



Final Review Memorandum

Date: September 12, 2017

STN: BL125653

Reviewer: Maria Rios, PhD

Through: Sanjai Kumar, PhD, Chief LEP

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

Type of Submission: Original BLA

Sponsor: Roche Molecular System, Inc.

Device: cobas® Zika, Nucleic acid test

Documents reviewed: Original Submission
Chemistry, Manufacturing and Controls (CMC)

Recommendation: Approval of this submission

Device description:

The **cobas®** Zika is a qualitative *in vitro* nucleic acid test (NAT) that detects Zika virus (ZIKV) RNA in plasma samples. The test is performed on the licensed fully automated cobas® 6800 System and cobas® 8800 System. The systems enables sample preparation followed by PCR amplification and the simultaneous detection of Zika RNA and the internal control in a single test of an infected, individual plasma sample. Two parameters are measured simultaneously for each sample: ZIKV RNA and the IC. Final results are automatically reported by the software.

The cobas® Zika test consists of: 1) cobas® Zika test kit, 2) cobas® Zika Control Kit, 3) cobas® NHP Negative Control Kit, and 4) the individual cobas omni reagents for sample preparation.

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. Plasma from all donors should be screened as individual samples.

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.

Clinical trial to support this submission was performed in collection time period between 04/04/2016 and 12/13/2016.

Data sources are included in the applicant's electronic submission located in the FDA's Electronic Document Room (EDR) at the following link:

(b) (4)

Review summary: In the initial review of this application dated April 7, 2017, for Zika Virus Nucleic Acid Test (cobas® Zika) to determine its acceptability for filing as a Priority Review Submission with timeline of 6 month. The review goal date is October 6, 2017.

The submission table of content indicates the presence of the following information: Non-clinical studies, Clinical studies and Statistical Data, and Chemistry, Manufacturing and Controls (CMC).

CMC section includes components that are specific for (1) the Zika test and (2) Omni Reagents and Common Components to all cobas licensed tests.

1. **Zika In Vitro Products Report** – describes assays specific components formulation and manufacturing of the finished product including composition of manufacturing for:
 - a. cobas ZIKV test kit: Master Mix-R2 (MMR-2) and RNA Internal Control
 - b. Zika Control Kit: Positive control of the assay information on Vial and Bulk material.
 - c. Describes Raw Material, Container and Closure Systems, Microbiology and stability.
2. **Zika In Vitro Substance Reports** – provides the Initial Performance Report describing design, synthesis and purification of the oligonucleotides in the cobas Zika and other reagents, including documentation on Process Validation and Specifications.
3. **Zika, Omni Reagents, and common components stability report** – describe completed and ongoing studies to define shelf life of product.
 - a. Zika specific reagents have ongoing studies with the current shelf life defined as follows: cobas Zika (480T) and cobas Zika Control Kit with shelf lives of 8 and 3 months respectively.
 - b. Omni Reagents and Common Components have defined shelf life of 24 months and studies were completed for other licensed cobas test that includes: cobas NPH Negative Control Kit, cobas Omni MGP, Lysis, Wash and Specimen Diluent Reagents.

4. Other documentation were provided containing information on measures taken to assure consistency in manufacturing, filling process, type and volume of container, closure type and manufacturing environment including:
 - a. Manufacturing Flowcharts;
 - b. Standard Operating Procedures;
 - c. Raw Materials;
 - d. Batch Product Records
 - e. Test Specifications
 - f. Validation Records
 - g. Bulk and Fill Containers and Closure Systems

5. Zika Antimicrobial Effectiveness Test – performed by external laboratory following current (b) (4) using (b) (4) of each of cobas Zika 480 MMX-R2 Vessel ((b) (4)) and cobas Zika Control Kit ((b) (4)), tested at (b) (4) and has passed specifications. Three reagent lots of each also passed the (b) (4) Validation acceptance criteria.

Reviewer Assessment:

During filing review missing documentation on test specification and Validation records to support this submission was identified.

The following are missing documents for Test Specifications

- Zika primers and probe, both individually and in the oligo pool
- Zika positive control, both in bulk and labeled containers
- MMX-R2 reagent, both as bulk and labeled vessels
- cobas Zika test kit
- cobas Zika control kit

The following are missing documents for Processes Validation

- Zika primers and probe
- MMX-R2
- Zika positive control
- cobas Zika test kit

The sponsor was informed and asked to provide the missing documentation. On July 11, additional but not complete documentation was provided. Still missing are the following documents:

1. Process Validation and specification for the following Zika In Vitro Product:
 - a. cobas Zika Test kit (480T)
 - b. cobas Zika Control Kit
2. Process Validation for Bulk normal human plasma (NPH) in the section “Zika Positive Control Stocks In Vitro Substance Report”
3. Batch production Records and Test Specifications for the Synthesis and Purification of ZIKA PROBE

Letter Ready comment to the sponsor:

1. Please provide the remaining missing documents in the CMC section to allow for substantive review of the application:

- Process Validation and specification for the following Zika In Vitro Product:
 - a. cobas Zika Test kit (480T)
 - b. cobas Zika Control Kit
 - Process Validation for Bulk normal human plasma (NPH) in the section “Zika Positive Control Stocks In Vitro Substance Report”
 - Batch production Records and Test Specifications for the Synthesis and Purification of ZIKA PROBE
2. In non-clinical specificity study report, you state that (b) (4) valid results were produced, (b) (4)
- Please clarify:
- a. why (b) (4) was chosen over (b) (4) for data analysis in this case.
 - b. whether there are other instances of (b) (4) based on interpretation of the results by software.
3. The data analysis for cross-reactivity study was performed using yet another (b) (4). Please indicate the differences between those (b) (4) versions and clarify which version (if a single) was used for data analysis throughout the studies. If different versions were used, please explain potential impact in the interpretation of the test results.
4. In the amendment dated July 10, 2017 under Validation Records. Report Number 201701-0070-BB-QOP-FR - Method Validation Report for Functional Performance Release Testing of cobas 6800/8800 Zika Test kits; on page 9 of 11; *Table 12: Acceptance Criteria and Results (Inter-Instrument)* present the results for Analyst 1 and Analyst 2. However, in the description of the study performance you indicate that a single analyst performed 2 assay run using 2 independents instruments. Please provide the correct table of results.

The above questions were provided to the SL and communicated with the sponsor.

The sponsor has submitted the missing documents requested in item 1, and provided responses and clarifications to the items 2 to 4 under “Letter ready comments”.

Final assessment:

The provided information were reviewed and found to be satisfactory to this reviewer. I have no additional questions or comments and recommend that submission to be approved.