



FINAL SOFTWARE / INSTRUMENTATION REVIEW MEMORANDUM

Submission Received: BL125653/0 – April 7, 2017
BL125663/0/2 – May 19, 2017
BL125663/0/5 – August 4, 2017
BL125663/0/6 – August 8, 2017
BL125663/0/7 – Please see note below
BL125663/0/8 – August 12, 2017
BL125663/0/9 – August 17, 2017
BL125663/0/10 – August 29, 2017

Reviewer: Sajjad Syed, Electrical/Software Engineer, DETTD/PRB

Through: David A. Leiby, Ph.D., Chief, DETTD/PRB
Pradip Akolkar, Ph.D., DETTD/PRB

To: Caren Chancey, Scientific Lead, DETTD/LEP

RPM: Vasantha Kumar, PhD., OBRR/PRMB

Product: cobas Zika Nucleic Acid Test
Applicant: Roche Molecular Systems, Inc.
Submission Type: Priority Biologics License Application (BLA)
STN: BL125653/0/5, BL125653/0/6, BL125653/0/8, BL125653/0/9,
BL125653/0/10. BL125663/0/7 – According to the RPM: “Amendment 7 has been voided (a mistake may have occurred while logging in and so RIMS must have needed to void amendment 7).”

Scientific Disciplines Reviewed: Software and Instrumentation

Recommendation: **Instrumentation / Software Approvable**

EDR link to the submission:

(b) (4)

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1 Purpose, Intended Use and Regulatory History

a. Purpose

The purpose of this priority BLA (BL125653/0) is to provide information regarding cobas Zika Nucleic Acid Test (NAT) performed on the cobas 6800/8800 Systems.

b. Intended use / Indications for use

(Excerpt from /blamain/summary/Summary.pdf)

The cobas Zika 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 in human plasma. 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.

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

c. Past and Concurrent Submissions

The Sponsor has mentioned the following submissions in their BLA 125653/0:

- According to the Sponsor (Roche), the cobas Zika was approved under IND16926 on March 30, 2016 to screen blood donations.
- The Sponsor states that the cobas 6800/8800 Systems also support licensed cobas MPX (BL 125576) and cobas WNV (BL 125575) tests. Common reagents and components shared between cobas Zika and cobas MPX and cobas WNV tests are outlined in BLA 125653/0 Chemistry-CMC omni section.

- The Sponsor clearly states that the cobas 6800 and cobas 8800 Systems have been cleared by CBER, together with the cobas 6800/8800 Systems Software and the cobas p 680 Instrument, in the Premarket Notifications BK140195 and BK140196.
- The Sponsor mentions that for users who have installed cobas Synergy Software to manage pooling for other RMS tests (such as cobas MPX and WNV), Synergy can also be used to communicate individual donor testing results for cobas Zika to an LIS, in a similar fashion to commonly-available middleware used for result management. Note that cobas Synergy Software has been cleared under a Premarket Notification BK160113.

d. Interactions for current submission (communication history)

- 04/07/2017: Submission received.
- 05/02/2017: The Sponsor was requested to provide further information pertaining to the Zika specific ASAP software module. The email detailing the request was relayed to the Sponsor on May 2, 2017 by the RPM (Dr. Vasantha Kumar). The Sponsor subsequently submitted the information in an Amendment BL125663/0/2 dated May 19, 2017.
- 07/06/2017: An internal mid-cycle meeting was held on July 6, 2017 to discuss the issues identified during the review of the submission BL125653.
- 08/04/2017 – 08/17/2017: The Sponsor submitted Amendments 5, 6, 8, 9 that pertained to the additional information questions raised by the review team on July 25, 2017.
- Note that Amendment 5 (STN 125653-0-5, Received on August 4th) contained the responses pertaining to manufacturing lot, aptamer, cobas Zika Control Kit, reagent lots discrepancy, etc. Amendment 5 did not contain responses to the software questions.
- Amendments 6, 8, 9 contained the Sponsor responses to the software reviewer (Mr. Syed) questions.
- Amendment 10 was submitted by the Sponsor containing the responses to the Software/Instrumentation related questions relayed to them on August 18, 2017.

2 Reviewer Summary of Software and Instrumentation

Firstly, it should be noted that based on the Sponsor responses in Amendments 6 to 10, the versioning of their various software packages has changed.

