

- a. Detailed genetic and antigenic characterization of the *B. microti* isolate used to prepare positive controls for the NAT assay (DOC-RPT-73-Attachment 19.1; and Attachment 19.2)
- b. Location, storage conditions and composition of the current stock of *B. microti* parasites. They also provided the Table 19.1 to show the current batches of cell banks manufactured as well as total vials, vials remaining and current storage location (Page 41-42 of 85)
- c. Plan for creating the *B. microti* cell banks (Pages 42-45 of 85)

Comments: The response is acceptable. Resolved.

21. **FDA CR#1 Question 20:** *The production of infected (b) (4) red blood cells is performed at the (b) (4) under contract. As the license holder for the manufacturing of the Babesia NAT, IMUGEN must demonstrate sufficient control over all manufacturing processes. Please provide additional information on the content of the contract with (b) (4). Please provide a copy of the IACUC protocol (#A98-04-003) that establishes the animal procedures performed as part of this manufacturing process. Please describe when and how manufacturing is transferred to (b) (4) and the content of the contract arrangements and the IACUC protocol for this alternate contractor.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor clarified that critical supplier audit was carried out on the (b) (4) and audit actions requests have been followed up and are being monitored. (b) (4) is the main supplier of the infected (b) (4) blood. The IACUC protocol (#A98-04-003; Attachment 20.1) was provided. A contract is being negotiated. The sponsor also stated that (b) (4) and has supplied material under the IND.

Comments: The response is acceptable for (b) (4). As the contract with (b) (4) is still not finalized, it became the basis of a 483 observation. Also in their 483 response, they have removed (b) (4). The issue was resolved.

22. **FDA CR#1 Question 21:** *The attachment LAB-MFG-8 describes the procedure for inoculating and harvesting B. microti infected blood from (b) (4) at the (b) (4) animal facility. The protocol is not specific or consistent with regard to the parasite inoculum used to infect (b) (4). In some cases blood from an infected (b) (4) is used to infect a naïve animal and in other cases parasites from a (b) (4) stock are used. It is not clear how many passages in animals have occurred since a (b) (4) stock was used to obtain infected RBCs (iRBCs) for preparation of high and low positive controls described in your BLA. The current process of preparing infected (b) (4) blood is not controlled sufficiently to ensure lot-to-lot consistency of prepared positive controls. In order to improve the consistency of iRBCs and reduce the possibility of antigenic drift over time, we have the following recommendations:*

- a. *Each new production batch of (b) (4) infected blood should start with an inoculum of parasites from the working cell bank.*
- b. *Define the inoculum size of the parasite that will be used to infect the (b) (4).*
- c. *IMUGEN should modify LAB-MFG-8 to include the added initial steps of (b) (4) from the working cell bank through the collection of blood from infected animals.*

d. *If passage from (b) (4) is required to establish parasite infection, please clarify how many passages from animal to animal are allowed under the protocol.*

Response (a-d): In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the requested details (Page 46-47).

Comments: The responses are acceptable. Resolved.

23. **FDA CR#1 Question 22:** *In the acceptance criteria for B. microti iRBC (LAB-MFG-1, Page 321.9), you indicate that the red blood cell must have (b) (4). However, for processed (b) (4) red blood cells the specifications call for a (b) (4). Please explain this difference in the specifications.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor clarified that (b) (4) applies to the manufacture of AFIA material. They incorrectly included this specification for the NAT assay. The specification for the manufacture of NAT positive control stock is (b) (4) (LAB-AQC-MOL-106; Attachment 15.1).

Comments: The response is acceptable. During the inspection, it was observed that the sponsor is not using the specification of (b) (4) (was using specification of (b) (4) parasitemia); and this issue became basis of a 483 observation. The issue was resolved in 483 responses (Lori Peters memo of Feb 12, 2018).

24. **FDA CR#1 Question 23:** *In the document NAT CMC overview part 1 (Page 108.13); one of the specifications to accept infected blood from (b) (4) is: (b) (4) in the blood samples received and tested by IMUGEN with a reference to LAB-MFG-1. LAB-MFG-1 does not provide sufficient instruction to determine evidence of (b) (4) nor instruct the technician to report their presence. The LAB-MFG-1 document should clarify what (b) (4) could be. It should also describe how to report the observation of such (b) (4) with the blood preparation.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor stated that LAB-MFG-1 (Attachment 23.1) has been amended to clarify the original specification from (b) (4)

Comments: The response is acceptable. Resolved.

25. **FDA CR#1 Question 24:** *For all oligonucleotide primers used in this assay, please provide information to demonstrate their specificity and subtype inclusivity showing*

sequence alignments among other Babesia species and apicomplexan parasites, and other relevant organisms whose genetic material may be found in donor blood.

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the detailed information on specificity and subtype inclusivity of the oligonucleotide primers (Pages 48-55 of 85).

Comments: The response is acceptable. Resolved.

26. **FDA CR#1 Question 25:** *Please provide the physicochemical acceptance criteria for the purchased oligonucleotides and documentation that the acceptance criteria were met for purity, sequence, and concentration.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the acceptance criteria for purity, sequence, and concentration for the purchased primers and probes and associated documents (Described in Tables 25.1-4; Attachment 25.1).

Comments: On Feb 17, 2017 the following IR was sent to sponsor “*In your responses to FDA question #25 on physicochemical acceptance criteria for the purchased oligonucleotides, in Table 25.1 and 25.2 you have stated that the purity requirement for oligo is (b) (4) and for (b) (4) is “pass.” Ideally oligos used in NAT screening assays are (b) (4) pure. Please clarify the acceptance criteria for the purity of the oligos. Additionally, the requirement for (b) (4) is a “pass” result from the contract manufacturer (b) (4) of the target calculated (b) (4). In documents submitted in attachment 25.1, the COA doesn’t have (b) (4) results (peak) from the contract manufacturer. Please clarify how the physiochemical characteristics of the primers and probes manufactured by contract manufacturer verified.*”

In their March 23, 2017 response (Question 13 of IR request) the sponsor stated that the purity requirement for oligos is (b) (4) and this was verified during the onsite vendor audit on January 10th, 2017. Imugen also verified during the onsite vendor audit on January 10, 2017 that each unit of custom oligonucleotide is analyzed by (b) (4) (DOC-RPT-78, “Supplier Audit Report of (b) (4) Attachment 13.1). The sponsor also stated that they will request a copy of the (b) (4) raw data for each delivered lot of oligos going forward.

The response is acceptable. Resolved

27. **FDA CR#1 Question 26:** *Please provide a copy of the Device Master Record, LAB-QA-44, which contains a list of all Raw Materials, both Critical and Non-Critical (referred to in LAB-MFG-9).*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the Device Master Record (LAB-QA-44; Attachment 26.1).

Comments: The response is acceptable. Resolved.

