

From: Wood, Lorraine
To: Wolfgang Pieken
Cc: Valencia, Iliana
Subject: Information Request for BLA 125588 and 125589
Date: Friday, April 14, 2017 9:53:00 AM
Attachments: image001.png
Importance: High

Sent on Behalf of Iliana Valencia

Dear Dr. Pieken;

We are reviewing your response to Information Request dated March 23, 2017 regarding resubmission of your biologics license application BL125588 for *Babesia microti* Nucleic Acid Test and BL125589 *Babesia microti* AFIA. We are providing the following comments and request for additional information to continue our review.

The following question is related to performance requirements for the infrastructure to support the (b) (4) software and assay systems.

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 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.

The following questions are related to verification and validation testing.

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.

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 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).

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) PCR 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.

The following question is related to ensuring that a complete and comprehensive documentation package is submitted for the new software version, Build 1.0.5.5.

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. The following questions are related to hazard and risk analyses and the procedures used to perform these analyses. An additional risk-related question focuses on cybersecurity considerations that have not been adequately captured in the risk documentation and elsewhere.

6. Risk management process: In the AFIA Amendment received March 20, 2017 in response to FDA Question 13, you stated that you updated your risk analysis to better align with ISO 14971. Your process appears to have changed as a result of your last amendment with the elimination of "likelihood" from your risk analysis and other changes as described in your document "Re-Analysis of Risk Assessment LAB-DSN-5" (Attachment_13.3-DOC-RPT-91.pdf). We are trying to locate the relevant processes/procedure(s) because they don't appear to be aligned with ISO 14971.

In section 2 of the re-analysis document, you stated that the risk analysis was performed according to "LAB-QA-62 Risk Management Procedure." However, in response to FDA Question 33 in your response document (001_AFIA Response to AI p 1 to 260.pdf) received December 13, 2016, you stated on page 35 that LAB-QA-62 was obsoleted and that the information was included in the revised LAB-QA-67 (Attachment 33.3). We reviewed the Design and Development Procedure (LAB-QA-67) (003_AFIA Response to AI p 497 to 737.pdf); however, LAB-QA-62 is not listed as obsoleted, but is referenced for use in developing the Risk Analysis.

Please provide the document LAB-QA-62 and any other risk related procedures that apply to the NAT and AFIA assays and to the (b) (4) software and associated hardware. Because it appears that you have updated your processes, please provide the latest documentation describing how you perform your risk related procedures.

7. Risk Management and ISO 14971 alignment: In the AFIA Amendment received March 20, 2017 in response to FDA Question 13, you provided updated risk information. We requested that you describe how your processes align with ISO 14971 but you did not provide an explanation. Language in your "Re-Analysis of Risk Assessment LAB-DSN-5" (Attachment_13.3-DOC-RPT-91.pdf) suggests misunderstandings in the applicant of ISO 14971 "Medical device – application of risk management to medical devices." We are attempting to understand what you changed by comparing your previous risk documentation to the latest documentation, in order to identify what should be addressed.

a. In your document "Re-Analysis of Risk Assessment LAB-DSN-5" (Attachment_13.3-DOC-RPT-91.pdf) in Table 3 in response to FDA Question 13, you provided estimates of Probability of Harm. Table 1 includes Failure Effect Codes mapped to both severity and probability. Specifying Severity for a particular harm is appropriate. However, please note that estimates of probability of harm are made within the context of each identified hazard and hazardous situation, and assigning probability of harm to a failure effect as you have done (independently of the hazardous situations and causes) is not consistent with risk analysis as outlined in ISO 14971. The different potential causes and resulting hazardous situations will affect the value of probability for that particular situation. Table 1 should be changed to align with ISO 14971, and the direct mapping to "Probability of Harm" removed.

b. In concert with part (a) above, the "Probability of Harm" in the document "Babesia microti AFIA device risk analysis" (Attachment_13.1-LAB-DSGN-5.xlsm) should be updated to reflect your assessment of "Probability of occurrence of harm" as a combination of probability of the hazardous situation occurring and the probability that the hazardous situation leads to harm. You do not need to identify P1 and P2 in this document, but your assessment of "Probability" should be specific to the "Potential Cause(s)" that you have identified.

