

**Final Review Memo**

STN#: BL125653/0

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To: Vasantha Kumar, Ph.D., RPM, IOD, OBRR

Applicant: Roche Molecular Systems, Inc.

Product: cobas[®] Zika assay on the cobas[®] 6800/8800 systems

Type of Submission: Original BLA

Recommendation: **Approval**

Application Data Source: e-submission located in the FDA's Electronic Document Room at:

(b) (4)

Executive Summary of the Review:

Roche Molecular Systems, Inc. submitted this BLA for its cobas[®] Zika assay, which is a qualitative in vitro nucleic acid screening test for the direct detection of Zika virus (ZIKV) RNA in human plasma. Non-clinical and clinical studies were conducted to collect data in support of this BLA submission.

This assay utilizes instruments and some common software that were previously reviewed for the cobas[®] MPX and cobas[®] WNV, and information was provided on assay-specific software and instrument software updates. Additional information and clarification were needed in several areas to complete the review of this BLA, which was communicated to the sponsor through a series of Information Requests (IRs). The sponsor has addressed all points during interactive review and provided responses to FDA for all IRs. The review of the additional information provided was found to be satisfactory with the committee deeming all issues resolved and now recommending approval of this BLA.

Background:

This Biologic License Application (BLA) was submitted by Roche Molecular Systems Inc., for the cobas[®] Zika nucleic acid test for use on the cobas 6800/8800 Systems. The cobas[®] Zika assay is the first blood screening assay for the Zika virus and may also be used to screen organ and tissue donors when donor samples are collected while the donor's heart is still beating. Testing with the cobas[®] Zika assay is to be performed on individual samples only. The FDA granted the request by Roche

Molecular Systems for a six-month priority review of the application, on the basis of an unmet public health need created by the Zika virus epidemic in the Americas and especially in the U.S. territory of Puerto Rico.

The cobas® Zika is designed for use on the cobas® 6800 and cobas® 8800 Systems. Two other blood screening assays have previously been approved for use with the cobas® 6800/8800 systems, the cobas® WNV (BL125575, approved November 2, 2016) and the cobas® MPX assay (BL125576, approved October 20, 2016). Review of the cobas® 6800/8800 systems therefore was focused primarily on the assay-specific analysis package (ASAP) and updates made to the system software since approval of the other two screening assays.

The cobas® Zika consists of the cobas® Zika Kit, cobas® Zika Control Kit, omni reagents, and common reagents. The test was developed to be available in a 480-test kit format only. The principles of the assay procedure are similar to the other approved screening assays on the cobas® 6800/8800 systems. RNA from the sample and added internal control are extracted from lysed plasma samples using magnetic glass particles, followed by washing, elution and RT-PCR, using specific probes and primers to discriminate target and controls. Accordingly, many components of the cobas® Zika are common to the cobas® WNV and cobas® MPX assay (omni Reagents and Common Components), with their manufacture, composition and performance having been reviewed in detail as part of those applications and provided again in this submission for completeness. The assay-specific components of the cobas® are the Zika primers and probes, contained in the cobas® Zika Kit's Master Mix Reagent 2 (MMX-R2), and the Zika Positive Control (PC) that constitutes the cobas® Zika Control Kit. The RNA Internal Control is shared with the licensed cobas® MPX (BL125576) and cobas® WNV (BL125575) tests, and the rest of the reagents were common to most cobas 6800/8800 tests. Manufacturing of all components takes place at the sponsor's (b) (4) facility.

Review Summary:

The review committee identified deficiencies during the review of the original BLA submission. The deficiencies and issues were discussed during review committee meetings, meetings with senior management of the Division and the Office, and subsequently conveyed to the sponsor in Information Requests dated May 2, May 15, June 6, July 25, August 18, September 25 and September 26, 2017, and teleconferences on July 13 and August 9, 2017. The IRs included a total of 32 deficiencies to be addressed; 20 were clinical, non-clinical, and CMC issues, 4 were statistical issues, and 8 were instrumentation/software issues. The review committee conducted an interactive review with RMS to address and resolve all remaining deficiencies. RMS submitted 14 amendments to address the deficiencies raised.

The review committee believed that the RMS responses and amendments adequately addressed all the issues in the IRs and there were no outstanding issues to this original submission.

