



Review Memorandum

STN: BL 125653

Product: cobas® Zika nucleic acid test for use on the cobas® 6800/8800 Systems

Sponsor: Roche Molecular Systems, Inc.

Date: 09/13/2017

Reviewer: Evgeniya Volkova, MS, MBA

Through: Sanjai Kumar, PhD, Chief, LEP

To: Caren Chancey, PhD, SL
Vasanth Kumar, PhD, RPM

Specific Scientific Disciplines Reviewed: Chemistry, Manufacturing, and Controls

Documents reviewed: Chemistry, Manufacturing, and Controls, Labeling, Non-clinical Pharmacology and Toxicology

Precedent-Setting Product: First product seeking approval for screening of plasma samples for Zika virus RNA

Recommendation: Approval

Summary:

The cobas® Zika nucleic acid amplification 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 Zika virus RNA. This test is intended for use to screen donor samples for Zika virus RNA in plasma 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. The test is not intended for use as an aid in diagnosis of Zika virus infection. This test is not intended for use on samples of other body fluids or cord blood.

Sponsor started clinical studies under an Investigational New Drug (IND) application #16926 in April 2016 and submitted this Biologics License Application (BLA) on April 7, 2017, requesting priority review.

First information request was sent to sponsor before filing meeting. The filing meeting was held on May 22, 2017, and FDA had issued a filing memo notifying

sponsor of deficiencies in the submission. The mid-cycle meeting was held on July 6, 2017, and FDA requested additional information from sponsor. RMS submitted several amendments containing responses to the information requests.

Summary of RMS's Response to FDA Information Requests:

Amendment #1.

cobas Zika NHP Negative Control Kit label, which is a part of cobas Zika PI, states "HIV-1 RNA, HIV-2 RNA, HCV RNA, HBV DNA, HEV RNA, WNV RNA, CMV DNA, Zika RNA, CHIKV RNA and DENV RNA not detectable by PCR methods". However, neither Certificate of Analysis from the bulk material manufacturer ((b) (4)) nor the SOP describing functional testing of NHP mention testing for CHIKV, DENV, or ZIKV. Please confirm which viral targets were used to prove negativity of the manufactured NHP and resolve the discrepancy.

In Amendment 1, sponsor submitted an updated version of test specifications for NHP, which included testing negativity for CHIKV, DENV and ZIKV by PCR using cobas CHIKV/DENV and cobas ZIKV tests.

Amendment #2.

FDA Question 2 from July 25, 2017. *The oligonucleotide aptamer appears to be a component of Zika MMX-R2, and the In Vitro Substance (IVS) report that you provided contains information on its sequence, production, and characterization. However, the exact function of the aptamer in the assay is not clear. Please provide a summary describing the role of the aptamer in the assay procedure.*

Sponsor explained that the aptamer is a ((b) (4)) oligonucleotide that due to its 3D structure can ((b) (4))
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FDA Question 3 from July 25, 2017. *According to the Zika Antimicrobial Effectiveness Test report, testing was performed on the cobas Zika 480 MMX-R2 Vessel ((b) (4)) and the cobas Zika Control Kit ((b) (4)). However, the material numbers for the cobas Zika 480 MMX-R2 and the cobas Zika Control Kit used elsewhere appear to be 7972555001 and 8129690190, respectively. Please clarify which materials were used to perform the testing.*

RMS indicated that the ((b) (4)) was performed on the non-commercial components, MMX-R2 Vessel ((b) (4)) and Zika Positive Control ((b) (4)), which have the same final formulation, were produced using the same process steps and at the same facility as the commercial components, MMX-R2 Vessel (07972555001) and Zika Positive Control (08129738001). Therefore, the results of the testing were considered valid for commercial components.

Table 1. Non-commercial and commercial material numbers for components and kits.

(b) (4) Testing – non-commercial components	Corresponding commercial components	Corresponding commercial kit
MMX-R2 Vessel (b) (4)	MMX-R2 Vessel (M/N 07972555001)	cobas [®] Zika (480T) (M/N 07972466190)
Zika Positive Control (b) (4)	Zika Positive Control (M/N 08129738001)	cobas [®] Zika Control Kit (M/N 08129690190)

FDA Question 4 from July 25, 2017. *The IVS section of the Omni Reagents and Common Components CMC only includes information on MGP Reagent and Protease. Please provide the IVS reports on the remaining common components and Omni reagents composing the cobas Zika test.*

Sponsor clarified that only 2 of the common components and omni reagents have intermediaries: proteinase solution and MGP reagent. The remaining components do not have any intermediaries and as such were described in the In Vitro Products Report.

Amendment #4.

FDA Question 12 from July 25, 2017. *In your submission BL125653, you stated that the (b) (4) was changed from (b) (4) to (b) (4) in order to update the (b) (4) in the algorithm from (b) (4) to (b) (4) (feasibility data collected with (b) (4) was subsequently reanalyzed with (b) (4)).” You have then concluded that “there is no impact to sample processing or result calculation between the versions of ASAP SW used in the pre-clinical and clinical studies.” However, in your non-clinical specificity study report (DH-04482.01-029.pdf), you stated that (b) (4) valid results were produced, (b) (4)*

Moreover, in your cross reactivity study (DH-04482.03-107F.pdf), you have stated that “testing was performed using cobas Zika configuration baseline 1.3 including software version 01.02.12, Zika Analysis Package software version 10.2.0 and (b) (4).” It is unclear what modifications have been implemented between various versions of the (b) (4) module and how they impact Zika test calculations. Please explain (b) (4) functionality, differences between (b) (4) versions, and specify (b) (4) version you intend to provide to the users. Please also clarify why (b) (4) was chosen over (b) (4) for data analysis in the non-clinical specificity study, and whether there are other instances of (b) (4) based on interpretation of the results by software.

RMS explained that the statement regarding changes between (b) (4) and (b) (4) not impacting calculations was made in error and that there were no other instances of (b) (4) based on interpretation of the results by software. Sponsor clarified that the sample in question was (b) (4) as invalid because different IC cutoffs in different versions of (b) (4) caused discrepant IC calls. Sponsor also provided a table summarizing the differences between the (b) (4) versions of (b) (4) and corrected Table 3 from System Document submitted in the original BLA to include (b) (4) versions used in different versions of Zika ASAP.

(b) (4)

- Additionally, since the BLA was originally submitted without some of CMC documents, including ZIKV-specific test validation and process validation records, FDA requested for the remaining documents to be submitted in the first information request, filing letter, and the information request sent after the mid-cycle meeting. Sponsor included these documents intermittently in the amendments until all appropriate records had been submitted.

Conclusions:

I have reviewed sponsor's responses to FDA's comments and requests, and in my opinion, RMS has adequately addressed all concerns.

I have no further comments and recommend approval of the application.