Quality Systems:

28. **FDA CR#1 Question 27:** *Please address the following deficiencies regarding the Design Control information:*

- a. *Your Design Plan did not include required elements such as design verification, design validation, design transfer, design changes or reference to a design history file. Additionally, your plan does not describe procedures for review, update and approval as the device evolves.*
- b. *Design inputs and outputs were not clearly stated and defined in your application. Both of these terms are mentioned in the CMC Overview on Page 108.103; however the text is very general and does not describe any specific inputs to the NAT device. Documents LAB-QA-70 and LAB-QA-71 are titled Design Inputs and Design Outputs respectively. Please provide these documents. There is no indication that these documents provide specific inputs and outputs of the NAT device. Additionally, design outputs are not clearly linked to design inputs nor are acceptance criteria for outputs clearly indicated. Please note that design inputs are the physical and performance requirements of a device. Design inputs are the basis of the design verification and validation; therefore, design inputs need to be defined and recorded as formal requirements that allow for confirmation to the design outputs. In addition, design output procedures should contain or make reference to acceptance criteria and shall ensure that those outputs that are essential for the proper functioning of the device are identified.*
- c. *Design review is mentioned in the CMC Overview Document part 3 on Pages 108.99 and 108.103, suggesting that a complete description is found in Attachment 4-9-2-6 LAB-DSGN-12. The list of documents that is the sole content of LAB-DSGN-12 does not offer sufficient explanation of how formal design reviews are planned or conducted, and it appears that design review was not performed for all phases of your design process. Please note design review should include the review of design verification data to determine whether design outputs met functional and operational requirements. The CMC Overview also suggests that Design planning is described in the document LAB-QA-67 and recorded on LAB-QA-28, the Design and Development Form. Please provide these documents which were not included in the submission. You have provided some description of the design review in the CMC Overview part 3, Page 108.104 including important types of items to be discussed at a design review meeting. Please provide the document LAB-QA-72 (Design Reviews) along with other*

related documents LAB-QA-62 (Risk Management Program), LAB-QA-76 (Design Verification), LAB-QA-75 (Design Validation), LAB-QA-74 (Design Transfer From), and LAB-QA-68 (Design Change Management).

- d. *The Design History File, described on Page 108.108 of the CMC Overview Document part 3 and in LAB-QA-69 should be provided. These will also be reviewed at the pre-license inspection and FDA expects to find all the documents listed in the table shown on Pages 108.108 and 108.109 to be completed, signed and dated with information about the design of the NAT specifically.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the updated documents associated with Design Control.

Comments: As part of Quality Systems, the Design Control documents were reviewed during inspection and were found deficient; and became basis of multiple 483 observations. The issues were resolved in 483 responses (Lori Peters memo of Feb 12, 2018)

29. **FDA CR#1 Question 28:** *Regarding your critical material suppliers, specifically: the (b) (4), please provide the following for each supplier:*

- a. *Details of your supplier qualification that was performed and descriptions of the supplier monitoring program*
- b. *Identify the date of the last on-site audit that was performed*
- c. *Quality Agreements*
- d. *Clarify the component(s) of the NAT assay (e.g., primers, probes, etc.) for which IMUGEN holds proprietary rights.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the requested information (Pages 59-60 of 85).

Comments: As part of Quality Systems, the critical vendor information was reviewed during inspection and was found deficient; and became basis of multiple 483 observations. The issues were resolved in 483 responses (Lori Peters memo of Feb 12, 2018)

Instruments and Software:

30. **FDA CR#1 Question 29:** *In your BLA you have provided Hazard Analysis document (064_Attachment 4-5-4 (b) (4) Hazard Analysis.pdf.) that includes potential hazards, severity estimation, hazard mitigation and updated severity estimation after hazard mitigation. However, information such as cause(s) of the hazard and/or verification that the method of control was implemented correctly is not included in your table. Your Hazard Analysis document should be in the form of an extract of the software-related items from a comprehensive risk management document, such as the Risk Management Summary described in ISO 14971. For example, Failure Mode and Effects Analysis (FMEA) can be one of the approaches that could be utilized to identify the hazards, their corresponding validation and verification, and construction of the table accordingly. Therefore please provide an updated table based on FMEA and ISO 14971 methodologies. For further information, please refer to FDA software guidance document, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>. Please also consult a possible example of FMEA table available at: <http://asq.org/learn-about-quality/process-analysis-tools/overview/fmea.html>*

Response: In the amendment received December 14, 2016 in response to FDA Question 29, 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 sent to the applicant on February 17, 2017 as new FDA IR Question 17: “*In your NAT Amendment response received December 14, 2016 in response to FDA Question 29 and in your AFIA Amendment received December 13, 2016 in response to FDA Question 34, you provided risk analysis information including reference to the risk analysis, (b) (4) Risk Analysis IT-CSV-PDF-41.*”

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

Response a: In the amendment received March 23, 2017 in response to FDA IR 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 IR 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 IR 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: *“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-LAB-DSGN-11.xlsx), 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: No response has been received. The issue was also communicated in the 2nd CR letter.

31. **FDA CR#1 Question 30:** *In your BLA submission you provided Software Requirements Specifications (SRS) in document (b) (4) Software Requirements Specification” (065_Attachment 4-5-5 SRS-(b) (4) IMUGEN.pdf) that describes the client/servicer application. The document includes 22 requirements for hardware, interface, software, performance, regulatory, system backup and restore, etc. Most requirements are too high level and do not include testable information. The requirements for workflow processes, boundary conditions and error recovery are missing. Please provide an updated copy of the Software Requirements Specification document, which should clearly document the functional, performance, interface, design and development requirements.*

Response: In the amendment received December 14, 2016 in response to FDA Question 30, the applicant provided an updated SRS where information has been inexplicably removed. The response was inadequate.

Comments: The following was sent to the applicant on February 17, 2017 as new FDA IR Question 16: *“In your original submission in the software requirements document (Attachment 4-5-5 SRS-(b) (4) IMUGEN) in Section 2.5 you provided Performance Requirements. In your NAT Amendment response received December 14, 2016 in response to FDA Question 30 and in your AFIA Amendment response received December 13, 2016 in response to FDA Question 35 you provided an updated Software Requirements Specification document where all performance requirements were removed. Please clarify why entire sections of requirements have been removed, and*

update and provide your requirements documentation to ensure all requirements are correctly captured.”

Response: In the amendment received March 23, 2017 in response to FDA IR 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.

Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 1: *“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 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: No response has been received. The issue was also communicated in the 2nd CR letter.

32. **FDA CR#1 Question 31:** *You have not provided an “Architectural Diagram” that should include a description of the software system partitioned into its functional subsystems, incorporating a description of the role that each module plays in fulfilling the software requirements. Please provide an Architectural Diagram of your software. It is recommended that you consult ISO 62304 (Medical device software - Software life cycle processes) to prepare your software documentation and conduct testing.*

Response: In the amendment received December 14, 2016 in response to FDA Question 31, the applicant provided an updated architecture diagram in Attachment 29.4.

Comments: This response is acceptable. Resolved.