The following were the major review issues identified by the committee. These issues were resolved with additional data provided by RMS and through interactive review:

1. Clinical sensitivity study structure, statistical analysis and labeling: Due to the cobas® Zika being a first-of-its-kind assay, there was no FDA licensed or approved assay available to use as either a comparator for clinical specificity or a qualifier for clinical sensitivity. As a result, the sponsor consulted with FDA during the pre-submission process (BQ160101) and designed a test to estimate clinical sensitivity by repeat-testing samples from the clinical specificity study that were reactive on the cobas® Zika and positive on the alternative NAT performed at (b) (4). This design was questioned by members of the review committee, who noted that since there was no comparator assay used during the clinical specificity study, no samples that were false-negative on the cobas® Zika would have been detected and included in the study, leading to a risk that the assay might fail to detect some circulating variants. After further discussion, it was concluded that the sensitivity of any unapproved alternate assay used to qualify samples would be undetermined and likely to be lower than the cobas® Zika, and that as a first-of-a-kind assay, approval could proceed without a clinical sensitivity study performed on clinical samples obtained outside the clinical specificity study. The recommendation was made to include the results of the clinical sensitivity study provided by the sponsor, but to not refer to it as a clinical sensitivity study. Additionally, the clinical and statistical reviewers noted that the sponsor performed two rounds of repeat testing, and that the lower bound of the 95% CI (93.1%) for Repeat Test 1 did not meet FDA's standard acceptance criterion of a lower-bound of 95%. The sponsor proposed a post-hoc analysis, which would consider samples as positive if they were reactive on any one of the two repeats. The review committee considered the sensitivity based only on Repeat Test 1, because during the blood screening process, no repeat testing is performed, and found it to be acceptable considering that there is no other Zika blood screening assay currently approved by FDA.
2. High invalid run rate observed on cobas® 6800 instrument at QualTex testing site: During testing of donor samples for the clinical specificity study, one cobas® 6800 instrument at QualTex, serial number (b) (4), had a failure rate of 9.8% (20/205 batches); all of the invalid batches on this instrument were due to positive and negative control failure. This issue was referred for investigation by BIMO during the inspection of the testing site. The inspector did not identify any issues that would indicate a systemic problem with the 6800 instrument and the issue was considered resolved.
3. Use of EDTA (index) plasma vs. unit plasma for repeat testing in sensitivity study: Protocol cX8-ZIKA-412 specified that repeat testing may be performed using plasma from the unit rather than index (EDTA) plasma. This was a concern to the review team because of the Clinical Stability study results which suggested that plasma from blood collected with (b) (4) anticoagulants may not perform as well as plasma collected with EDTA. In a teleconference on August 9, 2017, the sponsor was asked to provide additional data on whether EDTA or unit plasma was used for repeat testing. Data provided by the sponsor on August 16, 2017 indicated that of the 206 specimens that underwent repeat testing, 199 were tested with unit plasma. The sponsor also noted that there was typically a delay in testing these samples of several days while the plasma bag was shipped from the

collection site. The reviewers concluded that use of unit plasma could not be confirmed to have had an impact on the sensitivity study results.

4. Clinical Reproducibility Statistical Analysis: The statistical reviewer noted that tests of the 0.5x LoD Zika-positive panel member which generated non-reactive results on the cobas Zika assay were not included in the statistical analysis of variability attributable to different study factors. The sponsor was asked in the Information Request dated July 25, 2017, to redo the analysis to include these non-reactive samples to more accurately describe the variability of the assay. The sponsor responded on August 7, 2017 that since the cobas® Zika generates Ct values for reactive samples only, that it was not possible to include non-reactive samples for which no Ct value was generated. Clinical Specificity Statistical Analysis. The statistical reviewer requested that the sponsor clarify some of the data provided for the clinical specificity study in regards to invalid batches and invalid results on the cobas® Zika assay. The sponsor was asked in the Information Request dated July 25, 2017 to clarify whether the 123 invalid batches generated during testing for the specificity study were retested and to reconcile the 306 invalid results within valid batches from testing with the 228 non-evaluable donations described in Table 6 on page 35 on the Clinical Specificity Study report. The sponsor responded on August 8, 2017 that 6,919/6,940 (99.7%) of the unique donations within the 123 invalid batches were retested, and that the remaining samples were not available for retesting for a variety of reasons. The sponsor also clarified that 306 was the number of invalid results within valid batches, while 228 was the number of unique donations that never generated a valid result on the cobas® Zika (i.e., some of the 306 were valid upon retest, and some of the 228 were part of invalid batches). The statistical reviewer did not find the response to be sufficiently detailed; however, as the sponsor had included the correct invalid rate for the test based on 306 invalid results on the package insert, further information was not requested.
5. Reagent Lots used during the Clinical Specificity Study: The statistical reviewer noted a discrepancy between the Clinical Specificity Study Report, which stated that 5 reagent lots were used for testing, and the provided draft Summary Basis for Approval, which stated that 4 reagent lots were used for testing. This question was included in the Information Request dated July 25, 2017, and the sponsor responded on August 4, 2017 that while 5 lots were used under the Clinical Specificity Study Protocol cX8-ZIKA-412, only 4 lots were used for testing samples collected in U.S. States which were used in the data analysis for the Clinical Specificity Study. The 5th lot was used in initial testing of specimens in Puerto Rico only. The response was considered acceptable.
6. Conflict between system software versions requested for approval for different assays on the cobas® 6800/8800 Systems. During software review, it was noted that different versions of the cobas® 6800/8800 Systems software were submitted for approval in this BLA (SW v1.02.12) and BL125575/6 for cobas® WNV (SW v1.02.13). In the Information Request sent to the sponsor on July 25, 2017, the sponsor was requested to provide a comparison table between v1.02.12 and v1.02.13 and to explain how the later software version would impact performance of the cobas® Zika test. In their response of August 8, 2017, the sponsor stated that they intend to launch the cobas® Zika with SW v1.02.13 and

