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Summary Basis for Regulatory Action Template

Date: August 27, 2019

From: Krishna Mohan V. Ketha, Ph.D., Chair of the Review Committee

BLA/ STN#: 125699/0

Applicant Name: Roche Molecular Systems, Inc

Date of Submission: February 28, 2019

MDUFA Goal Date: December 27, 2019

Proprietary Name: cobas® Babesia test for use on the cobas® 6800/8800 Systems

Trade Name (common or usual name): cobas® Babesia

Intended Use/Indications for Use:

The cobas® Babesia test for use on the cobas® 6800 and cobas® 8800 Systems is a qualitative in vitro nucleic acid screening test for the direct detection of *Babesia* (*B. microti, B, duncani, B. divergens, and B. venatorum*) DNA and RNA in whole blood samples from individual human donors, including donors of whole blood and blood components, and other living donors. This test is also intended for use to screen organ and tissue donors when donor samples are obtained while the donor's heart is still beating. Whole blood samples from all donors may be screened as individual samples.

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

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

This test is not intended for use on cadaveric blood specimens.

Recommended Action:
The Review Committee recommends licensure of this product.

Review Office Signatory Authority: Nicole Verdun, M.D., Director, Office of Blood Research and Review

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Table 1: Reviews Submitted

Document Title	Reviewer Name	Document Date
Product Review (Product Office) • *Clinical* • *Non-Clinical*	 Babita Mahajan Miranda Oakley Caren Chancey	 July 24, 2019 July 31, 2019 July 30, 2019
Living Organ Donor and Cadaveric Donor Claim	Brychan Clark	July 30, 2019
Statistical Review • *Clinical and Non-Clinical*	 Paul Hshieh	 August 8, 2019
CMC Review • *CMC (Product Office)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DMPQ)*	 Rana Nagarkatti Nitin Verma Deborah Trout Karla Garcia	 July 31, 2019 July 30, 2019 August 8, 2019 July 03, 2019
Labeling Review(s) • *APLB (OCBQ/APLB)* • *Product Office*	 Twanda Scales Krishna Mohan V. Ketha	 July 9, 2019 August 19, 2019
Lot Release Protocols/Testing Plans	Kori Francis Varsha Garnepudi Swati Verma	August 6, 2019 July 31, 2019 July 30, 2019
Bioresearch Monitoring Review	Colonious King	August 20, 2019
Software and Instrumentation	Lisa Simone	August 5, 2019

1. Introduction

Roche Molecular Systems, Inc. (RMS) located at 4300 Hacienda Drive, Pleasanton, CA 94588, submitted an original Biologics License Application (BLA) for licensure of the cobas® Babesia test. The cobas® Babesia is a nucleic acid test (NAT)-based blood donor screening assay for *Babesia*.

The BLA application from RMS, was received on February 28, 2019 through the FDA's Electronic Submissions Gateway with electronic content only (STN 125699/0). The BLA was granted a standard 10-month review status with a final ADD of December 27, 2019. This submission was filed April 16, 2019 and the mid-cycle meeting was held on June 5, 2019. A chronological summary of FDA information requests, sponsor responses, telecons, and pre-submission meetings are listed in Table 2.

Table 2: Chronological Summary of Submission and FDA Correspondence

Date	Action	Amendment
December 20, 2016	Type B Pre-IND Teleconference with RMS	
February 21, 2017	Pre-Sub (Pre-IND) Meeting Request	BQ170020
May 5, 2017	FDA Feedback to Q Sub	
June 30, 2017	Original IND Application	IND17582
August 30, 2017	Issue Advice Letter for IND	
May 4, 2018	Pre-sub for Analytical studies	BQ180208
July 11, 2018	FDA Feedback to Q Sub	
August 24, 2018	Pre-sub for ASAP update/change Ct cut off	BQ180248
October 10, 2018	FDA Feedback to Q Sub	
February 28, 2019	Original BLA submission	BL125699/0
April 19, 2019	Information Request (IR) – Intended Use	
April 22, 2019	Response to IR	BL125699/1
April 23, 2019	IR - Facility & Quality Systems	
April 29, 2019	IR - Lot Release Protocol (LRP)	
April 30, 2019	Response to IR dated April 23	BL125699/2
April 30, 2019	Response to IR dated April 29	BL125699/3
May 23, 2019	IR - CMC, analytical, and clinical	
May 30, 2019	Response to IR dated May 23	BL125699/4
May 30, 2019	IR - Bioburden documentation	
May 30, 2019	Response to IR dated May 30	BL125699/5
May 31, 2019	IR – Bioburden - complete data	
May 31, 2019	Response to IR dated May 23	BL125699/6
June 3, 2019	Response to IR dated May 31	BL125699/7
June 3, 2019	IR-Roche Whole blood collection tube	
June 3, 2019	Response to IR dated June 3	BL125699/8
June 11, 2019	IR – Clinical, CMC, software issues, LRP	
June 11, 2019	Response to IR dated June 11 - LRP	BL125699/9
June 17, 2019	Response to IR dated June 11 - Clinical, CMC	BL125699/10
June 19, 2019	Response to IR dated June 11- Software	BL125699/11
July 11, 2019	IR – CMC documentation	
July 12, 2019	Response to IR dated July 11	BL125699/12
July 15, 2019	Telecon - Software clarification	BL125699/13
July 22, 2019	Response to July 15 Telecon clarification	BL125699/14
July 31, 2019	IR - IU, labeling, stability data clarification	
Aug 1, 2019	Response to IR dated July 31	BL125699/15

2. Background

Human babesiosis is a tick-borne zoonosis caused by infections of humans with intra-erythrocytic protozoa of the genus *Babesia*. Babesiosis can also be transmitted by transfusion of blood and blood components and by transplantation of solid organs collected from an infected donor. Babesiosis is transmitted in many parts of the world but the highest prevalence is reported in the United States (U.S.). The first documented human case of babesiosis in the U.S. was identified in 1968. The vast majority of U.S. babesiosis cases are caused by *B. microti*, the species that is prevalent in the Northeast

and upper Midwest. Less commonly, other *Babesia* species such as *B. duncani* and related organisms are implicated in transmission of *Babesia* in several western U.S. states, while transmission of *Babesia* by "*B. divergens*-like" agents have been reported in multiple U.S. states.