33. **FDA CR#1 Question 32:** *You have provided a software design specification (SDS) document (066 Attachment 4-5-6 SDS (b) (4) IMUGEN.pdf) for the (b) (4) [REDACTED]. The document includes the modules for the (b) (4) [REDACTED] Process Role, PCR Role, Report Role, Audit Role, and Admin Role. These each illustrate the control flow among the User, the UI, the Data Model and the Data Storage. The database schematic is presented in Figure 1 on Page 566, definitions are included in Section 2.4 starting on Page 569, and all components are described by Field with included Notes and Type. However, none of the fields have specified measurable or testable values. There is no traceability from the requirements enumerated in document “065_Attachment 4-5-5 SRS-(b) (4) IMUGEN.pdf” to this SDS document to describe how the requirements in the Software Requirements Specifications (SRS) are implemented. Please add the missing requirements to your software requirement specifications, including all step-by-step workflow requirements, for both AFIA and NAT, and provide all updated design control documentation that is affected.*

Response: In the amendment received December 14, 2016 in response to FDA CR Question 32, the applicant provided an updated SDS in Attachment 29.5 that is missing testable details and test case information. The response was inadequate.

Comments: The following was sent to the applicant on February 17, 2017 as new FDA IR Question 18: “In your NAT Amendment response received December 14, 2016 in response to FDA Question 32 and in your AFIA Amendment received December 13, 2016 in response to FDA Question 37, you stated that for the (b) (4) software, you included an updated Software Design Specification and Traceability Matrix that “contain measurable and testable values.” Thank you for providing these updates and the detailed information. Several Risk ID/SRS entries in your traceability table do not trace to software design specifications, and some trace to testing that does not appear to relate to the corresponding risk/requirement. This makes it difficult to assess the adequacy of your proposed mitigations. Note that necessary testing at the unit, integration and

system level is often different and more comprehensive than qualification testing.

- a. For example, Risk ID 24/SRS 24 addresses a risk that PCR results might be modified. No design information was provided on how this would be performed, and the referenced V&V test cases don't appear to test any attempts to modify PCR results to ensure the risk is properly mitigated. The tests are "Script #15 Create NEW PCR plate template and import results from multiple submitters" and "Script #9: Create slide(s), and add specimen to slide(s) from single submitter." Step #9 is "Click SAVE SLIDE, Close Slide." How do these tests verify that software prevents any modification of the PCR results? Please provide the correct documentation.*
- b. Risk ID 34/SRS34 involves risk of loss of sample origin, but has no associated SDS. The requirement itself is vague and the corresponding testing refers to step #16 of a test script. However, the test script ends after 13 steps. Please clarify the risk and requirement, and provide corrected documentation.*
- c. Risk ID 39/SRS 39 refers to a test script that was not provided. This portion of the testing documentation is blank. Please provide the correct documentation.*
- d. Risk ID 49/SRS 49 does not include testable information and is not traceable to an SDS. Some of the relevant information appears in the test case; however, specifics of the device design should be captured in the requirements and specification documentation, and not documented solely in testing documentation. Please update your SRS and/or SDS with the appropriate design information accordingly, and provide the correct documentation.*
- 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.

Response: In the Amendment received March 23, 2017 in response to FDA IR 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, references to "or later" were removed, and traceability and SRS documents were updated accordingly.

Comments: The response is acceptable. Resolved.

Response 2: In the amendment received December 14, 2016 in response to FDA CR Question 32, the applicant provided an updated SDS in Attachment 29.5 that does not contain explicit design specification information traceable to requirements. The response was inadequate.

Comments 2: The following was sent to the applicant on February 17 as new FDA IR Question 19: *“In your NAT Amendment response document received December 14, 2016 in response to FDA Question 32 and in your AFIA Amendment response received December 13, 2016 in response to FDA Question 37, you provided a Software Design Specification document. This version 1.1 of the document does not appear to be substantially changed over version 1.0 provided in your original submission. Many screen shots are presented but it is not always apparent what has changed from one screen to the next, what is expected to appear on the screen, what information the user entered, and what are the system responses when the user does something unexpected. Each of these specifications should include explicit text about what should appear on the screen and what the device and/or user is expected to do. It is not sufficient to collect screen shots of a completed system and state that these encompass a software design specification without additional information. It is not reasonable to expect a designer/tester/reader to compare successive screen shots to determine for themselves what has changed between the two screen shots. This increases the opportunity for misunderstanding, inadequate design and testing.*

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

Response: In the Amendment received March 23, 2017 in response to FDA IR 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: The response is acceptable. Resolved.

34. **FDA CR#1 Question 33:** *You have provided a traceability document (067_Attachment 4-5-7 IMUGEN (b) (4) Traceability Analysis.pdf) that includes items for each of 22 high level requirements. The “Verification and Validation Tests” in the form of references to Installation Qualification tests or Operational/Performance Qualification tests are*

included and associated hazards are identified. However, the traceability of requirements and specifications to testing and hazards are not comprehensive. This is due in part to inadequately formulated requirements, which are often vague and untestable as written, and the use of test cases that are mostly limited to using valid values and workflow actions.

- a. Please provide verification and validation information for all software requirements (including missing requirements mentioned in other deficiencies), which should include the unit, integration and system level test protocols with pass/fail criteria, and test report, summary and test results.*
- b. Please provide traceability information described at the detail level of individual software requirements rather than the high level software requirements, R1-R22. This includes traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing in an enumerated manner.*

Response: In the amendment received December 14, 2016 in response to FDA Question 33, the applicant provided an updated traceability matrix in Attachment 29.3. 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 was sent to the applicant on April 14, 2017 as new FDA Question 2: *“Verification and validation testing: 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). 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: No response has been received. The issue was also communicated in 2nd CR letter.

35. **FDA CR#1 Question 34:** *In the document, “082_Attachment 4-5-11 IMUGEN (b) (4) Unresolved Anomalies_04172015.pdf” you provided one unresolved anomaly: “PCR Results import - The PCR Results import template to be printed does not currently highlight Ct values which exceed a specified threshold. The laboratory technician performing the experiment cross checks the output of the (b) (4) template with the (b) (4) printout and is trained to identify Ct values over specified threshold which would require the sample to be retested. Accordingly, as there is a manual check of the Ct values performed, this anomaly does not impact the safety or efficacy of the product.” This anomaly could be associated with a false negative if a sample is not retested when it should be. This anomaly and mitigation information was not included in the hazard analysis, and no requirements were added to address this. Please correct this anomaly and update the associated design documentation.*

Response: In the Amendment received December 14, 2016, you stated that this was not an anomaly in software, but an issue caused by a technician reviewing paper records. The non-conformance was raised and a CAPA initiated with retraining. Change control was implemented in the FMEA Risk Analysis (Attachment 29.1).

This question was additionally asked in the February 17, 2017 IR as FDA IR Question 21. In the Amendment received March 23, 2017, the applicant provided an updated SDS and additional validations in the traceability matrix supporting new risk R26a to address this.

Comments: The response is acceptable. Resolved.

36. **FDA CR#1 Question 35:** *You did not provide information on Cybersecurity related to all instruments, hardware and software incorporated into the system, including Off-the-Shelf components. The (b) (4) system includes at least (b) (4) types of servers and multiple workstations/clients, at least (b) (4) of which has established connectivity to the outside world. Please provide information on the Cybersecurity aspects of your device, including, but not limited to, the following facets of information security with respect to communication features of your device, associated software and other required components: confidentiality, integrity, availability and accountability. Confidentiality assures that no unauthorized users have access to the information. Integrity is the assurance that the information is correct - that is, it has not been improperly modified. Availability suggests that the information will be available when needed. Accountability is the application of identification and authentication to assure that the prescribed access process is being done by an authorized user.*

Response: In the amendment received December 14, 2016 in response to FDA Question 35, the applicant provided an Information Technology Security Policy in Attachment 29.6 that is not related to security concerns during device operation. The response was inadequate.

