

Subject: Information Request related to the Complete Response from Imugen, dated December 12, 2016, in response to the FDA Complete Review (CR) letter, dated September 29, 2015, of the BLA *Babesia microti* arrayed Fluorescence Immunoassay. We are providing the following comments and request for additional information to continue our review. Please provide the responses to all questions by March 17, 2017.

1. In the response to question #11 in the CR letter, the Imugen response (pages 16&17) as well as the Attachments 11.1 and 11.2, a stability protocol (DOC-STB-24) and a stability report (DOC-STB-RPT-24) refer to other stability reports: DOC-STB-RPT-6, DOC-STB-RPT-22, DOC-STB-RPT-23 and DOC-STB-RPT-20 (page 3 of 15). Please confirm that all the data reported in these individual reports have been included in the result section of DOC-STB-RPT-24 (pages 6-10). Please provide any additional stability data that have not been included in DOC-STB-RPT-24. This data is necessary to evaluate the stability of Babesia AFIA kit components.
  - a. The real time stability studies only include (b) (4), DOC-STB-24, page 6 of 13). The data provided for the other (b) (4) and (b) (4) are derived from stability testing of kit components which are supportive but not sufficient to establish the shelf life of an assembled finished device at the time of licensure. In order to generate additional stability data that could be considered for establishing a shelf life of the finished device, FDA recommends testing of 2 additional finished devices among the conformance lots (b) (4) described in Attachment 19.2, Table.1, before their current assigned expiration dates. Please provide results for additional finished devices obtained according to protocol DOC-STB-24. Initial stability results can provide interim expiration dating at the time of licensure. Expiration dating of the Finished Device Lot can be extended by amendments to the BLA as data accumulate.
2. In the response to question #12 in the CR letter, you have provided data to demonstrate the absence of microbial cross reactivity and interference in the B. microti AFIA (DOC-RPT-35; Attachment 12.1).
  - a. The data provided shows that there was no interference of bacteria in the B. microti AFIA. However, the conclusion that there was no cross reactivity is inappropriate. To demonstrate cross reactivity, please test plasma from individuals with antibody reactivity to bacterial infections on the Babesia AFIA.
  - b. You refer to DOC-PRO-28, submitted in your BLA, as the protocol that was used to generate the bacterial spiked samples. Please provide the version history of this document. Please indicate the changes that were made to the protocol in the version used in the current study.
  - c. Similarly, please provide the version history of the document LAB-SER-BIFA-1. Please indicate the changes that were made to the protocol in the version used in the current study.

3. In response to question #13 in the CR letter, you have provided data to demonstrate the absence of cross reactivity for P. falciparum (DOC-PRO-43 and DOC-RPT-59).
  - a. Please explain the differences between the sample set of 4 P. falciparum samples obtained from the (b) (4) and the 20 samples from (b) (4).
  - b. On page. 2 of 4 of Attachment 13.2 you state that the specimen data sheet for the 20 P. falciparum samples is attached. This specimen sheet could not be located in the submission. Please provide the specimen data sheet for the (b) (4) samples as well as the samples obtained from (b) (4).
  - c. In the conclusion of DOC-RPT-59 you state that 4/4 previous (b) (4) samples identified as P. falciparum reactive by (b) (4) were positive in the Babesia AFIA at 1/64. Is there any indication these (b) (4) would be reactive at 1/128? Is there a rationale for not reporting the cross reactivity of P. falciparum specimens with Babesia as 4/24?
4. In response to question #14 in the CR letter, you have provided data to demonstrate the absence of cross reactivity for ANA (DOC-PRO-49 and DOC-RPT-71).
  - a. Please explain the differences between the earlier sample set of 20 ANA specimens and the 20 samples from (b) (4).
  - b. Please provide the specimen data sheet for all 40 samples used for the ANA study.
5. In response to question #16 in the CR letter, you present a comprehensive Master Validation Plan and describe results that seem to be reported in DOC-RPT-46. Please provide this document. Please provide DOC-RPT-60 so that we may evaluate the Validation Study and establish the date on which the manufacturing processes and assay procedures were validated and locked. We expect this information is found in DOC-RPT-60.
6. In response to question #18 in the CR letter,
  - a. Attachment 18.1, page 267, a flow chart is provided describing Finished Device Lot final release testing. This chart and the associated text state that if a component has not been approved in previous release testing, then the manufacturing proceeds by a specified worksheet, however, if the component has been approved in previous release testing, manufacturing follows a different path. Does the underlined “previous release testing” mentioned in the previous sentence refer to Finished Device Lot testing or the in-process testing that is expected for the release of a manufactured component?