Most cases of *B. microti* infections are asymptomatic and never diagnosed. While the duration of *B. microti* infections in healthy adults is not precisely known, in limited studies, the parasitemic period is reported to last from 2 to 7 months, but parasitemia may persist for more than 2 years. *Babesia* transmission is generally seasonal and coincides with tick activity (traditionally May-September) in affected states, but tick-borne and transfusion-transmitted infections are reported throughout the year. Transfusion of blood and blood components collected from asymptomatic infected donors may result in TTB, leading to potentially fatal clinical illness in blood transfusion recipients.

The cobas® *Babesia* shares assay principles, manufacturing technologies, controls, and common reagents with other FDA-licensed cobas® donor screening assays developed for use on the cobas® 6800/8800 Systems. These systems provide fully integrated, automated sample preparation, nucleic acid extraction, target amplification and detection. Three other blood screening assays have previously been licensed for use with the cobas® 6800/8800 systems, the cobas® WNV (BL125575), the cobas® MPX (BL125576), and the cobas® Zika (BL125653). For the cobas® Babesia, total nucleic acid from the sample and the added internal control are extracted from lysed whole blood samples using magnetic glass particles, followed by washing, elution and RT-PCR, using specific probes and primers to discriminate target and controls.

3. Chemistry Manufacturing and Controls (CMC)

a. Manufacturing Summary

i) In Vitro Substance

The In Vitro Substance Report contained the Initial Performance Report, Final Reports, as well as separate reports on synthesis/purification (where applicable), chemical formula/structure, characterization, and stability of the following test components:

- Aptamer (b) (4)
- *Babesia* Positive Control Stock
- *Babesia* oligonucleotide pools (primers and probes)
- Uracil-N-Glycosylase (UNG) and Z05D DNA Polymerase
- Generic Master Mix Buffer
- MMR2 Internal Control (IC) Primers and Probe
- RNA Internal Control Stock

The Initial Performance Report described the design process for primers and probes used in the kit. Roche proprietary software was used to design sets of primers and probes located in the most conservative regions of the *Babesia* genome and assessed for exclusivity and inclusivity. The assay included one set of primers and a probe specific for *B. microti*, three primers and a probe specific for *B. duncani*, *B. divergens*, and *B. venatorum*, and one set of primers and probe for the IC (same as in cobas Zika).

The In Vitro Substance Report section for the Omni Reagents and Common Components consisted of reports, including information on chemical formulas/structures and characterization of the materials. Test specifications and validation records for the common components such as aptamer, RNA IC, IC primers and probes, MMX buffer, bulk and stock enzymes UNG and Z05 D were provided in the original submission. Final reports for process validation for cobas® Babesia MMR-2, cobas® Babesia positive control and kit, and validation of normal human plasma, and interim report of functional testing of the Roche Whole Blood Collection Tube were also included in the submission. Additional sections described the raw materials and bulk and fill container and closure systems and contained manufacturing flowcharts, batch production records and SOPs. Executed batch records for three consecutive lots of cobas® Babesia were submitted and final release testing demonstrated that all kits passed the QC specification with no reported deviations.

ii) In Vitro Product

The In Vitro Product Report described the assay specific components needed to perform the cobas® Babesia test on the cobas® 6800/8800 Systems. There were no differences in formulation between the investigational product and the to-be-marketed product. The product was not sterile, and the sponsor validated (b) (4) for the cobas® Babesia test components. All components passed the test criteria. The cobas® *Babesia* shares assay principles, manufacturing technologies, controls, and common reagents with other FDA-licensed cobas® donor screening assays developed for use on the cobas® 6800/8800 Systems (Table 3).

Table 3: cobas® Babesia assay kits and components

Kit	Components	Omni Reagent/Common Component/Assay Specific
cobas® Babesia – 480T (480 Tests)	Babesia Master Mix Reagent 2: • Generic Buffer • Primers • Probes • Aptamer • Enzymes RNA Internal Control Proteinase Solution Elution Buffer Master Mix-R1	 • Common Component • Assay Specific • Assay Specific • Common Component • Common Component Common to cobas *Babesia* and Zika Common Component Common Component Common Component
cobas® Babesia Control Kit	Babesia Positive Control	Assay Specific
cobas® NHP Negative Control Kit	Normal Human Plasma Negative Control	Common Component
cobas® omni Wash Reagent	Wash Reagent	Omni Reagent
cobas® omni Specimen Diluent	Specimen Diluent	Omni Reagent
cobas® omni Lysis Reagent	Lysis Reagent	Omni Reagent
cobas® omni MGP Reagent	MGP Reagent	Omni Reagent

iii) Stability

The Stability Report for the cobas® Babesia, omni, and common components described stability studies that have been performed or were still ongoing on the test components to confirm the initial shelf life claim and support future shelf life. The kit components were stored at the recommended storage conditions and evaluated visually and in functional tests at predetermined time points using predefined acceptance criteria. The stated shelf life claims were as follows:

Table 4: Shelf life of cobas® Babesia assay components

Kit/component	Material Number	Storage	Shelf Life
cobas® Babesia	08244049990(NC) 08244049190	2 – 8°C	18 months
cobas® Babesia Control Kit	08460981990 08460981190	2 – 8°C	18 months
Roche Whole Blood Collection Tube	08827907001	2 – 8°C	16 months
cobas® NHP Negative Control Kit	07002220190	2 – 8°C	24 months
cobas® omni MGP Reagent	06997546190	2 – 8°C	24 months
cobas® omni Lysis Reagent	06997538190	2 – 8°C	24 months
cobas® omni Wash Reagent	06997503190	15 – 30°C	24 months
cobas® omni Specimen Diluent	06997511190	2 – 8°C	24 months

Product Quality

b. Testing specifications

The analytical methods and their validations and/or qualifications reviewed for cobas® Babesia kit were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of *Babesia* test for use on the cobas® 6800/8800 Systems is listed in the table below. The activities performed, and inspectional history are noted in the table 5.

Table 5: Manufacturing facility details for cobas Babesia

Name/Address	FEI Number	Inspection/ Waiver	Justification/ Results
Roche Molecular Systems, Inc. 1080 US Highway 202 S Branchburg, NJ 08876-3733 Final kit manufacturing	2243471	Waiver	Team Biologics July 2019 NAI

Team Biologics performed a surveillance inspection of the Roche Molecular Systems, Inc. facility in July 2019. No FDA Form 483 was issued, and the inspection was classified as no action indicated (NAI).

e) Container Closure System

Not Applicable

f) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

Versioning: cobas® System Software: v1.3.9 ("cobas® 6800/8800 Systems SW v1.3"), cobas® Babesia ASAP (Assay Specific Analysis Package) Software v11.1.0, and cobas® Synergy Software v1.3.