Comments: The following was sent to the applicant on February 17, 2017 as new FDA Question 20: *“In your NAT Amendment response received December 14, 2016 in response to FDA Question 35 and in your AFIA Amendment received December 13, 2016 in response to FDA Question 39 with respect to cybersecurity, you provided the document, “Information Technology Security Policy, IT-SEC-POL-1.” You stated that this describes “control of confidentiality information and accountabilities.” This policy appears to apply to your corporate networks and business policies rather than for the device itself. Please note that you should identify risks associated with not only confidentiality, but integrity and availability, and take steps to reduce risk that device functionality is intentionally or unintentionally compromised by inadequate cybersecurity considerations. The (b) (4) system appears to include at least three types of servers and multiple workstations/clients, at least one of which has established connectivity to the outside world. Your risk documentation appears to contain some mitigations for potential cybersecurity risks, although you have not identified many of the possible causes to demonstrate that these mitigations would be adequate.*

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

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.

Response: In the Amendment received March 23, 2017 in response to FDA IR 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 tie these risks to 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. *“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.

Additional Information on Risk Documentation and Processes: We recognize your effort to improve your approach to risk analysis and encourage you to seek additional opportunities to continue this effort. We understand that effective risk management can be challenging, and have prepared our comments to encourage your continued efforts in this area. You have included references to both ISO 14971 and FMEAs and the risk tables you provided contain a mix of terminology and concepts.

Because you stated that your processes align with ISO 14971, please consider the following references. Note that much of TIR 32 has been incorporated into IEC 80002-1, although there remain some unique discussion sections on software risk management within the software life cycle that are not included in IEC 80002-1.

- *AAMI TIR 32: Medical device software risk management*
- *IEC 80002-1: Medical device software - Part 1: Guidance on the application of ISO 14971 to medical device software*
- *You might also find TIR 24971 useful in your understanding of ISO 14971.*
- *ANSI/AAMI/ISO TIR 24971 Guidance on the application of ISO 14971.*

You might find value in some industry publications related to the risk management process. Please consider the following from AAMI (Association for the Advancement of Medical Instrumentation). Note that these articles were part of the public discourse at the time seminal industry standards were being formulated or revised, and should be viewed as information and not construed as regulatory requirements. If you do not have subscription access, you may be able to locate articles online or by contacting the authors directly.

- *The goal of the following is to provide an understanding of risk management principles to developers of medical device software: Jones, P., Jorgens, J., Taylor, A., Weber, M., Risk Management in the Design of Medical Device Software Systems, *Biomedical Instrumentation & Technology Journal*, Volume 36, Number 4, July/August 2002.*
- *AAMI Horizons produced an issue focusing on Risk Management, and the link below includes a link to the Table of Contents.*
<http://www.aami.org/productspublications/horizonsissue.aspx?ItemNumber=1954>

Cybersecurity considerations are becoming a larger and larger concern for systems that allow connectivity to the outside world; for example, by way of a network, external storage device, and/or user interface. Some manufacturers include cybersecurity risks in their risk documentation directly, while others perform separate risk management activities for cybersecurity considerations. It is your choice, although you should consider security-related causes to the hazardous situations you identify. Please refer to the following FDA guidance documents, including section VI “Medical device cybersecurity risk management” in the postmarket guidance for a discussion on risk management specific to cybersecurity.

- “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices – Guidance for Industry and Food and Drug Administration Staff,” issued October 2, 2014 and available at <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356190.pdf>
- “Postmarket Management of Cybersecurity in Medical Devices - Guidance for Industry and Food and Drug Administration Staff,” issued December 28, 2016 and available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm482022.pdf>

Note that there are subtle differences in risk management for cybersecurity, which may complicate the traditional ISO 14971 approach. Because your goal is to be aligned with ISO 14971, you might consider the following popular reference in this area:

- AAMI TIR57 “Principles for medical device security—Risk management”

Note that you may use any number of different methodologies to identify the possible hazards, harms, hazardous situations, etc., that are relevant for your device. Some applicants provide their fault trees and FMEA tables, while others have created a custom table that allows the capture of all information outlined in ISO 14971. Exactly how you present the information is not dictated, but keep in mind that a goal of the review is to assess the scope of your risk management efforts. To do this, we wish to see the hazards, harms, hazardous situations, causes, and mitigations in a single location, with the premitigation assessment of each risk and the postmitigation assessment of each risk clearly shown. This allows us to determine if your proposed mitigations and their ability to reduce the identified risks are reasonable. Traceability to any requirements that implement risk mitigations and the associated testing should also be included.

Response: No response has been received. The issue was also communicated in 2nd CR letter.

37. **FDA CR#1 Question 36:** *In the document 065_Attachment 4-5-5 SRS-(b) (4)_IMUGEN, you have stated that “When testing and data collection is complete,*

laboratory managers will use the software to produce reports of sample results which are electronically transmitted to the submitting entity (Page 547).” However, it is not clearly described how these results are transmitted to these facilities. As your service expands in the future, you will be collecting and reporting greater amounts of data. Please explain how these data will be managed and coordinated between your laboratories and blood establishment facilities.

Response: In the amendment received December 14, 2016 in response to FDA Question 36, 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.

The following are IR Questions sent 2/17/2017 that were not directly tied to previous questions, but arose during the review in progress.

38. **FDA IR Question 14:** *In your original submission, in the Software Description document (Attachment 4-5-3 Imugen (b) (4) software description) on the second page, you stated that a version of (b) (4) will be compiled for commercial release which eliminates the Repository study option. Please provide the following:*

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

Response: In the Amendment received March 23, 2017 in response to FDA Question 14, the applicant stated that the (b) (4) software will no longer be compiled for commercial release. The software will only be used in-house. Corrections described in the response have been made resulting in software version “Build 1.0.5.5” which is described in the updated version documentation Revision History (IT-CSV-PDF-24). This is acceptable. However, the applicant is requested to ensure all design documentation is updated to reflect the final version.

Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 5: *“Documentation package for Build 1.0.5.5: In the NAT Amendment received March 23, 2017 in response to FDA Question 14, you stated that the (b) (4) software*

will no longer be compiled for commercial release, but that the final version will be Build 1.0.5.5. Please review the documentation provided, and ensure that all design documentation including appropriate verification and validation testing corresponding to version Build 1.0.5.5 has been provided.

Response: No response has been received. The issue was also communicated in 2nd CR letter.

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

- a. Please provide testing documentation that supports this claim.*
- b. Please update your traceability matrix and testing documentation to explicitly include testing of the mitigations you identified in your risk analyses documents, including testing of the mitigations related to labeling and information for safety. References to testing of risk control measures can also be included in your risk documentation if this is easier. This is necessary to review how you determined that your mitigations appropriately reduce the risk to acceptable levels.*

Response: In the Amendment received March 23, 2017 in response to FDA Question 15, the applicant stated that two additional risks (and corresponding testing) were added to address unexpected conditions. The applicant did not provide convincing evidence to support that all unexpected conditions were identified and tested.

Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 3: *“User interface error checking: In the NAT Amendment received March 23, 2017 in response to FDA Question 15, you stated that two additional risks were added, but it is not clear if this represents all unexpected conditions. Two conditions were included: R26b “Software must protect against import of corrupt or incomplete source file” and R26c “Software must not allow input of invalid result values.” Testing for R26b does not describe what was tested and why; it just illustrates that an uncharacterized file was rejected on import. Testing for R26c is limited to error*

checking on the IFA Slide screen. R29 describes software error detection functionality but the referenced testing in the traceability matrix (Attachment_15.2-IT-CSV-IMD14-16-TM&DocDetails.pdf) refers to IT-CSV-IMD14-07-OPQb, 6.8.11, #11, that does not appear to test or detect error conditions.

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

Response: No response has been received. The issue was also communicated in 2nd CR letter.

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

Response: In the Amendment received March 23, 2017 in response to FDA Question 22, the applicant provided an updated NAT risk assessment document (Attachment_22.1-LAB-DSGN-11.xlsm) where hazards and requirements are correctly identified. New mitigations are included that do not require an agreement with the customer.

Comments: The response is acceptable. Resolved.

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

where templates are imported, selected, and then results are imported.

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

Response: In the Amendment received March 23, 2017 in response to FDA Question 23, the applicant created two new risks related to error checking and imported data files, performed corresponding testing, and updated the relevant design control documents, FMEA Risk Analysis (Attachment 15.1, IT-CSV-PDF-41), Traceability Matrix, (Attachment 15.2, IT-CSV-IMD14-16-TM) and SRS (Attachment 15.3, IT-CSV-IMD14-13-SRS). However, the applicant did not answer the posed questions. The interface with the (b) (4) instrument should be appropriately tested but the only documentation provided was a script with undefined inputs, making it impossible to know what was tested and if the testing was comprehensive.

Comments: The following was sent to the applicant on April 14, 2017 as new FDA Question 4: *“PCR device interface verification: In the NAT Amendment received March 23, 2017 in response to FDA Question 23, you reported two new risks related to error checking and imported data files and provided relevant design control documents. However, you did not respond to the question. We could not identify explicit information about the file format or interface with the (b) (4) instrument (R27 and R28). We could not confirm that the interface was appropriately tested because the only documentation for R26b provided was a script 6.8.3 (IT-CSV-IMD14-07-OPQc) with undefined inputs. Please respond to the original questions (a) regarding content and format of the imported data files, and (b) comprehensive testing of the system to ensure that the interface performs as intended.*

Response: No response has been received. The issue was also communicated in 2nd CR letter.

Facility:

42. **FDA CR#1 Question 37:** *The facility description in your BLA was limited and a determination of the adequacy of the overall facility and facility control could not be determined. Please provide the following information:*
- a. *Details regarding the overall construction of the facility (i.e., brick and mortar); the location of manufacturing activities, quality labs, office space, warehouse, etc.; and choice of building materials comprising the manufacturing and donor testing areas.*
 - b. *Security measures of the facility and within your production areas.*
 - c. *Description of your building monitoring system: identify which elements the system monitors and include a summary of the performance qualification that was performed.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the following:

- a. Details on the construction of the building (Pages 65-70 of 85) as requested.
- b. Security measures of the facility and within your production areas (Pages 70-71 of 85).
- c. Description of the building monitoring system (Pages 71-73 of 85)

Comments: During the inspection a few deficiencies in security systems and building monitoring system were observed; and these issues became the basis of 483 observations. The issues were resolved in 483 responses (Lori Peters memo of Feb 12, 2018).

43. **FDA CR#1 Question 38:** *Please provide a detailed narrative of the manufacturing flow, in addition to flow diagrams of how personnel, materials (raw materials, in-process materials, finished product), and waste are moved through the facility. In your narrative please include a complete description of all manufacturing activities or donor testing that occur in each room and the facility controls you have in-place to prevent cross-contamination.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the requested information (Pages 73-78 of 85).

Comments: The response is acceptable. Resolved.

44. **FDA CR#1 Question 39:** *Please provide a list of all additional products or assays, other than B. microti, that are manufactured or manipulated in the same areas used to produce the assay that is the subject of this application. Information provided should include a brief description of the type and developmental status of the additional products or assays and indicate the areas into which these other products or assays will be introduced, whether on an ongoing or campaign basis, and what manufacturing steps will be performed in the multiple-use area(s).*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the details of additional assays (Table 39.1; Pages 78-79 of 85).

Comments: The response is acceptable. Resolved.

45. **FDA CR#1 Question 40:** *Please provide the cleaning qualification data and disinfectant effectiveness studies for cleaning agents used in your facility and the Biosafety Cabinets (BSCs). Demonstration of facility cleaning should include, but is not limited to: bench top workstations, walls, floor, and any other facility surface material.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the details of cleaning/disinfecting procedures (Pages 79-80 of 85).

Comments: During the inspection, a few deficiencies in cleaning/disinfecting procedures became the basis of 483 observations. The issues were resolved in 483 responses (Lori Peters memo of Feb 12, 2018).

46. **FDA CR#1 Question 41:** *Please provide the qualification summary of the HVAC system, details of the room classifications and justification for the classification, rooms serviced by each HVAC, and airflow patterns and pressure differentials that are used to prevent cross-contamination in your manufacturing area. In addition, please provide facility schematics that indicate the room classifications of your facility.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor stated that “*all manufacturing occurs in unclassified, temperature-controlled manufacturing rooms or Biosafety Cabinets as appropriate for the particular manufacturing step (LAB-VAL-4). The air to the unclassified manufacturing rooms is supplied through an HVAC system which is routinely maintained (SOP-LAB-IQC-135). The intake air is filtered through (b) (4) rated filters.*”

Comments: The response is acceptable. Resolved.

47. **FDA CR#1 Question 42:** *Details of your environmental monitoring program were not described in sufficient detail. Please provide the following information:*
- a. *Details of your environmental monitoring program and system used for the monitoring.*
 - b. *Indicate your monitoring sites throughout the facility and in the BSCs and describe the criticality of these monitoring sites.*

- c. *The results of your environmental monitoring that is performed during the manufacture of your conformance lots.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the requested information.

Comments: The response is acceptable. Resolved.

48. **FDA CR#1 Question 43:** *In your BLA, you identify (b) (4) sources of water, (b) (4) which are used in the manufacture of the components of the assay. Please identify which components of the assay are manufactured with the specific water type. In addition, please provide a validation data summary for the water purification system.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor clarified that no internal water purification system is used in NAT manufacture.

Comments: The response is acceptable. Resolved.