- b. The results of the Validation Report for the Finished Device Lots are given in DOC-RPT-52. These results are reported as pass or fail (all results passed). This is satisfactory for the answer to this CR question, however anticipate that the raw data will be examined at the pre-license inspection.
  - c. After a Finished Device Lot is tested for release and approved, where is the instruction that the components labeled with the same finished device lot number must always be used with components of the same finished device lot?
7. In response to question #21 in the CR letter, Imugen states that ‘A critical supplier audit was carried out on the (b) (4) and audit actions requests have been followed up and are being monitored.’ Such an audit indicates Imugen’s intent to comply with the FDA requirement that there is complete control over the infected red blood cell manufacturing process. However, the statement is vague and does not reveal how (b) (4) is being monitored for compliance with the agreed protocols, LAB-MFG-8. Additionally, the contract is under negotiation; finalized and signed would better indicate control over the process.

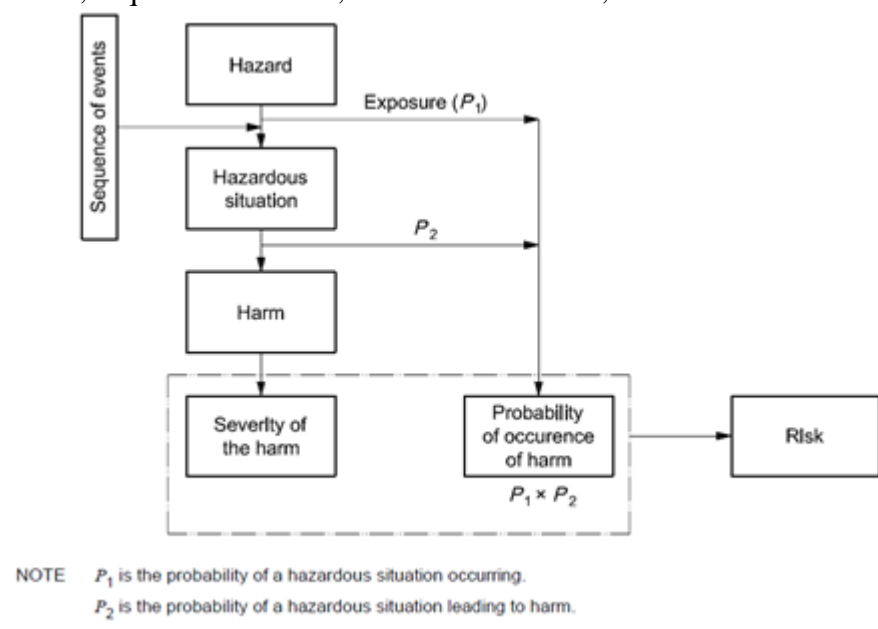
The animal protocol for this study is part of this manufacturing process and it is under the (b) (4). The IACUC protocol (#A98-04-003) indicates that the IBC (Institutional Biosafety Committee) approval was pending at the time the copy of the protocol was added to the submission to the FDA. It should be approved before any animal procedure will be done under this protocol. What is the current status? Also, in the (b) (4), the sponsor is proposing (b) (4) year) to be used. Please provide a projection of how the sponsor will handle enough (b) (4) to scale up the manufacturing process, if needed, in the future for licensed blood donor testing.