The Versioning of the System is as follows:

Cobas 6800/8800 System Software: SW v1.02.13 (As identified in Amendment 6).

Zika ASAP Software module: c-v10.1.0. (As identified in Amendment 6).

Key test features of the system/assay:

Sample type: Plasma

Amount of sample required: 1000 µL

Amount of sample processed: 850 µL

Test Duration: Results are available within less than 3.5 hours after loading the sample on the system.

Maximum Number of Tests per Run Results Release: 96 tests including controls. Batches of 96 tests, with up to 3 assays per batch.

Maximum Throughput (8 hrs | 24 hrs): Cobas 6800 → 384 | 1,344 tests. Cobas 8800 → 960 | 3,072 tests.

During the original review (July 2017) of the submission (BL125653/0), the Sponsor had provided data from various studies they had conducted including analytical study, feasibility study, cross reactivity supplemental study, clinical specificity and sensitivity study. These studies in large part did support safe operation of Zika assay on cobas 6800/8800 systems that utilizes Zika ASAP software package. The Sponsor had also provided verification activities to support Zika ASAP package internal testing before deploying it on the cobas systems.

Now, although the end results of number of these studies did support correct operations of ASAP package with cobas Zika test, there were issues which were observed during the clinical studies, results analysis and hazard mitigation. These issues were relayed (July 2017) to the Sponsor in an Information Request. The Sponsor subsequently responded back in Amendments 6 to 9. The Sponsor provided further clarification in Amendment 10 (August 29, 2017). These issues and their assessment are shown below:

- It was noted that the Sponsor had instrumentation error, hardware clogging, etc. during their clinical studies. The Sponsor was asked for further clarification and specific versioning of the system and software. The Sponsor responded by providing updated versions of their hardware and software which incorporates fixes of the defects observed during the clinical studies. Based on the additional information provided about the versioning, *the response is considered Adequate.*
- There was an initial confusion on what version of the (b) (4) package the Sponsor was utilizing. Hence, the Sponsor was requested further information pertaining to this point. The Sponsor subsequently responded in Amendments 6 to 9 stating that they had made a mistake in a statement regarding the changes between (b) (4) and (b) (4) would not impact result calculation. The Sponsor also clarified that they intend to launch cobas Zika ASAP SW v10.1.0 which contains (b) (4). The Sponsor further clarified in Amendment 10 that adjustment of (b) (4) parameters does not impact the sensitivity and specificity (S&S) of the assay. The Sponsor has clarified that they updated the (b) (4) sub-module to ensure a hypothetical risk of a sample with very low Ct count is not falsely accounted as a negative. Due to the (b) (4) update, this sample is now categorized as invalid instead of a false negative. Hence, this change does not affect the sensitivity and specificity of the assay. *In light of the information provided, response is Adequate.*

- The reviewer noted that in the responses (Amendments 6 to 9), the Sponsor stated that the majority of the issues that led to invalid results had been mitigated in SW v1.02.12. The Sponsor then claimed that a high number of invalid results in valid batches were attributable to issues with sample quality or pre-analytic sample handling. The reviewer acknowledges that clot detection error can occur due to inconsistent samples. The instruments were able to detect these clots successfully. Another frequent error was Liquid Level detection error during the sample transfer. The Sponsor states in their responses that they have mitigated this error by “exclude routine weekly cleaning of the sample pipettor by the operator.” The reviewer was unclear on what the Sponsor meant by exclusion of routine maintenance as mitigation. The Sponsor clarified (in Amendment 10) by explaining that there has been no case of adverse event or contamination that has been observed due to removal of weekly maintenance. According to the Sponsor, this routine weekly maintenance is the actual root cause of loose stop disks. In addition, the contamination is already mitigated by the actual instrument components (aspiration and dispensing modules) that ensure splashes do not occur in the first place. *Hence, based on this clarification, the response is Adequate.*

Please refer to section 3 below to view the details of the issues described above and subsequent clarification questions, Sponsor responses and their assessment.