49. **FDA CR#1 Question 44:** *In your BLA submission, you claim categorical exclusion of an environmental assessment based on 21 CFR 25.34 (d). This is not appropriate given that your submission is classified as a BLA, thus the class action considerations should be based under 21 CFR 25.31 Human drugs and biologics. Please change the requested action of your claim for categorical exclusion to 21 CFR 25.31(c) and state in your justification specifically, “To IMUGEN’s knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment” as per 21 CFR 25.15(d).*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor states that “*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, as per 21 CFR 25.15(d). This is meant to replace the original categorical exclusion claim submitted in the BLA, which was incorrectly based on 21 CFR 25.34(d).*” DOC-MEM-32 (Attachment 44.1)

Comments: Your justification for a categorical exclusion from preparation of an environmental assessment for the NAT assay is not satisfactory as provided in your December 14, 2016 Complete Response Letter to Item #44. You must revise your justification to indicate how your finished device lots for the NAT assay meets the exclusion criteria. The issue was communicated in the 2nd CR letter.

50. **FDA CR#1 Question 45:** *Please note that a pre-license inspection is required for your Norwood, MA facility prior to approval of your biologic license application.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor acknowledged the requirement for FDA pre-license license inspection.

Comments: The response is acceptable. Resolved.

Equipment:

51. **FDA CR#1 Question 46:** *In reference to the major pieces of equipment including the Real Time PCR system and the (b) (4) used in the manufacturing/testing process, there were no details in regards to the status of this equipment as shared or dedicated, if this equipment is product contact or how many machines are used in the process. Additionally, it is not clear if this equipment is also used for other manufacturing campaigns not associated with B. microti NAT and testing. Please provide a listing of all critical pieces of equipment (including the number of machines) and indicate if the equipment is shared or dedicated, has product contact, and identify the room location in your facility.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the list of critical piece of equipment in Table 46.1 (Pages 82-83 of 85).

Comments: The response is acceptable. Resolved.

52. **FDA CR#1 Question 47:** *Please provide equipment qualification data to support your equipment operating parameters for the Real Time PCR system and the (b) (4) Information provided should include the following:*

- 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.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor provided the IQ, OQ and PQ of the representative Real Time PCR system and the (b) (4); not all the machines as requested.

Comments: The information presented for IQ and OQ qualifications is acceptable. The sponsor need to provide the protocol that is used for PQ qualification of new machines and for requalification after major repairs. “In your response document “BLA Complete

Response BL125588/0 Imugen Response” dated Dec 14, 2016 to FDA CR Question 47c you have provided representative PQ for (b) (4). You have not provided the protocol or SOP that is used to qualify a new machine or out of service machine. Please provide the protocol that is used for conducting performance qualifications.” The issue was communicated in the 2nd CR letter.

53. **FDA CR#1 Question 48:** *It is unclear if a cleaning validation was performed for the major pieces of equipment including the Real-Time PCR system and the (b) (4). Please provide cleaning validation summary reports performed for all major pieces of equipment.*

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has provided the details of cleaning practices Imugen follows on Page 84-85 of 85.

Comments: During the inspection, a few deficiencies in cleaning/disinfecting procedures became the basis of 483 observations. The issues were resolved in 483 responses (Lori Peters memo of Feb 12, 2018).

Labeling:

54. **FDA CR#1 Question 49:** *The intended use statement as provided is not correctly worded. FDA offers the following suggestion for the intended use statement for the Babesia microti NAT:*

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

This test is intended for use as a donor screening test to detect B. microti DNA in whole blood samples from individual human donors, including volunteer donors of whole blood and blood components, as well as other living donors. It is also intended for use to screen organ and tissue donors when specimens are obtained while the donor’s heart is still beating.

This test is not intended for use on specimens from cadaveric (non-heart-beating) donors.

This test is not intended for use on samples of cord blood.

This test is not intended for use as an aid in diagnosis of Babesia microti infection.

Response: In the response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016, the sponsor has accepted the intended use statement suggested by FDA.

Comments: The response is acceptable. Resolved.

Appendix II

The following questions were provided in second CR letter dated June 13, 2017. The response to the CR letter was submitted on October 10, 2017. The detailed resolution of inspectional issues (FDA CR#2 Question 1) is available in EDR (CBER INSPECTION folder) in Lori Peters (483 Response Review) memo dated February 12, 2018. The detailed resolution of Questions 6-13 regarding Software and Instrumentation is available in Lisa Simone memo in EDR dated February 7, 2018. The resolution of Questions 14-20 on facility and equipment are available in Lori Peters memo in EDR “DMPQ Review Memo” dated Feb 12, 2018. The rest of the deficiencies (Question 2 - 5, 21) are discussed below.

Inspectional Issues

1. **FDA CR#2 Question 1:** *FDA/CBER conducted a Pre-License Inspection (PLI) of the Imugen, Inc. facility from March 6 through 10, 2017, and noted serious concerns with regards to QSR/cGMP at the end of the inspection. We received the response to the observations cited on FDA Form 483 on April 17, 2017, and find that it does not sufficiently address the concerns noted during the inspection. Your corrective actions do not appear to be fully implemented or comprehensive to address the underlying issues. Examples include:*
 - *An evaluation of the impact to test results, specifically, false positive or false negative, which could adversely impact recipient safety is not performed, for example, following unplanned equipment maintenance or repair, operator error, or non-validated/verified design changes.*
 - *Your manufacturing procedures are not sufficiently detailed to provide consistent lot-to-lot reproducibility of your finished device lots for the NAT assay.*
 - *Changes to the device design are not verified or validated in accordance with your design change procedures.*
 - *Inadequate segregation between operations for blood donor screening and clinical testing to prevent mix-up of equipment and test samples.*
 - *The cleaning procedures and process are insufficient to maintain a sanitary environment.*
 - *Insufficient personnel are available to perform and oversee all aspects related to manufacturing of finished device lots and testing of donated blood samples.*
 - *Inadequate investigations of exceptions are performed to determine root cause of events and initiate further corrective actions to prevent re-occurrences of issues.*
 - *Operator training and instructions are not sufficient to manage the entry of the results of the blood donor samples to prevent vulnerabilities related to data integrity and traceability.*
 - *The equipment maintenance and calibration program does not include the management of all pieces of equipment used for manufacturing and testing of blood donor samples.*

- *Insufficient number of critical pieces of equipment to continuously perform blood donor screening activities at the suggested throughput level.*

The deficiencies described in the FDA Form 483 issued at the close of the inspection referenced above are an indication of your Quality Control unit not fulfilling its responsibility to assure the accuracy of the test results of donated blood samples. Approval of a biologics license application or issuance of a biologics license constitutes a determination that the establishment and the product meets applicable requirements to ensure the continued safety, purity, and potency of such products; whereas, for your situation, this also applies to the continued accuracy of the test results. Applicable requirements for the maintenance of establishments for the manufacture of a product, or test result provider, include, but are not limited to, the good manufacturing practice requirements.

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

Your response will need to demonstrate that the corrective actions to the inspectional observations as listed on FDA Form 483 have been fully implemented and you will need to provide the supporting evidence of implementation including any related studies or verification/validation reports, as applicable. The unsolicited amendment received on May 18, 2017 did not include implementation of all corrective actions to each inspectional observation.

Comments: The responses were reviewed by Lori Peters (DMPQ), Babita Mahajan (DETTD), and Robert Duncan (DETTD) and were acceptable. The details are available in EDR (CBER INSPECTION folder) in Lori Peters 483 Response Review Memo dated February 12, 2018. Resolved.