8. In response to question #22d in the CR letter, you indicate the integrity of (b) (4) passages of parasites in (b) (4) has been validated (LAB-MFG-8). The document, LAB-MFG-1, the certificate of analysis for “Babesia microti infected (b) (4) whole blood processing and testing for AFIA/ NAT” should show a record of the infection passage, with a criterion that passage number be less than or equal to (b) (4) or specify how the number of passages in (b) (4) will be tracked and documented for each lot of infected red blood cells. Please provide a copy of the current version of LAB-MFG-1.
9. In response to question #27 in the CR letter, updated SOP LAB-MFG-15 describes the slide manufacturing process. Step 12 of the SOP captures the number of slides that fail the (b) (4) during the manufacture of a new batch of AFIA slides. However, it does not specify the maximum number of failed slides that is acceptable during the manufacture of a new batch of slides. Imugen should develop, based on historical data, acceptance criteria for the maximum number of failed slides above which the batch of slides will be rejected and an investigation will be triggered to determine the root cause for this failure. The slides are the most critical component of the AFIA assay and their manufacture should be sufficiently controlled to ensure batch to batch consistency. Please

comment on such an acceptance criterion, if one already exists or the proposal to establish one.

10. The response to question #31 in the CR letter is not sufficient. Table 31.1 provides summary results and does not show operator-to-operator variability. Because the AFIA test results rely on the (b) (4) by the technician, in particular during in-process testing and for the positive control on every slide, your SOPs require the intensity score be within a narrow range as an acceptance criterion. For this intensity score to be accurate the operator-to-operator (i.e. (b) (4) ) variability needs to be assessed and processes need to be in place to minimize any differences. Please provide data to demonstrate that the technician-to-technician variability is acceptable. Please also provide training material that is used to train and verify the uniform performance of (b) (4)
11. In response to question #31 in the CR letter, part c of your answer, the procedure from SOP LAB-SER-BIFA-1 is restated, “A sample which scores (b) (4) is considered reactive. ... a reactive sample must be retested in duplicate.” However, page 22/28, step I. of that SOP, says that “additional retests (N=2 or 3) may be required at the discretion of the supervisor to further evaluate any inconclusive findings in order to yield interpretable results.” If multiple retests of the same samples are required, what is the algorithm to make the final interpretation from the 5 or 6 results and how are these results captured in the (b) (4)? Please revise LAB-SER-BIFA-1 accordingly.
12. In response to question 33 in the CR letter, a revised version of LAB-DSGN-1, the design plan was submitted. In section 3.8, page 528 of the Imugen Complete Response, it is stated that all changes must follow LAB-QA-24. LAB-QA-24 of the original BLA refers to LAB-QA-26, the description of the (b) (4) system as the means by which Imugen documents are controlled. LAB-QA-26 of the original BLA describes that all changes to documents are controlled, require approval by proper authority and date recorded for such approvals. The Imugen response to the CR letter contains numerous documents that have version numbers greater than the version number of the same document submitted in the original BLA, some of them by multiple steps. When were the changes made, who were they approved by and what specific changes were made? For example, LAB-AQC-SER-85 was submitted in the original BLA as version 1.3. In the CR Response, the same document was version 1.5. There are no dates or approvals noted for the multiple changes made in version 1.5. Of all the changes, the most significant are (b) (4) instruction that may have been moved to LAB-MFG-34; however that document was not included in the CR Response. Please provide it and some description of the documentation of changes to LAB-AQC-SER-85 as an example of document control.
13. In your AFIA Amendment response received December 13, 2016 in response to FDA Question 34 you stated that you used FMEA and ISO 14971 methodologies for your Risk Analysis, and you provided the document “B. microti AFIA Risk Analysis” (Attachment-33.5\_LAB-DSGN-5.xlsx). In the tab “Front page” you provided a risk matrix and described levels for “Severity” and “Likelihood” to estimate risk. Your definition of

likelihood values focuses on failures and the frequency that a failure would occur; however, this does not align with likelihood or probability in ISO 14971, which focuses on occurrence of harm rather than failure. Risk in ISO 14971 is the combination of the probability of occurrence of harm and the severity of that harm. Risk estimation considers two likelihoods: the likelihood of a hazardous situation occurring and the likelihood of the hazardous situation leading to harm. These are both considered when determining the overall probability of harm for a particular combination of events. Figure E.1 from ISO 14971 provides a good pictorial representation of the relationship of hazard, sequence of events, hazardous situation, and harm.