Device Description: The cobas® Babesia test is intended for use with the cobas® 6800/8800 System, which is a platform that allows users to perform multiple PCR-based in vitro nucleic acid amplification tests. The platform consists of either the cobas® 6800 System or the cobas® 8800 System, and both these instruments provide fully integrated, automated sample preparation, nucleic acid extraction, and target amplification and detection. The main system functionality is provided by two software components; the cobas® 6800/8800 Systems Software and an Assay Specific Analysis Package, or ASAP, to implement the assay specific functionality.

The cobas® 6800/8800 Systems Software provides basic functionality such as a Graphical User Interface (GUI), instrument management, database functionality, and report engines. It provides interfaces to the LIS (Laboratory Information System) and to middleware, such as the cobas Synergy Software, which can also be used to receive test orders and transmit individual donor test results to the LIS. These basic functions do not change when a new ASAP is added to the system.

The ASAPs are built using a common software framework and include assay (test) specific software configuration and instrument operational parameters, including test and process definitions, algorithms, and result calculation. To perform a specific test (e.g., cobas® Babesia), a user selects the test from the cobas 6800/8800 SW GUI, which in turn loads the ASAP module and initiates the hardware/software procedures pertaining to sample transfer, specific sample preparation, amplification and detection of the specified analyte.

Risk Management: A risk analysis was performed for use of the cobas® Babesia assay on the cobas® 6800/8800 Systems. Twenty-two risks related to the *Babesia* assay were identified, including six for the new *Babesia* whole blood collection tubes, six for invalid results or batches (delaying the availability of a rare blood group products or platelets to the recipient), eleven for false negative results (resulting in release of contaminated blood/organ/tissue), two for false positive results (resulting in a needlessly destroyed unit, rejection of an organ for transplantation, or transient donor anxiety), two for operator or user infection, and one for donor exposure to chemicals. Risk control measures implemented to reduce these risks to acceptable levels were provided. The applicant claimed that no risk events concerning the cobas Babesia test occurred during testing.

Twenty-seven cybersecurity-related risks were identified, with risk control measures that reduced all to acceptable levels. Possible ASAP-related root causes of cybersecurity risks include manipulation of a system component, configuration management that allows unauthorized access to configuration information, and weak key management (cryptography). Critical risk controls include authentication (code signing) of the ASAP software code and review of all ASAP packages to ensure integrity prior to installation.

Unresolved Anomalies: The applicant stated that no issues or anomalies remain for the Babesia ASAP SW v11.1.0. Unresolved anomaly information was provided for the cobas 6800/8800 Systems Software v1.3; however, this information is identical to the information provided in previous cobas assays approved on software version v1.3 (i.e., cobas WNV, MPX and Zika). The risks associated with these unresolved anomalies is assessed to be acceptable.

Testing: Testing was provided to support use of the *Babesia* ASAP on System Software v1.2 and System Software v1.3 because both versions were used during the non-clinical and clinical studies. The *Babesia* assay will only be marketed for use on System Software v1.3 (specifically, v1.3.9). The applicant reported that all test cases for the related requirements met the acceptance criteria and no issues were found during verification. Verification was provided for the new Ct min cutoff change originally described in IND 17582/23. Uncertainty testing for sample size accuracy was performed for the new sample type. Some deviations were observed from a viscous and "clotty" sample, which the applicant attributed to the whole blood not having been mixed properly with cobas PCR media upon retrieval. These were flagged and retested, and then added into the uncertainty calculation. All uncertainty requirements for sample size accuracy were met.

Development Management: The software development activities included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation testing, defect tracking, configuration management and maintenance activities to ensure the software conforms to user needs and intended use.

Review Issues

During the review, the following issues were raised and resolved:

- *Missing cybersecurity risks related to the ASAP were provided, along with the cybersecurity FMEA, the Product IT Security Threat Model, assessment of criticality of data processed, and the assessment of the system's exposure to cyber-attacks.*
- *Interoperability information for the interface to cobas Synergy Software was provided to verify the appropriate software version information and to confirm that pooling functionality cannot be initiated with the software.*
- *Risk management processes were updated just prior to receipt of this submission. The update raised concerns that risks associated with certain hazardous situations were being underestimated in two ways. First, the severity of harm associated with a false positive, false negative, and invalid/delayed result all appeared to be lowered and assigned to the same value (Severity 6: "harm...with no permanent damage"), while individual risk descriptions referred to potentially life-threatening harm (which are descriptions of Severity 8 and 10 harms). Second, hazardous situations that would appear to be associated with different harms (i.e., the "common medical practice" scenario and the "worst-case" scenario) were combined into a weighted risk score that was not explained. A telecon with the applicant was held where these concerns were discussed.*

  Based on FDA's recommendations and information in ISO 14971 ("Medical devices – Application of risk management to medical devices"), the applicant reversed most of the recent changes and is currently engaged in process improvement initiatives related to risk management. Eighteen of the twenty-two risks were updated to higher severity values to more reasonably capture the true risk of harm. Changes in the risk table demonstrate that the applicant originally underestimated several risks, including underestimating two risks that ended up as High (red) prior to risk reduction activities. The applicant justified all remaining residual risks and stated that the overall residual risk is acceptable. The response was found to be acceptable and all issues were resolved.

5. Analytical Studies

The analytical/non-clinical characteristics of the cobas® Babesia on the cobas® 6800/8800 Systems was evaluated through a series of studies to assess the performance of the assay under a variety of conditions using intact and lysed *Babesia* specimens from *B. microti*, and where possible using all four *Babesia* species.

Since there is no, currently available, primary standard for *Babesia*, RMS used the following source material as *Babesia* Secondary Standards (lysed or non-lysed) for all the analytical studies:

- *B. microti* - hamster infected RBCs (ATCC, *B. microti* Gray, Strain 30221)
- *B. duncani* - hamster infected RBCs (ATCC, *B. duncani* Strain PRA 302)
- *B. divergens* - sheep RBCs infected with *B. divergens* (Oniris, Strain B128)
- *B. venatorum* - sheep RBCs infected with *B. venatorum* (Oniris, Strain C201)

5.1 Limit of Detection (LoD) studies

The LoD of cobas® Babesia was determined using two approaches:

- using (b) (4) spiked into EDTA whole blood, and
- using parasites from animal specimens diluted in EDTA whole blood

i) LoD for *Babesia* species using (b) (4)

The analytical LoD for the cobas® Babesia assay was determined using three panels prepared by (b) (4) Each of the three panels, prepared using (b) (4), consisted of (b) (4) members for each *Babesia* species (b) (4) for *B. microti*), with expected levels ranging from (b) (4) iRBC/mL (b) (4) LoD) to (b) (4) iRBC/mL (b) (4) LoD), and a negative panel member. The acceptance criteria for the LoD according to a 95% PROBIT model were set to be (b) (4) iRBC/ml for *B. microti* and (b) (4) iRBC/ml for *B. duncani*, *B. divergens*, and *B. venatorum*. For each species, a total of (b) (4) replicates per concentration level and per dilution series was distributed across (b) (4) reagent lots and (b) (4) cobas® 8800 Systems. LoD results did not vary significantly by reagent lot. The results were determined to be acceptable (Table 6).