Review Issues

- FDA CR#2 Question 2:** *In your response document “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016, to FDA CR Question 8, you have submitted the data from updated precision studies. The results of the PCR precision study were analyzed in two ways, qualitatively (agreement) and quantitatively (Ct). For the quantitative analysis based on the exact Ct value, there were (b) (4) undetected results eliminated from the analysis for panels (b) (4) LOD, (b) (4) LOD and (b) (4) LOD respectively. This would underestimate the variability. However, if they were included, there were no appropriate values to impute the Ct. We recommend that you remove the variability analysis conducted on the Ct values from these table (results) since the estimated variability for Ct values is not accurate. Reporting percent agreement would be sufficient for this product.*

Response: In the response document “Imugen Response to FDA Complete Response Received June 13, 2017” dated Oct 10, 2017, the sponsor followed FDA’s recommendation and have submitted the updated report DOC-RPT-26 (Attachment 2.1).

Comments: The response is acceptable. Resolved.

3. **FDA CR#2 Question 3:** *In your response document “BLA Complete Response BL125588/0 Imugen Response” dated Dec 14, 2016 to FDA CR Question 9 on cross-reactivity studies, the data for Chagas cross-reactivity are presented with potentially interfering substances in DOC-RPT-31. It is stated that all samples were of plasma samples. Please clarify if these plasma samples are positive for Chagas antibody or parasite nucleic acid.*

Response: The sponsor stated that in the Submission Issue Teleconference (BQ170068) with the FDA held on July 6, 2017. FDA informed Imugen that Chagas testing is no longer required for cross-reactivity testing.

Comments: The response is acceptable. Resolved.

4. **FDA CR#2 Question 4:** *In your response document “Imugen Response to STN 125588 Babesia microti Nucleic Acid Test (NAT) - Information Request” dated March 23, 2017, to FDA IR Question 11 on stability studies, you have provided the updated protocols and data. Please provide the updated stability report with additional time points.*

Response: In the response document “Imugen Response to FDA Complete Response Received June 13, 2017” dated Oct 10, 2017, Imugen provided updated DOC-STB-RPT-25 (Attachment 4.1) and DOC-STB-RPT-26 (Attachment 4.2) documents with the current stability time points.

Comments: The response is acceptable. Resolved.

Chemistry Manufacturing and Controls

5. **FDA CR#2 Question 5:** *BLA approval requires evaluation and lot release testing of at least three conformance lots that were manufactured using validated manufacturing processes described in the license application, in a lot size that is similar to that proposed for subsequent production. The time required for lot release testing and FDA review of the lot release test results must be considered in the production process. Please provide the batch size information of currently manufactured lots that can sustain uninterrupted supply of test reagents cleared through FDA Lot Release for ongoing testing requirements.*

Response: In the response document “Imugen Response to FDA Complete Response Received June 13, 2017” dated Oct 10, 2017, Imugen clarified that the sponsor is aware

of FDA's requirement. Additionally, Imugen provided the list of NAT finished device lots manufactured since August 2016 (Page 5-6 of 39).

Comments: The response is acceptable. Resolved.

Software and Instrumentation

The following questions were sent on April 14, 2017 in response to information received on March 23, 2017 (to information request sent on February 17, 2017 to "BLA Complete Response BL125588/0 Imugen Response" dated Dec 14, 2016). A status update on these questions was provided on May 23, 2017, which generally indicated that work was in progress and that the requested information would be provided. The detailed resolution of FDA CR#2 Questions 6-13 regarding Software and Instrumentation is available in Lisa Simone memo in EDR dated February 7, 2018.

6. **FDA CR# 2 Question 6:** *Performance requirements for (b) (4) hardware and software (sent as FDA Question 1): In the NAT amendment received March 23, 2017 in response to FDA IR Question 16, you stated that performance requirements "relevant to IT infrastructure for general lab operation ... is beyond the scope of the (b) (4) software" and were removed. This is not reasonable because the (b) (4) software requires proper operation of the underlying infrastructure to meet its intended use. Your documentation has inconsistently described the components of the system, and it is not clear what hardware supports the (b) (4) software and database functionality. You should include requirements related to the infrastructure that is necessary to support the intended use of the device for both the NAT and AFIA assays. This appears to include the components in the Hardware Network Diagram in section 2.3.2 in your Architectural Design document provided in Attachment 29.4 of your response received December 14, 2016, and any other relevant components not identified in this diagram.*
 - a. *Please clarify all of the required components for your system, including PCs, printers, network connections, etc. Explicitly identify the boundaries of the system with respect to your corporate network.*
 - b. *Please include all requirements related to required capacity for throughput, database capacity and accessibility, connectivity, uptime, etc., in order for the underlying infrastructure system to meet the required needs of the system. These requirements should include testable metrics to ensure that they can be met.*
 - c. *Include all test plans, test results and verification and validation testing for these performance requirements.*
 - d. *Update your traceability matrix to include this information.*

- e. Update your risk documentation to include risks associated with the performance needs of the system, and include the mitigations you implemented to reduce those risks to acceptable levels.
7. **FDA CR#2 Question 7:** Verification and validation testing (sent as FDA Question 2): In the NAT amendment received December 14, 2016 in response to FDA CR Question 33, you provided an updated traceability matrix in Attachment 29.3 and referred to IQ and OPQ testing. The testing is incomplete. Note that process validation testing (Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)) testing are not the same as verification and validation testing outlined in part (a). Please refer to FDA's guidance document, "General Principles of Software Validation," with a particular focus on section 5.2.5, located at <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf>. As outlined in the premarket software guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," please ensure that you provide unit, integration and system level test protocols, including pass/fail criteria, test report summary, and tests results. It is difficult to assess the adequacy of a test script by viewing only raw test steps without a description of the test plan and protocol and a summary of results.
8. **FDA CR 2 Question 8:** User interface error checking (sent as FDA Question 3): In the NAT Amendment received March 23, 2017 in response to FDA IR Question 15, you stated that two additional risks were added, but it is not clear if this represents all unexpected conditions. Two conditions were included: R26b "Software must protect against import of corrupt or incomplete source file" and R26c "Software must not allow input of invalid result values." Testing for R26b does not describe what was tested and why; it just illustrates that an uncharacterized file was rejected on import. Testing for R26c is limited to error checking on the IFA Slide screen. R29 describes software error detection functionality but the testing that is included in the traceability matrix (Attachment_15.2-IT-CSV-IMD14-16-TM&DocDetails.pdf refers to IT-CSV-IMD14-07-OPQb, 6.8.11, #11) does not appear to test or detect error conditions.
- a. Please provide a summary description of all user interface requirements and the types of error checking that is performed to identify problems with data interactions with the user via keyboard, barcode scanning, etc., and list the corresponding testing used to ensure proper functionality of the system. Please do not refer to entire design documents, but develop a direct response to this question. This is necessary to assess how the system responds to unexpected conditions and assess the scope of the error checking of the system.
- b. Please provide the corresponding design control documentation for the user interface requirements and error checking in (a).