that SW v1.02.13 is a patch to SW v1.02.12 which addresses an anomaly that affects cobas® multiplex assays only and did not affect the cobas® Zika. The sponsor also intends to launch cobas® Zika ASAP Software v10.1.0, which enables compatibility with cobas Synergy Software (BK160113). The response was considered acceptable.

7. Conflict between possible results reported by the (b) (4) and the final results reporting. During software review, it was noted that while the (b) (4)

(b) (4)

The response was considered acceptable.

8. Updates to (b) (4) in Zika Calculation Package. During software review, it was noted that the sponsor referred to updates to the (b) (4) from (b) (4) to (b) (4), and that differences were observed in (b) (4)

(b) (4) version was used. In the Information Request sent to the sponsor on July 25, 2017, the sponsor was requested to explain (b) (4) functionality, differences between (b) (4), and specify (b) (4) version was to be provided to the users, and also to 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.

The sponsor responded on August 14, 2017 that (b) (4) would be included in the ASAP version for launch (SWv10.1.0) and presented a table of updates to changes in parameters made between (b) (4) versions (b) (4). The sponsor also clarified that (b) (4) was not chosen over (b) (4), but that data was originally analyzed using (b) (4) and re-analyzed using (b) (4). This caused the (b) (4)

In the Information request sent to the sponsor on August 18, 2017, the sponsor was asked to further clarify whether the revisions to the (b) (4) parameters would affect the sensitivity and specificity of the assay. The sponsor responded on August 29, 2017 that sensitivity and specificity of the cobas® Zika would not be affected by the (b) (4) changes because (b) (4)

(b) (4) The response was considered acceptable.

9. Mitigations for invalid batches and results between system software and ASAP version changes. During software review, it was noted that hardware and software issues occurred that led to invalidation of batches, and also to invalid results within valid batches during the clinical studies which were performed using System Software Version 01.01.09 and ASAP 9.1.0. The sponsor then

requested approval for the cobas® Zika assay on the 6800/8800 systems using SW v01.2.12 and ASAP nc-10.2.0 (c-10.0.0) without noting whether updates were made to the SW and ASAP to mitigate the issues detected during clinical testing. In the Information Request sent to the sponsor on July 25, 2017, the sponsor was requested to describe all of the new features/safeguards implemented to reduce the occurrences of the errors/issues observed during the studies, and to provide verification and validation testing pertaining to these safeguards, updated hazard/risk analysis, and any new anomalies introduced.

The sponsor responded on August 17, 2017 that 4 of 14 invalid batches and 89 of 306 invalid results in valid batches could be attributed to known issues in SW v1.01.09 that were mitigated in SWv.1.02.12, but that many invalid results in valid batches were due to sample quality or pre-analytic sample handling issues. Tables were provided describing the mitigations for invalid batches and invalid samples in valid batches in SWv.1.02.12. In table 3 of the response, the sponsor noted that a tip handling error was being caused by loose stop disks in the sample pipettor, and that the suggested mitigation was “The periodic maintenance procedure was adapted to exclude routine weekly cleaning of the sample pipettor by the operator.” Since such a change to the instrument maintenance routine could adversely affect the performance of all assays run on the cobas® 6800/8800 instrument, in the Information request sent to the sponsor on August 18, 2017, the sponsor was asked to provide further information on the possible effect of this change to the maintenance routine. The sponsor responded on August 29, 2017 that no negative effect is expected or has been observed because the risk of contamination was mitigated by the stop disk itself and not the weekly cleaning. The response was considered acceptable.

10. Qualification regarding use of plasma testing for organ and tissue donors. During clinical review, it was noted that ZIKV RNA may persist longer in organs and in other body fluids than it does in plasma; thus, a negative result obtained in testing plasma may not mean that other cells or tissues recovered are not infected with ZIKV. The sponsor revised the procedural limitations section of the product insert to add this qualification and the matter was considered resolved.

To resolve all other issues identified in the IRs, FDA was engaged through interactive review with RMS. All the issues identified in the IRs have been addressed by RMS in the amendments responding to the IR and are determined by the committee as resolved.

Conclusions:

The reviewers in the committee reviewed the original submission and amendments. The committee believes that all the review issues have been resolved and therefore recommends an approval to this BLA.