RECOMMENDATION: Please note that the cobas 6800/8800 Systems and associated instrument and software have been previously reviewed and assessed for their safety and effectiveness in prior submissions. Hence, the subject submission (BL125653) instrumentation / software review focused on Zika specific ASAP module and its ability to apply the parameters defined, characterize the Curve, and calculate the final results that should be either Reactive, Non-Reactive or Invalid. Specific issues pertaining to exact anomaly mitigation, (b) (4) sub-module revision and its impact on the sensitivity/specificity, SW/ASAP versioning were also addressed by the Sponsor during the review.

Therefore based on the software documentation provided and supporting analytical and clinical studies conducted with the cobas 6800/8800 Systems using Zika ASAP module, the instrumentation and software areas of the subject submission BL125653 are adequate. The software reviewer (Mr. Syed) *recommends Approval* of the submission in terms of instrumentation and software.

Please refer to the SBRA software section below, which Mr. Syed drafted for the SL (Dr. Chancey). This draft was emailed to Dr. Chancey on Tuesday September 12, 2017.

DRAFT SOFTWARE SBRA SECTION:

Roche cobas Zika donor screening assay operates on cobas 6800/8800 Systems.

Roche cobas 6800/8800 Systems and p680 pooler instrument were reviewed under the pre-market notifications (510ks) BK140195 and BK140196. These submissions were cleared in October of 2016. Cobas 6800/8800 Systems currently support licensed cobas MPX (BL 125576) and cobas WNV (BL 125575) donor screening assays. The Sponsor states that the cobas Synergy software (cleared under BK160113) can also be optionally utilized to manage individual donor Zika testing results between the cobas 6800/8800 Systems and a Laboratory Information System (LIS).

Since the cobas 6800/8800 Systems, associated p680 instrument and software have been reviewed numerous times in submissions noted above, the subject software/instrumentation review primarily focused on the Assay Specific Analysis Package (ASAP) related to the cobas Zika assay. This pathway of concentrating the instrumentation/software review to cobas Zika specific ASAP module was discussed and agreed upon between CBER and the Sponsor in a prior pre-submission BQ160101.

The ASAP module contains the assay-specific parameters that are utilized by cobas 6800/8800 Systems to perform cobas Zika test and obtain final results.

The points listed below are a Summary of information provided by the Sponsor in the original BLA 125653 and its subsequent amendments.

- **Versioning:** The Sponsor states that cobas Zika assay will operate on Cobas 6800/8800 System Software (SW) Version 1.02.13. The cobas Zika specific ASAP module version is listed as c-v10.1.0.
- **Device Description:** The cobas 6800/8800 Systems Software (SW) provides basic functionality such as a Graphical User Interface (GUI), instrument management, database functionality, report engines, and LIS interfaces. These basic functions do not change when a new ASAP is added onto the system. An ASAP module encompasses information related to an individual assay such as cobas WNV, MPX, Zika.

The ASAP modules are deployed on the Instrument Gateway (IG) and on the Instrument Manager (IM) for each cobas 6800/8800 System. The ASAPs are built using a common software framework and include assay (test) specific software configuration. An individual ASAP consists of instrument operational parameters, Assay Curve fitting Algorithms, Result Calculation, Result Detail View, Test and Process Definitions, Analysis Workflow Rules, Configuration Presentation.

To perform a specific test (cobas Zika, WNV, etc.), a user selects the test from 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 Analysis:** A Risk Analysis was performed by the Sponsor on the ASAP software. The Sponsor has provided “cobas Zika for use on cobas 6800/8800 Systems” Risk Management Report in their submission. The report provides a summary of the risk management activities, identified product risks, and implemented mitigations for the cobas Zika test. The identified risks include those associated with the product safety and performance. The mitigation measures that reduce the risks related to the impacts of potential failure modes and hazards are also provided and traced to the risks in the Failure Mode Effects Analysis (FMEA) table. The Sponsor has claimed that no risk events concerning the cobas Zika test have occurred during all the testing. Overall, the Risk Management and mitigating features are in place to reduce the risks posed by the ASAP software failure.