9. **FDA CR#2 Question 9:** PCR device interface verification (sent as FDA Question 4): In the NAT Amendment received March 23, 2017 in response to FDA IR Question 23, you reported two new risks related to error checking and imported data files and provided relevant design control documents. However, you did not respond to the question. We could not identify explicit information about the file format or interface with the (b) (4) (R27 and R28). We could not confirm that the interface was appropriately tested because the only documentation for R26b provided was a script 6.8.3 (IT-CSV-IMD14-07-OPQc) with undefined inputs. Please respond to the original questions (a) regarding content and format of the imported data files, and (b) comprehensive testing of the system to ensure that the interface performs as intended.
10. **FDA CR#2 Question 10:** Documentation package for Build 1.0.5.5 (sent as FDA Question 5): In the NAT Amendment received March 23, 2017 in response to FDA IR Question 14, you stated that the (b) (4) software will no longer be compiled for commercial release, but that the final version will be Build 1.0.5.5. Please review the documentation provided, and ensure that all design documentation including appropriate verification and validation testing corresponding to version Build 1.0.5.5 has been provided.
11. **FDA CR#2 Question 11:** Risk processes (sent as FDA Question 9): In the NAT amendment received March 23, 2017 in response to FDA IR Question 17, you included updated risk documentation. There is some better alignment with ISO 14971 “Medical device – application of risk management to medical devices,” but the table in the (b) (4) Hazard Analysis (Attachment_15.1-IT-CSV-PDF-41.xlsx) is not an FMEA and does not align with terminology used in ISO 14971. Consider the following:
- What does your “Probability” correspond to in ISO 14971? It is not clear what your “Probability” refers to so it is difficult to assess the risk table. The “Scoring System” tab refers to Likelihood, not Probability. For example, Risk 2 “password hacked” has a Probability of 4 which is high, so it is unclear if this refers to P1 or P2 or the combination. In the “Front page” tab of the NAT Risk Analysis (Attachment_22.1-LAB-DSGN-11.xlsm), the Likelihood definitions specifically refer to failures. This suggests that your probability is still focused only on P1 and does not include probability of a hazardous situation leading to harm. Please revisit your risk management processes and provide a clear description of your processes and how they align with ISO 14971. State explicit the scope of “probability” in your documentation and ensure your risk documentation includes all aspects of probability. As a start, we suggest removing the notion of “failure” from your definitions.
 - 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.xlsx) and its alignment with ISO 14971, and ensure that you make the same changes to both risk documents for consistency regarding clear traceability with hazards, hazardous situations, causes, traceability to mitigations in manuals and SOPs, etc. We recommend that you should harmonize the format you are using to capture risk information so that all use the same terminology and methods, or you should provide a clear description and process for each that allows independent review.*

12. **FDA CR#2 Question 12:** *Cybersecurity considerations (sent as FDA Question 10): In the NAT Amendment received March 23, 2017 in response to FDA IR Question 20, you provided several documents including an updated (b) (4) Risk Analysis” (Attachment_15.1-IT-CSV-PDF-41.xlsx). Please note that we assess the adequacy of your cybersecurity features based on the threats and vulnerabilities you identify in your risk assessment. Without your analysis and identification, it is difficult for us to determine if the mitigations you implement are adequate. We do not have a clear picture of the client server and database components and connectivity to other systems. We see mention of some mitigations and some evidence of threats in several documents, but you have not provided a comprehensive view of the security risks to your system. The following suggest that the analysis activities we requested and described in the cybersecurity premarket guidance have not occurred.*

- *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.

The following question was generated in response to information provided in the May 23, 2017 communication to FDA.

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

Comments: The responses to question 6-13 are acceptable. The details are available in Lisa Simone memo in EDR dated February 7, 2018. Resolved.

Facility (DMPQ)

The detailed resolution of FDA CR#2 Questions 14-20 is available Lori Peters DMPQ review memo in EDR dated February 12, 2018.

14. **FDA CR#2 Question 14:** *In your response document “BLA Complete Response BL125588/0 Imugen Response” dated December 14, 2016, to FDA CR Question 44 on categorical exclusion, your justification from a categorical exclusion for preparation of an environmental assessment for the NAT assay is not satisfactory. Please revise your justification to indicate how your finished device lots for the NAT assay meets the exclusion criteria.*

Equipment Qualification (DMPQ)

15. **FDA CR#2 Question 15:** *The equipment qualification reports you provided for the NAT Extraction Systems in your Complete Response Letter date December 14, 2016, response to question #47 do not appear to be performed in accordance with a protocol with defined acceptance criteria. In addition, the reports do not appear to include a sign-off review by Quality. Based on your performance qualification protocol for the new NAT extraction systems, please perform an evaluation of the results of the performance qualifications for the legacy NAT extraction systems and determine if the systems were adequately qualified and meet the criteria outlined in the protocol. Please provide a copy of the evaluation(s).*
16. **FDA CR# 2 Question 16:** *In the September 29, 2015, Complete Response Letter, Item #47C, you were asked to provide the performance qualification report summaries for all data collected from all machines used on all shifts, you have only provided the performance qualification data for (b) (4) of the (b) (4) NAT extraction units. Please provide the performance qualification reports for the remaining NAT Extraction systems (b) (4) in use for blood donor screening operations.*
17. **FDA CR#2 Question 17:** *Please provide a summary and a copy of the procedure related to the performance verification activities that are performed on the current NAT extraction systems to ensure the systems are functioning correctly and not resulting in a false positive or false negative test result. Please ensure your response describes the frequency of performing the verification activities.*
18. **FDA CR#2 Question 18:** *We acknowledge that you intend to qualify additional pieces of NAT equipment to perform manufacturing and blood donor screening activities for licensure of your BLA. For each new piece of equipment, please provide the applicable equipment performance qualification (PQ) protocol and the executed report. The protocols shall include defined tests to be performed, representative number of samples to be tested, and the acceptance criteria.*
19. **FDA CR# 2 Question 19:** *The cleaning of the NAT equipment used for manufacture of assay components and to perform blood donor screening shall be documented in procedures to ensure consistent cleaning between operators. Please provide a copy of the cleaning procedures.*
20. **FDA CR#2 Question 20:** *Please perform an evaluation of the cleaning agents and cleaning process (indicated to include (b) (4) you utilize to determine if the cleaning is effective at removing contaminating material from your NAT equipment including the extractors, PCR set-up system, Please perform an evaluation of the cleaning agents and cleaning process (indicated to include (b) (4) you utilize to determine if the cleaning is effective at removing contaminating material from your NAT equipment including the extractors, PCR set-up system, and thermocyclers.*

Please provide a copy of the applicable equipment cleaning reports demonstrating the removal of contaminants.

Comments: The responses to question 14-20 are acceptable. The details are available in Lori Peters DMPQ review memo in EDR dated February 12, 2018. Resolved.

Labeling

21. **FDA CR#2 Question 21:** *Please submit the updated summary of application.*

Response: Imugen provided the intended use statement.

Comment: Though the summary was not provided, FDA prepared the Summary Basis of Approval (SBRA) document and shared the performance characteristic of the NAT assay with sponsor for concurrence. Resolved.