It is not clear how your use of “likelihood” captures the probability portion of risk as outlined in ISO 14971. Please provide your processes related to risk management and explain how your processes align with ISO 14971. We recommend that you revisit how you define “likelihood” so that it is better aligned with ISO 14971 and provide an update on your risk analysis table. This should be aligned with the risk-related requests elsewhere in this communication

14. In your AFIA Amendment response received December 13, 2016 in response to FDA Question 34, you provided the document “B. microti AFIA Device Risk Analysis” (Attachment- 33.5\_LAB-DSGN-5 .xlsx), which includes analysis of risk for several topics including device safety and human factors. Using a spreadsheet with filtering is an excellent method to capture and explore risks with use of your device and we encourage you to leverage this method.

You have identified a number of relevant hazards, but you have not drilled down to the level of individual hazardous situations and harms for these hazards. For example, H82 (Babesia microti AFIA BLA-37) lists “Complex instructions or user interface using software leading to incorrect assay procedure.” There are a number of possible causes and hazardous situations that could lead to harm, but you have presented them as a whole rather than exploring each individually. From the list of countermeasures listed, it is

clear that you have identified several possible problems that could occur and have likely already performed this analysis, but you have not captured the individual details. Mitigations for H82 appear to include both protective measures and information for safety, and should be assessed and presented individually. It is impossible to determine which mitigations apply to which issues.

In several places, your “potential causes” column has some “harm” information mixed in. If more than one “harm” could occur (e.g., incorrect results and invalid results are often associated with different types of harm with often different severity levels), you should have a separate row for each harm because the severity rating is applicable to each harm, not to each hazard. For example, for H82, you have listed both “incorrect results” and “invalid results” in this single row, although the possible harms associated with these two hazards are often different. “Incorrect results” and “invalid results” likely represent several different risks and each should be analyzed and addressed individually. You will also have separate entries for different hazardous situations if the probability factors are different for each (i.e., likelihood of a hazardous situation occurring and the likelihood of the hazardous situation leading to harm).

In your “Review hazards & risk” tab in column D, you combine “Hazard” and “Risk” when these are actually two different concepts. This should naturally resolve itself by ensuring each risk has its own row. Creating a unique column for “Harm” will also allow you to decouple harm from “Potential Cause” and better identify individual hazardous situations that could lead to harm.

Performing your risk activities at this level allows you to fine-tune how and where you address risk reduction activities in your design, and ensure you have considered different ways harm could occur. In many instances, you have combined them into the same entry and have lost the ability to ensure that each risk is dealt with optimally. It can be difficult to identify the overall reduction in risk without considering them individually. This can be misleading because if you haven’t explicitly listed specific causes or situations, it is difficult to ensure that you’ve identified and implemented the appropriate mitigation(s) (countermeasures) for each of those situations. Using spreadsheet filtering will allow you to quickly see the impact of a particular mitigation or the scope of a particular harm or hazard. Finally, when you are assessing the post-mitigation risk, you do so based on each mitigation individually, which you have not done.

- a. There are a number of references to the (b) (4) software in this document, although it is not clear how these risks are related to the risk information in the (b) (4) Risk Analysis (Attachment- 34.1\_IT-CSV-PDF-41.xlsx), or how traceability is maintained between this and (b) (4) design control documentation. Please explain how the (b) (4)-related information between these two documents is aligned, and how traceability to the requirements is captured.
- b. Please provide an update to this risk analysis to identify for each hazard, a list of possible harms, and the hazardous situations/causes that could allow each of those harms to arise from that hazard. Each should be in a unique row. This is

necessary to understand the range of possible hazardous situations and to understand how your mitigations reduce each risk to acceptable levels. This will allow a one-to-one mapping with the individual mitigations and more appropriate assessment of the post-mitigation risk. It will also allow you to filter the table looking for trends and assess the impact of different factors, such as the importance of some mitigations or causes.