c. You have added the term "failure effect" to your risk documentation. This term is used in FMEAs but is not used in ISO 14971. Please clarify how this maps to your support of ISO 14971. Your document "Re-Analysis of Risk Assessment LAB-DSN-5" (Attachment_13.3-DOC-RPT-91.pdf) does not explain how failure effects are related to harms, because they are not the same thing. One failure effect may be associated with more than one kind of harm; for example, a false positive and a false negative are generally associated with different harms and have different severities and sometimes different probabilities of harm. However, you combined false negative and false positive in several cases. You should consider consistently adopting terms from ISO 14971 and be consistent with a particular methodology. Please update your risk documentation accordingly. We suggest removing "failure effect" and including columns consistent with ISO 14971.

d. In the document "Babesia microti AFIA device risk analysis" (Attachment_13.1-LAB-DSGN-5.xlsm) it appears you eliminated the term "likelihood" and replaced it with "probability." In the "Front page" tab, the Probability 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. Note that this will require more than changing column names and definitions, but will require that you ensure each row in the table is specific to one cause/situation, and that the value of Probability is the probability that the cause/situation would lead to harm. Harm should be added to the table. This is necessary to produce an assessment that is aligned with ISO 14971.

8. Risk Analysis and Traceability: In the AFIA Amendment received March 20, 2017 in response to FDA Question 14, you provided document "Babesia microti AFIA device risk analysis" (Attachment_13.1-LAB-DSGN-5.xlsm). In the

NAT Amendment received March 23, 2017 in response to FDA Question 17, you provided the (b) (4) Hazard Analysis (Attachment_15.1-IT-CSV-PDF-41.xlsx) and the NAT Risk Analysis (Attachment_22.1-LAB-DSGN-11.xlsm). In the "Review hazards & risk" tab for both assay analyses, your risk information is presented generally, without specifics. You have not established clear one-to-one traceability between specific potential causes and hazardous situations and the "Countermeasures to take." Many of the countermeasure entries include several individual countermeasures, and it is not clear how these countermeasures would be adequate to mitigate the potential causes, because the potential causes are not specific. For example, H80 in the AFIA analysis lists several potential causes related to mistakes in manual activities, but you have not explicitly listed the types of mistakes that could be made, the possible harm (severity) of each mistake and the probability associated with each. This should be done, so you can identify the appropriate countermeasures for each.

For all your analyses, please provide additional specifics for each cause/hazardous situation that could occur, and provide countermeasures and pre/post risk assessment for each one. This should capture specific situations, how these situations could come about, and how you address each. For example, if a warning is to be placed in the operator's manual to address an identified risk, a reference for the explicit warning would appear in your risk documentation for that particular situation. If the information is contained in a manual or SOP, a specific reference within that documentation should be provided. This is necessary to understand that you have identified and considered specific situations that could lead to harm, and identified, implemented and tested mitigations to reduce these risks to acceptable levels. We expect to be able to trace from the identified situations to the specific warnings or guidance you provide as a countermeasure.

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.xlsm), the Likelihood definitions specifically refer to failures. This suggests that your probability is still focused only on P1 and does not include probability of a hazardous situation leading to harm. Please revisit your risk management processes and provide a clear description of your processes and how they align with ISO 14971. State explicit the scope of "probability" in your documentation and ensure your risk documentation includes all aspects of probability. As a start, we suggest removing the notion of "failure" from your definitions.

b. What is your process to determine the new level of Probability as the result of the identified mitigation(s)? Please provide your risk documentation that describes how this is determined.

c. Please refer to comments made regarding the "Babesia microti AFIA device risk analysis" (Attachment_13.1-LAB-DSGN-5.xlsm) and its alignment with ISO 14971, and ensure that you make the same changes to both risk documents for consistency regarding clear traceability with hazards, hazardous situations, causes, traceability to mitigations in manuals and SOPs, etc. We recommend that you should harmonize the format you are using to capture risk information so that all use the same terminology and methods, or you should provide a clear description and process for each that allows independent review.

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-SECPOL-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/fdagovpublic/@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.

Thank you

Lorraine

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