- **Testing:** The Sponsor has provided a description of Validation and Verification activities specific to cobas Zika assay. The Sponsor outlines testing activities that were performed to ensure that the cobas Zika assay on the cobas 6800/8800 Systems conform to the requirements defined in the documentation. The Sponsor has provided a verification report that details verification/validation activities conducted. Some of the requirements tested and passed include: “the ASAP shall assign the following targets to the parameters: Target 1: ZIKA”, “the ASAP shall assign the following targets to channels: Target 1: channel 3 (HEX)”, “the ASAP shall report the target results for an RMC as valid or invalid”. The Sponsor has also provided verification activities to support Zika ASAP module internal testing before deploying it on the cobas Systems.

In addition, the Sponsor has conducted analytical and clinical studies that validate the Systems and ASAP Zika module functionality in actual screening laboratories. The Sponsor has utilized cobas 6800/8800 Systems and Zika specific ASAP module to conduct feasibility study, cross reactivity supplemental study, clinical specificity and sensitivity study.

Please note that the Sponsor is requesting licensure in BL125653 for the following software versions: for the cobas 6800/8800 system software version SW v1.02.13; and for the Zika ASAP module, c-v10.1.0. The previously-licensed version of the cobas 6800/8800 system software (SW) in use with the cobas MPX and WNV assays was SWv1.01.09. The Sponsor has now provided a list of key new features and anomaly fixes associated with the subsequent version update to SW v1.02.13. Some of these revisions relate to assay functions such as pressure-based liquid level detection; under-aspiration surveillance (which detects insufficient volume transfer of patient samples); prevention of “cyclor timeout” run aborts by increasing timeout from 30 seconds to 40 seconds; and installation of a Microsoft Service Patch.

- **Unresolved Anomalies:** The Sponsor states that they do not have any anomalies associated with the cobas Zika ASAP module. The Sponsor has identified that SW v1.02.13 fixes an anomaly that was leading to mismatched results when the information was being transmitted from cobas 6800/8800 Systems to the LIS. This anomaly only affected the cobas MPX assay and NOT Zika assay. The patch in the SW v1.02.13 replaces the single affected library and updates the associated configuration files.
- **Development Management:** The Sponsor does provide a summary of their software development life cycle plan, describing the processes that have been put into place to manage the various software development life cycle activities, including a summary of the configuration management and maintenance activities. The Sponsor also provides a description of the software system partitioned into its functional subsystems. The Sponsor has included a Traceability Matrix (TM), which details the links between the requirements, design, implementation, validation and testing. The Sponsor has provided ASAP specific TM that pertains to their cobas Zika assay.

Please note that the cobas 6800/8800 Systems and associated instrument and software have been previously reviewed and assessed for their safety and effectiveness in prior submissions. Hence, the subject submission (BL125653) instrumentation / software review focused on Zika specific ASAP module and its ability to apply the parameters defined, characterize the Curve, and calculate the final results that should be either Reactive, Non-Reactive or Invalid. Based on the software documentation provided and supporting analytical and clinical studies conducted with the cobas 6800/8800 Systems using Zika ASAP module, the instrumentation and software areas of the subject submission BL125653 are adequate. Specific issues pertaining to exact anomaly mitigation, (b) (4) sub-module revision and its impact on the sensitivity/specificity, SW/ASAP versioning were also addressed by the Sponsor during the review.

3 Deficiencies Relayed to Sponsor and Subsequent Responses

After assessing the submission BL125653/0, the software reviewer had number of deficiencies that were relayed to the Sponsor on July 25, 2017. The Sponsor responded in multiple Amendments (6, 8, and 9) to address the software/instrumentation deficiencies. These amendments were submitted between August 4th and August 17th. After assessing these responses, further clarification deficiencies were relayed to the Sponsor via email on August 18, 2017. The Sponsor responded in Amendment 10 to those deficiencies as well. The software reviewer (Mr. Syed) deficiencies, Sponsor multiple responses and reviewer's assessment are shown below:

1. *(Listed as FDA Question 9 in July 25, 2017 letter)* In your System.pdf, you have provided a Risk Management Report. In the report, you have briefly identified Risk 64063 which pertains to Anticoagulants interfering with the assay performance and consequently resulting in false negatives. For further explanation of this risk, you have stated “see attached memo for justification of residual red risk (Pate_Memo_RMD Residual Red Risk Justification_Risk64063).” Please note that we were unable to locate this justification memo in your submission. Hence, please submit the justification memo and provide further information about this risk, how this risk relates to the instrumentation (hardware/software), and possibility/frequency of this scenario occurring at a user site.