(b) (4)

ii) LoD using *Babesia* culture specimens diluted in human whole blood

The LoD for the cobas® Babesia assay was also evaluated using three panels prepared using iRBC (b) (4) from animal cultures for each of the four *Babesia* species. Each of the three panels, prepared using EDTA whole blood from (b) (4) different blood donors, consisted of (b) (4) members for each dilution series, with expected LoD levels ranging from (b) (4) LoD to (b) (4) LoD, and a negative blank. Each panel member was then diluted in the *Babesia* Whole Blood Collection tube containing (b) (4) (b) (4), using (b) (4) different whole blood input volumes (b) (4) and (b) (4) to evaluate the efficacy of less than optimal sample volume.

The titer of the *Babesia* Secondary Standard in iRBC was determined by the (b) (4) cobas® 8800 and (b) (4) cobas® 6800 systems. The acceptance criteria were that the LoD would be (b) (4) iRBC/mL for *B. microti*, (b) (4) iRBC/mL for *B. duncani*, or (b) (4) iRBC/ml for *B. divergens* and *B. venatorum*, according to a 95% PROBIT model. The results of the LoD testing are shown in Tables 7 and 8.

(b) (4)

Table 8. LoD testing using (b) (4) whole blood input volume

***Babesia* species**	**Lot (b) (4) (iRBC/mL)**	**Lot (b) (4) (iRBC/mL)**	**Lot (b) (4) (iRBC/mL)**	**Overall (iRBC/mL)**	**95% CI**
B. microti	(b) (4)			6.1	5.0-7.9
B. duncani				50.2	44.2-58.8
B. divergens				26.1	22.3-31.8
B. venatorum				40.0	34.1-48.7

Overall, the LoD testing for the cobas® Babesia was appropriately performed to evaluate the performance of the assay with all four *Babesia* species, considering potential variables such as primer/probe performance as well as the concentration of iRBC in whole blood and the amount of *Babesia* RNA contained within each iRBC. The data reviewed was found adequate and acceptable.

Review issues

- *An IR was communicated to RMS on May 22, 2019 seeking clarification regarding the difference in final LoD estimation (6.1, (b) (4) iRBC/mL) for B. microti in various studies.*
- *RMS responded on May 30, 2019 clarifying that the (b) (4) iRBC/mL (b) (4) LoD estimation was based on dilution factor of the (b) (4), while the 6.1 (b) (4) iRBC/mL LoD was based on dilution factor of non-lysed secondary standards and the different input volumes.*

5.2 Inclusivity studies

Inclusivity studies were performed to ensure consistent detection of all four claimed *Babesia* species. The goal of the study was to test at least 10 individual positive specimens per *Babesia* species; however, due to non-availability of clinical specimens for *B. duncani, B. divergens* and *B. venatorum*, the Roche Secondary Standards described previously were used at approximately 4x LoD to test these three species. For *B. microti*, 10 unique clinical specimens were tested neat and diluted to approximately 4x LoD. The study adequately demonstrated inclusivity for *B. microti* clinical specimens and inclusivity for the other three species by the Roche Secondary Standards. The results support the intended use claims.

5.3 Analytical specificity

The specificity the of cobas® Babesia was evaluated for potential cross-reactivity in specimens spiked with microorganisms. *Babesia*-negative whole blood in (b) (4) at a ratio of (b) (4) was spiked with the following microorganisms at 10^5 - 10^6 copies, CFU, or IU/mL: *Anaplasma phagocytophilum, Staphylococcus aureus, Staphylococcus epidermidis, Propionibacterium acnes, Borrelia burgdorferi, Borrelia hermsii, Borrelia parkeri, Borrelia recurrentis,* Human Immunodeficiency virus type (b) (4) (HIV- (b) (4), Hepatitis B virus (HBV), Hepatitis C virus (HCV), West Nile virus (WNV), Parvovirus B19, *Plasmodium falciparum*, and *Candida albicans*. The microorganism-spiked negative whole blood was divided into two aliquots, the first aliquot was left untreated and the second aliquot was spiked with the Roche *B. microti* Secondary Standard at ~ 3x LoD concentration. Testing was performed in three runs, using (b) (4) reagent lot and (b) (4) cobas 6800 system. The cross-reactivity testing demonstrated that the specificity and sensitivity of the cobas® Babesia assay were unaffected by the presence of the tested potentially cross-reactive organisms. Additionally, Ct and RFI values for the IC, and for *Babesia* in spiked specimens, did not appear to be affected by the presence of potential cross-reactants. Overall, the cross-reactivity study was appropriately conducted, and the results were found to be acceptable.

5.4 Endogenous interference

The effect of potential endogenous interfering substances on the specificity of cobas® Babesia was evaluated using *Babesia*-negative EDTA whole blood from 10 donors spiked with five different potential interferents as follows: albumin at 60 g/L, bilirubin at (b) (4) g/L, hemoglobin at ≥ 20g/dL, human DNA at 2 mg/L, triglycerides at 33 g/L, (b) (4) . The interfering substances-spiked negative whole blood was divided into two aliquots, the first aliquot was left untreated and the second aliquot was spiked with the Roche *B. microti* Secondary Standard at ~ 3x LoD concentration. Testing was performed across (b) (4) runs, using (b) (4) reagent lot and (b) (4) cobas 6800 system. Overall, all samples spiked with *Babesia* were found to be reactive for *Babesia* and all the negative samples were non-reactive for *Babesia*. The results were found acceptable.

Review issue

- *The study report noted that two valid results were manually excluded due to an operator error resulting in a hemoglobin concentration below the target value. Additionally, out of the 21 invalid results noted, 4 were due to "calculation error for target (target and IC non-reactive)"; the remaining 17 were due to failure to aspirate correct sample volume. An IR was communicated to RMS on May 22, 2019 seeking clarification regarding the inclusion/exclusion of the valid/invalid results. The sponsor responded on May 30 that their root cause investigation did not implicate any exogenous or endogenous substances as interferents as most failures were in the no interferent or solvent control specimens. The response was acceptable and this issue was resolved.*

5.5 Exogenous interference

The sensitivity and specificity of cobas® Babesia was evaluated using negative EDTA whole blood from (b) (4) donors spiked with 14 different potential interferents (acetaminophen, acetyl salicylic acid, atorvastatin, atovaquone, azithromycin,

fluoxetine, loratadine, nadolol, naproxen, paroxetine, sertraline, ascorbic acid, ibuprofen, and phenylephrine HCl) (b) (4) . For atovaquone and phenylephrine HCl, no CLSI (b) (4) guideline was available; the concentrations used for these were recommended by the medical and scientific affairs department. The interfering substances-spiked negative whole blood was divided into two aliquots, the first aliquot was left untreated and the second aliquot was spiked with the Roche *B. microti* Secondary Standard at ~ 3x LoD concentration. Testing was performed across (b) (4) runs, using (b) (4) reagent lot and (b) (4) cobas® 8800 system. Overall, the results were determined to be acceptable.

Review issues

- *The study report noted that five results were excluded due to "calculation error for target (target and IC non-reactive)." A sample with a negative IC should be considered invalid based on the acceptance criteria that all samples should have valid IC results. It was not clear which specimens were excluded from the final analysis and why.*
- *Additionally, the scientific basis for the selection of concentrations for atovaquone and phenylephrine HCl were not provided. Both these comments were communicated to RMS in the IR dated May 22, 2019.*
- *RMS responded on May 30, 2019 that the root cause investigation did not implicate any exogenous/endogenous substances as interferents as most failures were in the no interferent or solvent control specimens. Additionally, RMS revised their exogenous interference results table to reflect the one IC failure in an acetaminophen-spiked specimen.*
- *Regarding the drug concentrations, RMS clarified that the therapeutic dose of Atovaquone corresponds to 750 mg, which is equivalent to 1226.7 µmol/L. Regarding Phenylephrine HCl, the therapeutic concentration corresponds to a range of (b) (4) . The test concentration was defined at (b) (4) maximum concentration (b) (4) which would give (b) (4)*
  All the above responses were acceptable and the issues resolved.

5.6 Dilutional sensitivity

(b) (4) well-characterized *B. microti* clinical specimens serially diluted to (b) (4) and (b) (4) LoD in WB:(b) (4) ratio) were tested using the cobas® Babesia to evaluate the dilutional sensitivity of the assay. Testing was performed using (b) (4) lots of reagents and (b) (4) cobas® 8800 system, with (b) (4) total replicates per concentration level per clinical specimen. The acceptance criteria were that (b) (4) of replicates at approximately (b) (4) LoD and 100% of replicates at approximately (b) (4) LoD would be reactive. All (b) (4) replicates of each tested specimen, at both (b) (4) and (b) (4) LoD, were reactive for *Babesia* with reactive ICs. No invalid results or runs were observed among the (b) (4) testing runs. The results were found to be acceptable.

5.7 Repeatability within laboratory

The repeatability of cobas® Babesia in the laboratory was evaluated between days, operators, reagent lots, Whole Blood Collection Tube lots, instruments and runs, using panels prepared from human whole blood spiked with *B. microti* infected RBC at three different concentration levels. The concentrations used were approximately 3x, 1-2x and

0.5x LoD, based on the (b) (4) *B. microti* whole blood LoD of 6.1 iRBC/mL. For each panel member, 180 *Babesia* Whole Blood Collection Tubes, divided evenly across 3 lots of Whole Blood Collection Tubes, were prepared using a (b) (4) to (b) (4) -fill the tubes. The fill volume was not specified. The panels were divided between days, operators, reagent lots, tube lots, instruments and runs. Testing was performed using one cobas® 8800 system and two cobas® 6800 systems. The results showed overlapping, two-sided 95% CIs for each specific variable tested (days, operators, reagent lots, tube lots, instruments and runs). Overall, the results were found to be acceptable.

5.8 Clinical specimen stability

This study evaluated the stability of clinical specimens by testing (b) (4) individual *B. microti* positive specimens spiked into (b) (4) negative individual donors (b) (4) . The *Babesia* (b) (4) as described and indicated in Figure 1 below:

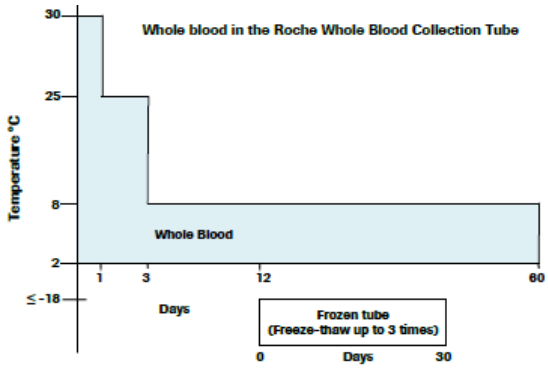
(b) (4)

(b) (4)

(b) (4)

(b) (4) The results were found acceptable and support the claims in the Package Insert (PI) as depicted in Figure 2.

Figure 2: Storage conditions of whole blood in the Roche Whole Blood Collection Tube



Review issues

- *For the clinical specimen stability study RMS proposed storage conditions including up to three freeze-thaws for specimens in whole blood stored at ≤-18°C. However, it was not clear from the study protocol as to how many freeze-thaw cycles were performed for each group of frozen tubes prior to testing with cobas® Babesia.*
- *There was a discrepancy in the submission whether* (b) (4) *RMS was requested to clarify the storage conditions for* (b) (4) *and the basis for the recommendation of three freeze-thaws as an acceptable storage condition.*
- *The above two comments were communicated to RMS on* June 11, 2019 and a response was received on June 17, 2019 clarifying that *the basis for the recommended storage conditions including the three freeze-thaws was based on testing conducted at* (b) (4) *. At time point* (b) (4) *Due to an operator error, the whole blood collection tubes were stored between time point* (b) (4) *stringent storage conditions passed the acceptance criteria as well.*
  RMS response was acceptable and the issue was resolved.