Sponsor Response (Amendment 6 – August 8th, 2017. The entire Sponsor response is available in 125653_03_Response.pdf located in STN 125653-0-6 folder):

RMS would like to clarify that Risk 64063 describes the risk of the “unequal assay performance with the different anticoagulants”, that this risk is related to specimens collected in (b) (4)-based anticoagulants, and is not related to instrumentation (hardware/software). The risk mitigation is to remove the claims for specimen stability for samples collected in (b) (4) anticoagulants from the cobas® Zika package insert; thus, the exclusion of the option for testing samples collected in (b) (4) anticoagulants should substantially reduce the risk of occurrence at user sites. This risk is maintained in the RMS Risk Management Report in the event that a user tested plasma collected in a (b) (4) anticoagulant. The risk is evaluated further in the memo for the justification of residual red risk (Pate_Memo_RMD Residual Red Risk Justification_Risk64063) (Attachment 2) A summary of the memo is provided below: "The risk identified during technical performance verification (TPV) studies is that, when tested with cobas® Zika, the Zika virus-spiked samples exposed to (b) (4) anticoagulants yielded some false negative results for samples at LOD. False negative results were not observed for samples that had been collected, stored, or otherwise exposed to non-(b) (4) anticoagulants, such as EDTA (ethylenediaminetetraacetic acid). This observation lead to a conclusion that (b) (4) anticoagulants may interfere with cobas® Zika performance and, in the worst case, could lead to a false negative result."

Reviewer Assessment: *The Sponsor has clarified that the subject risk is **not** related to the instrument or software. It is related to the actual specimens collected in (b) (4)-based anticoagulants. The Sponsor’s risk mitigation is to remove the claim for specimen stability for samples collected in (b) (4) anticoagulants from Zika package insert. This will notify the user not to use the samples exposed to (b) (4) anticoagulants since they will yield false negative results. The Sponsor has identified this risk and has updated their labeling accordingly to ensure that user does not use samples that are exposed to (b) (4)-based anticoagulants. **Hence, Response is Adequate.***

2. **(Listed as FDA Question 10 in July 25, 2017 letter)** In your BLA125653 System.pdf file, you have stated that you are seeking licensure for the cobas Zika test performed on cobas 6800/8800 instruments with System Software version 1.02.12 (“SW v1.02.12”). You have also stated that you are planning to launch ASAP version c-v10.0.0 with the cobas Zika test. However, you recently submitted a BLA supplement (BL125575/6) that pertains to cobas West Nile Virus (WNV) ASAP SW v10.0.1 for use with the cobas 6800/8800 Systems with System Software v1.02.13. Hence, it is unclear what version of the System Software will be subsequently installed on the cobas 6800/8800 to ensure cobas Zika test operates on these systems. Please provide a comparison table between v1.02.12 and v1.02.13. Please also explain v1.02.13 impact on cobas Zika test.

Sponsor Response (Amendment 6 – August 8th, 2017. The entire Sponsor response is available in 125653_03_Response.pdf located in STN 125653-0-6 folder):

RMS intends to launch the cobas® Zika test with cobas® 6800/8800 Systems SW v1.2.13. RMS also has revised the cobas® Zika Assay-specific Analysis Package (ASAP) Software, and intends to launch with cobas® Zika ASAP SW v10.1.0. cobas® 6800/8800 Systems SW v1.2.13: SW v1.2.13 is a patch to SW v1.2.12, and can only be installed after installation of SW v1.2.12. SW v1.2.13 represents a patch to address an anomaly that could, under certain conditions, cause discordance between the information displayed on the cobas® 6800/8800 Systems Software user interface and information sent to customer’s LIS. This anomaly is only associated with multiplex assays, such as the cobas MPX assay (BL125576). The patch replaces the single affected library (b) (4) and updates the associated configuration files for the instrument hardware, Instrument Gateway (IG), Instrument Manager (IM), and Pooling Instrument Manager (PIM) with the new software version number. cobas® Zika ASAP Software v10.1.0: cobas® Zika ASAP SW v10.0.0 is fully compatible with cobas® 6800/8800 Systems SW v1.2.13; no changes were required to the ASAP software as a result of the patch in SW v1.2.13. However, RMS has revised the cobas® Zika ASAP SW in order to make the assay compatible with cobas® Synergy Software (BK160113). For users that have installed cobas® Synergy Software to manage pooling for other RMS tests (such as cobas® MPX and cobas® WNV), the software can also be used to communicate individual donor testing results for cobas® Zika to an LIS, in a similar fashion to commonly-available middleware used for result management.