5.9 Cross contamination

The cross contamination rate of the cobas® Babesia test during sample processing and amplification/detection was evaluated by running target negative EDTA WB: (b) (4) in a checkerboard pattern with WB: (b) (4) spiked with $1x10^7$ particles/mL of *B. microti* armored RNA (aRNA). Five cross contamination runs were performed using (b) (4) lot of reagents and (b) (4) cobas 6800 system. Clean runs with (b) (4) only were performed (b) (4) the set of cross contamination runs. The results showed no cross

contamination across the five runs; all *B. microti* aRNA-spiked samples were reactive for *Babesia* with valid ICs, and all negative samples were non-reactive with valid ICs. Additionally, the final clean run showed no carry-over contamination. The results were acceptable.

5.10 On board and open kit stability

On board and open kit stability of the cobas® Babesia test were tested using (b) (4) The 480T test specific reagent cassettes were tested for on board stability after (b) (4) to support the secondary objective of establishing that 480-test cassettes could be used at least 20 times after loading on cobas® 6800/8800 Systems. For each time point, (b) (4) replicates of (b) (4) LoD *Babesia* were tested for sensitivity, (b) (4) replicates of (b) (4) LoD *Babesia* were tested for repeatability, and (b) (4) replicates of (b) (4) were tested for specificity. The study was performed using (b) (4) of reagents and (b) (4) cobas® 8800 system. (b) (4) runs were performed with no invalid results. The acceptance criteria provided were appropriate and were met at all timepoints tested and the results demonstrated that the cobas® Babesia 480T test cassettes are stable for at least 60 days at 4°C (open kit) and 20 hours at (b) (4) (on board), and the 480T test cassettes could be re-used at least 20 times.

5.11 Within-tube precision

The precision and repeatability within the cobas® primary tubes were assessed using (b) (4) The results met the sponsor's acceptance criteria, with all spiked specimens reactive and all negative specimens non-reactive, with valid ICs reactivity on all specimens. The results were determined to be acceptable.

5.12 Performance tolerances for primary tube volumes and ratios

The performance tolerance of the Whole Blood Collection Tube was assessed by (b) (4) The results met the acceptance criteria for both the contrived and clinical specimens for all (b) (4) ratios tested with all *Babesia*-

spiked samples reactive for cobas® Babesia and all negative samples non-reactive, with valid IC reactivity. The results were acceptable.

5.13 Primary tube specimen collection

This study was designed to assess primary tube performance, qualify different workflows, and determine the whole blood draw volumes using (b) (4) different methods. *Babesia* negative whole blood from (b) (4) donors was collected into (b) (4) primary whole blood collection tubes, divided between (b) (4) tube lots. (b) (4) different inversion methods (b) (4) inversions) were tested with (b) (4) tubes/donor/lot collected by (b) (4)

Upon arrival, the amount of foam and the weight of collection tubes was recorded for each donor as a direct comparison of collection methods. Testing was performed using (b) (4) lot of cobas® Babesia, (b) (4) cobas® 6800 system and (b) (4) cobas® 8800 Systems. The study included (b) (4) runs, with two results reported as invalid due to "calculation error for the target (target and IC non-reactive)." Both the invalid results were successfully repeated. The IC failure rate was 0.06% overall and was no higher than 1% for any workflow batch, across all primary tube lots and workflow variations tested. The two IC failures were in the tube lot (b) (4) inversions/no centrifugation group and the lot (b) (4) /with centrifugation group, generating failure rates of (b) (4) respectively. Since both invalid samples were IC failures, the sample failure rate was the same as the IC failure rate. All samples were non-reactive for *Babesia*. Foaming varied by donor, often reduced by centrifugation, and did not appear to affect the results. Overall, review of the data was found to be acceptable.

Review issues

- *In the primary tube specimen collection report one measurement-result for the* (b) (4) *draw group was excluded as an outlier. Since standard deviation and range are measures for the performance of the two draw methods, an IR was communicated to RMS on June 11, 2019 to clarify this discrepancy.*
- *RMS response on June 17, 2019 clarified that the observed outlier was due to an operator error when the draw volume of the affected tube was determined. An analysis, including the outlier, demonstrated no significant difference between the two methods of mean draw volumes. RMS response was found acceptable and the issue was resolved.*

5.14 Clinical specimen stability – EDTA tube

The clinical specimen stability of *Babesia* in whole blood samples collected in EDTA was evaluated, to test the performance of samples under conditions that simulated the handling, transport and processing of donated blood samples prior to collection into the *Babesia* Whole Blood collection tube. The positive test samples were prepared by spiking (b) (4) negative EDTA whole blood specimens with *Babesia*-positive clinical specimens at (b) (4) iRBC/mL of *B. microti*; negative samples were tested unspiked. The clinical specimens were stored undiluted at 2-8°C prior to use, and each specimen was used to spike (b) (4) of the (b) (4) negative individual donors. Aliquots of each specimen

were stored under different times and conditions, and then diluted into (b) (4) at a (b) (4) (WB:(b) (4) ratio prior to testing.

For each timepoint, (b) (4) spiked replicates (b) (4) per donor) were tested. At T0, 1 unspiked replicate per donor was also tested. Testing was performed using (b) (4) cobas® 8800 system and (b) (4) lot of reagents. (b) (4) runs were performed for the study, containing 211 valid results and 1 result that was invalid due to an anomaly calculated for the target. The invalid sample was repeated successfully. For each tested timepoint, (b) (4) (100%) of spiked replicates were reactive for cobas® Babesia with reactive ICs. At timepoint T0, all unspiked replicates were non-reactive for cobas® Babesia with valid ICs. The Cts and RFIs for *Babesia* and IC did not vary significantly between time points. The results met the acceptance criteria for each time point and the sponsor concluded that whole blood collected in EDTA could be stored for up to 12 days prior to dilution in the Whole Blood Collection Tube, with a maximum of 72 hours at 25° C and no more than 24 of that 72 hours at 30° C. The samples could then be stored for a further 36 hours following (b) (4) dilution at 2-25° C. The methods, acceptance criteria and storage recommendations were acceptable.

6. Clinical Studies

The clinical studies supporting this application were performed under IND #17582. Blood donors in regions predicted to be high endemic, low-endemic, or non-endemic for *B. microti* were included in the clinical study to evaluate the performance of the cobas® Babesia.

6.1 Clinical Specificity Study

The clinical specificity study was performed under a single protocol (cX8-BAB-440). The protocol describes procedures and analyses with an objective to estimate the specificity of the cobas® Babesia assay on the cobas® 6800/8800 in donations from donors of whole blood and blood components. Testing was performed at five external sites that included Central Pennsylvania Alliance Laboratory (CPL), Mississippi Valley Regional Blood Center (MVRBC), The Community Blood Center (CBC), Versiti Indiana (formerly Indiana Blood Center), and Innovative Blood Resources (IBR). The samples were tested from October 17, 2017 to September 29, 2018.