The verification of the cobas® Zika ASAP SW v10.1.0 is documented in “cobas® 6800/8800 ZIKA IVD Test – ASAP Verification Report ZIKA v10.1.0 – on cobas® 6800/8800 Platform” (DH-04482.03-217B_01.pdf), which has been provided for review in Attachment 3 to this response.

Reviewer Assessment: The Sponsor has clearly identified now that they intend to launch the cobas Zika test with cobas 6800/8800 Systems SW v1.2.13. The Sponsor states that v1.2.13 fixes an anomaly that was leading to mismatched results when the information was being transmitted from 6800/8800 to the LIS System. This anomaly only affected the MPX assay and NOT Zika assay. The patch replaces the single affected library (b) (4) and updates the associated configuration files. The Sponsor also intends to launch cobas Zika ASAP Software v10.1.0, which enables compatibility with cobas Synergy Software (BK160113). **Hence, Response is Adequate.**

3. **(Listed as FDA Question 11 in July 25, 2017 letter)** In your Att15.01_10474225_SDE 000 02.pdf (submitted as part of BLA 125653 Amendment 2), you have stated that (b) (4)

(b) (4)

Sponsor Response (Amendment 6 – August 8th, 2017. The entire Sponsor response is available in 125653 03 Response.pdf located in STN 125653-0-6 folder):

This question refers to Section 3.5.6.1 of the 10474225 SDE 000 (b) (4) specification document (Approximation Validity Check): (b) (4)

*This means that the values falling in the range sets are only classified as Positive or Negative based on these sets cutoffs. Any other result or value not consistent with the cutoff is deemed "Invalid". Hence, Zika assay is setup to only produce Positive, Negative, Invalid results. **Based on the explanation and reassurance provided by the Sponsor, Response is Adequate.***

4. *(Listed as FDA Question 12 in July 25, 2017 letter)* In your submission BL125653, you have 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 have 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.

Sponsor Response (Amendment 8 – August 12th, 2017. The entire Sponsor response is available in 125653 07 Response.pdf located in STN 125653-0-8 folder):

(b) (4) As discussed in the response to Question 10, RMS intends to launch with cobas® Zika ASAP SW v10.1.0, which contains (b) (4). The statement regarding the changes between (b) (4) and (b) (4) not impacting result calculation was made in error. (b) (4) was not chosen over (b) (4) for data analysis in the non-clinical specificity study. (b) (4) was included in the ASAP which was installed on the instrument when performing the non-clinical specificity study, but these data were re-analyzed with (b) (4). The valid runs contained (b) (4) valid results, (b) (4)

RMS at this time would like submit additional information on Table 3 from the System document in the original BLA submission, which summarized the various ASAP used during the pre-clinical and clinical studies. The (b) (4) versions have now been added to the table, and a few minor typos were corrected (Table 2, highlighted in bold red font).

(b) (4)

(b) (4)

Reviewer Assessment: The Sponsor has clarified various versions of (b) (4) package used during the analysis of their studies including non-clinical specificity study. The Sponsor has clearly identified now that they intend to launch with cobas Zika ASAP SW v10.1.0, which contains (b) (4). The Sponsor has also stated that they incorrectly stated in the original submission that the changes between (b) (4) and (b) (4) did not impact result calculation. The Sponsor has removed the statement and has provided a detailed table comparing all three (b) (4) versions. It appears that (b) (4) are (b) (4). These

parameters include (b) (4), etc. It appears to the reviewer that the Sponsor has iterated through various versions of (b) (4) modules to reduce the number of Invalid results due to their Internal Controls (IC) parameters. However, the reviewer believes that this point needs to be verified by the Sponsor, since adjustment of these parameters should not impact the sensitivity and specificity of the assay. **Hence, additional confirmatory information was required. Please refer to Clarification Question 1 in Section 3.1 which contains Sponsor subsequent response (amendment 10) and reviewer assessment.**