Index testing was completed if the valid test result was reactive or non-reactive. If the result of the test on the individual donor sample was invalid, then the individual donor sample was tested again, up to two times, until a valid result was obtained. If the test result was still invalid after the second retest, the result was reported as invalid. For samples reactive on cobas® Babesia, additional testing was required. Additional testing included repeat testing with cobas® Babesia, simulated 1:6 pool, two alternative *Babesia* NAT, and anti-*Babesia* IgM and/or anti-*Babesia* IgG serology to confirm *Babesia* infection; reactivity on alternative NAT or serology confirmed the presence of *Babesia* in the index reactive donation. The alternative NAT1 was developed by BSRI that detects only *B. microti*, while the alternative NAT2 is the RMS in-house assay and detects all four *Babesia* species. The *Babesia* serology assays (IgG/IgM) are immunofluorescence-based assays and developed by Quest Diagnostics. Donors with index reactive donations were eligible to enroll in a follow-up study. Follow-up testing included cobas® Babesia, alternative NAT, and anti-*Babesia* IgM and anti-*Babesia* IgG serology tests (Table 9).

Table 9: Interpretation of cobas® Babesia results

Interpretation	cobas Babesia Index Test Result	Retesting on Index Donation			Follow-up Sample Testing (F1, F2, F3, F4)	
		Alternative NAT1	Alternative NAT 2	Anti-Babesia IgM/IgG	Alternative NAT 2	Anti-*Babesia* IgM/IgG
True Positive	Reactive	At least 1 Reactive/Positive Result				
False Positive	Reactive	Negative	Non-reactive	Negative	Non-reactive	Negative
True Negative	Non-reactive	N/A				

A reactive result on cobas® Babesia was considered true positive if any of the following were observed:

· Index donation was positive on Alternative NAT 1 or 2
· Index donation was positive for anti-*Babesia* IgM or anti-*Babesia* IgG
· Follow-up sample was positive on Alternative NAT 2
· Follow-up sample was positive for anti-*Babesia* IgM or anti-*Babesia* IgG

Samples from 168,981 blood donations were tested as individual donations using six reagent lots. During the clinical trial (IND17582), RMS updated the calculation package to add a minimum reactive Ct threshold of 6 cycles for the *Babesia* target on the cobas Babesia assay to address two donations that had abnormal *Babesia* Ct values. All study data were re-processed using the new Assay Definition File (ADF) and the original results were compared to the new results (both were included in study data). The two samples that were originally cobas® *Babesia* reactive were defined as invalid when recalculated with the new ADF. No other differences occurred between the results of evaluable samples.

Table 10 shows the comparison of cobas® Babesia results and donation status for 168,981 evaluable donations from which whole blood samples were tested individually. A total of 99.993% (168,970/168,981) donations had non-reactive cobas® Babesia results. Specificity of cobas® Babesia was 99.99% with a 95% CI of 99.996-100%.

Table 10: Comparison of cobas® Babesia results with donation status by endemicity

Region	Number Tested	True Negative	True Positive	False Positive	Specificity % (95% CI)
High-Endemic	143,939	143,929	8	2	99.99 (99.995-100.00)
Low-Endemic	14,217	14,217	0	0	100.00 (99.974-100.00)
Non-Endemic	10,825	10,824	1	0	100.00 (99.966-100.00)
Overall	168,981	168,970	9	2	99.99 (99.996-100.00)

Eleven (0.007%) out of 168,981 donations had reactive cobas® Babesia results (index and follow-up test results). Nine donations with reactive cobas® Babesia results were confirmed true-positive by Alternative NAT on their index donation. All nine donations were reactive on their simulated 1:6 pool result, as well as repeat 1, 2, and 3. There were no index donations with reactive cobas® Babesia results that were confirmed positive by anti-*Babesia* IgM or anti-*Babesia* IgG, and negative on Alternative NAT 1 or Alternative NAT 2. The remaining 2 of the 11 donations with reactive cobas® Babesia results were classified as false-positive based on additional testing on their index donation and/or follow-up testing.

6.2 Clinical Sensitivity

Clinical Sensitivity of the cobas® Babesia in known-positive whole blood samples was evaluated per protocol cX8-BAB-445. Testing was performed at three sites (American Red Cross [ARC], Mississippi Valley Regional Blood Center [MVRBC], and RMS using three reagent lots, and tested either on a cobas® 6800 or cobas® 8800 Systems. The cobas® 6800/8800 Systems software version was 1.3.08 and the assay specific analysis package (ASAP) for cobas® Babesia was version 11.0.3.

A total of 203 specimens, comprising both clinical and contrived specimens, confirmed positive for *Babesia* by an in-house validated NAT assay, were evaluated in this study. The in-house NAT uses unique primers and probes than those used in the cobas® Babesia test. All specimens were tested neat and diluted 1:6 (to simulate pools of 6). Each specimen was tested once at each of the three testing sites for a total of 609 neat and 609 diluted 1:6 determinations (with *Babesia*-negative whole blood PCR media mixture).

Clinical Samples: A total of 131 clinical specimens were tested in this study. All clinical samples were determined to be NAT-positive for *B. microti* with a laboratory-developed test at Mayo Clinic. All clinical specimens were remnant frozen whole blood samples collected in EDTA from a U.S. population and were mixed with cobas PCR media at a 1:7 ratio, to mimic a neat sample, as is collected from donors. No clinical samples were available for *B. duncani*, *B. divergens*, and *B. venatorum*.

Contrived Samples: A total of 72 contrived samples each made from a unique whole blood-PCR media mixture were prepared using *Babesia* Secondary Standards as follows:

- 18 spiked with *B. microti*; 6 each at low, medium, and high concentrations
- 18 spiked with *B. duncani*; 6 each at low, medium, and high concentrations
- 18 spiked with *B. divergens*; 6 each at low, medium, and high concentrations
- 18 spiked with *B. venatorum*; 6 each at low, medium, and high concentrations

Low, medium and high concentrations were approximately 18x, 36x and 72x LOD for neat samples, respectively. For the 1:6 diluted pools, the low, medium and high concentrations were approximately 3x, 6x and 12x LOD, respectively. Results: All 203 (clinical and contrived) neat and 203 diluted (1:6) known-positive samples had reactive cobas® Babesia results (Table 11). Overall sensitivity of the cobas® Babesia was 100% (95% CI: 98.2%-100%) in both neat and diluted (1:6) samples.

Table 11: Sensitivity of cobas® Babesia in known *Babesia*-positive samples

Sample type	Organism	No. Reactive/ No. Tested	Sensitivity (95% Exact CI)
Clinical	*B. microti*	131/131	100 (97.2% - 100)
Contrived	*B. microti*	18/18	100 (81.5% - 100)
	B. duncani	18/18	100 (81.5% - 100)
	B. divergens	18/18	100 (81.5% - 100)
	B. venatorum	18/18	100 (81.5% - 100)
Overall		203/203	100 (98.2% - 100)

Review Issues

- *Detailed information on the pedigree of the clinical samples used for the sensitivity study were not provided in the BLA. Additionally, in the clinical study report the final sensitivity of the cobas® Babesia was reported to be 100% (95% Exact CI: 99.4%–100%) using a total sample size of 609. However, since the same 203 samples were used at the three sites, it was suggested that the sensitivity should be calculated based on 203 samples (and not 609) to reflect more appropriate 95% CI values.*
- *RMS responded on June 17, 2019 and provided the detailed information for the clinical samples used for the study. Regarding the clinical sensitivity of cobas® Babesia, RMS revised the results table to reflect the 95% CI calculated for a total of 203 samples. The response to both of the above issues were acceptable.*

6.3 Clinical Reproducibility

The clinical reproducibility for cobas® Babesia was performed per protocol cX8-BAB-444. Testing was performed at three sites (ARC, MVRBC, and RMS). This study evaluated the reproducibility of the cobas® Babesia for use on the cobas® 6800/8800 Systems across lot, site, day, and batch using multiple lots, sites, days, batches, instruments, and operators. The total number of test results per concentration was as follows: 3 lots x 3 sites x 5 days x 2 batches x 3 replicates/concentration = 270 test results/concentration. The reproducibility of cobas® Babesia was established by testing a 13-member panel, with three expected concentrations for each of the four *Babesia* species and a negative panel member. Table 12 shows the percent agreement results by panel member concentration.

Table 12: Clinical reproducibility results of cobas® Babesia

				Standard Deviation [SD] and Percent Coefficient of Variation [CV (%)]											
				Within-Batch		Between-Batch		Between-Day		Between-Site		Between-Lot		Total	
Babesia species	Expected *Babesia* concentration	n*/N	Mean Ct	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV%
B. microti	~0.5 x LOD	258/270	33.7	0.55	1.6	0.08	0.3	0.06	0.2	0.00	0.0	0.41	1.2	0.69	2.1
	1-2 x LOD	269/269	32.5	0.32	1.0	0.08	0.3	0.09	0.3	0.00	0.0	0.16	0.5	0.38	1.2
	~3 x LOD	270/270	31.6	0.22	0.7	0.08	0.3	0.04	0.1	0.00	0.0	0.12	0.4	0.27	0.8
B. duncani	~0.5 x LOD	171/270	31.0	1.29	4.2	0.00	0.0	0.00	0.0	0.00	0.0	0.23	0.7	1.31	4.2
	1-2 x LOD	269/269	28.2	0.75	2.7	0.23	0.8	0.00	0.0	0.20	0.7	0.14	0.5	0.83	2.9
	~3 x LOD	268/268	26.9	0.47	1.8	0.22	0.8	0.00	0.0	0.13	0.5	0.21	0.8	0.58	2.2
B. divergens	~0.5 x LOD	142/270	31.5	0.60	1.9	0.00	0.0	0.15	0.5	0.12	0.4	0.17	0.5	0.65	2.1
	1-2 x LOD	270/270	27.8	0.29	1.1	0.13	0.5	0.04	0.1	0.12	0.4	0.02	0.1	0.34	1.2
	~3 x LOD	270/270	26.7	0.19	0.7	0.03	0.1	0.09	0.3	0.04	0.2	0.11	0.4	0.24	0.9
B. venatorum	~0.5 x LOD	266/270	30.0	0.47	1.6	0.24	0.8	0.15	0.5	0.23	0.8	0.20	0.7	0.62	2.1
	1-2 x LOD	270/270	27.3	0.48	1.8	0.07	0.2	0.08	0.3	0.03	0.1	0.09	0.3	0.50	1.8
	~3 x LOD	270/270	26.2	0.37	1.4	0.00	0.0	0.00	0.0	0.04	0.1	0.12	0.4	0.39	1.5

*number reactive/number tested

Results: A total of 3,506 valid tests were performed. A 100% agreement (95% CI: 98.6 - 100) was demonstrated for 1-2x LOD and 3x LOD panel members from all four species, meeting the study acceptance criteria of ≥ 91.9% of the lower bound of the two-sided CI. The study results were found to be acceptable.

BIMO – Clinical/Statistical/Pharmacovigilance

A Bioresearch Monitoring (BIMO) clinical investigator inspection was conducted at one domestic clinical study site participating in the conduct of Study Protocols cX8-BAB-440, cX8-BAB-444, and cX8-BAB-455. The inspection did not reveal substantive problems that impact the data submitted in this original Biologics License Application.

7 Advisory Committee Meeting

It was determined that this regulatory submission did not require presentation at an Advisory Committee meeting prior to approval.

8 Other Relevant Regulatory Issues

None.

9 Labeling

The Advertising and Promotional Labeling Branch (APLB) found the proposed Instructions for Use (IFU), and the package and container labeling, acceptable from a promotional and comprehension perspective.

10 Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Review Committee reviewed the original submission and related amendments. All review issues have been resolved therefore; the Review Committee recommends licensure of the cobas® Babesia for use on the cobas® 6800/8800 Systems.

b) Risk/ Benefit Assessment

The cobas® Babesia is intended for detection of *Babesia* DNA and RNA in whole blood specimens. The assay has an estimated LoD range of 5.0-7.9 iRBC/mL for *B. microti* and LoD range of 28.9-55.7 cp/mL for *B. microti* transcripts. The clinical studies demonstrated a sensitivity of 100% (95% CI of 98.72-100), indicating low probability of a false negative result and the assay specificity of 100% (95% CI of 99.99-100) in clinical trials suggests the low probability of false positives. The cobas® Babesia with high clinical sensitivity and specificity will significantly improve blood safety and public health by reducing the transfusion of *Babesia*-infected blood and outweighs any risk to the donor and the safety of the nation's blood supply.

c) Recommendation for Postmarketing Activities

No postmarketing activities have been proposed for this application.