5. **(Listed as FDA Question 13 in July 25, 2017 letter)** In your Clinical Study (Clin Study _cX8_Zika_412.pdf), you have listed specific instrument errors that led to invalidation of batches. Some of these Hardware / Software errors include: sample pipetting errors in transfer module, processing module error mode, sample module stoppage of samples loading, etc. For number of these errors, the mitigation was to reboot the system and repeat the entire batch. You have also listed issues that led to invalid results within valid batches. These issues include: clot detected during aspiration, liquid level detection error, anomalies during calculations, volume errors during reagent dispense/supernatant removal, etc. It is noted that all of these issues/errors occurred on System Software Version 01.01.09 and Assay Version Number 9.1.0. It is also observed that since the clinical testing completion, you have updated your System Software Version to SW v1.02.12 and ASAP module to nc-10.2.0 (c-10.0.0). It is unclear exactly what changes were implemented to mitigate the issues detected during the clinical testing. Hence, please describe all of the new features/safeguards you have implemented to reduce the occurrences of the errors/issues observed during various studies. Please also provide verification and validation testing pertaining to these safeguards, updated hazard/risk analysis, and any new anomalies introduced.

Sponsor Response (Amendment 9 – August 17th, 2017. The entire Sponsor response is available in 125653_08_Response.pdf located in STN 125653-0-8 folder):

There were 14 invalid batches with issues related to hardware and software in Clinical Study cX8_Zika_412. Four of these invalid run batches, as well as 89 of the 306 invalid results in valid batches, can be attributed to known issues in SW v1.01.09 that have been fixed or mitigated via workaround in SW v1.02.12. It however is important to note that a high number of invalid results in valid batches were attributable to issues with sample quality or pre-analytic sample handling. Table 2 summarizes the issues which led to the 14 invalid batches observed in the study. The table describes the issue root cause and indicates whether they are associated with known issues in SW v1.01.09, and whether they have been fixed or mitigated in SW v1.02.12. Verification documentation is referenced where applicable, and is included in Attachment 2. Table 3 provides similar information associated with issues which led to the 306 invalid results in valid batches; the referenced verification document is included in Attachment 2. A description of the error codes observed in cX8_Zika_412 is provided below in Table 1. (Reviewer Note: The tables are available in the 125653_08_Response.pdf for viewing).

Reviewer Assessment: *The Sponsor has stated that the majority of the issues that led to invalid results have been mitigated in SW v1.02.12. The Sponsor also explains that a high number of invalid results in valid batches were attributable to issues with sample quality or pre-analytic sample handling. The reviewer notes that there were numerous instances of “clot detection during aspiration” error that were classified by the Sponsor as sample quality issue. The reviewer understands that issues can occur due to inconsistent sample quality. The instruments were able to successfully detect clots, hence supporting clot detection functionality. However, the Sponsor has also listed Liquid Level detection error during the sample transfer, which needs further clarification. The Sponsor states that they have mitigated this error by “exclude routine weekly cleaning of the sample pipettor by the operator.” The reviewer is unclear what the Sponsor means by “exclusion of routine maintenance” as mitigation. The Sponsor has also listed Heat Sealer malfunction that is currently being fixed. The reviewer needs further information about current mitigations for the heat sealer problem as well. Hence, additional confirmatory information was required. Please refer to Clarification Question 2 in Section 3.1 below, which contains Sponsor subsequent response (amendment 10) and reviewer assessment.*

3.1 Clarification Questions and Sponsor Responses:

The questions below are clarification inquiries that were based on the Sponsor responses in Amendments 6 to 9, received in August 2017. The Sponsor responded to these questions in their Amendment 10, submitted on August 29, 2017.

1. In your Question 12 Response (provided in 125653_07_Response.pdf), you have provided a description of (b) (4) configuration files. Reviewing the response and the tables, it appears that (b) (4) files have been revised to reduce the invalid results. However, it is unclear if (b) (4) parameters revisions can impact the Sensitivity and the Specificity of the assay. Please confirm that the performance of the assay, as it relates to the Sensitivity and Specificity, is not impacted by these revisions.

Sponsor Response (Amendment 10 – August 29, 2017. The entire Sponsor response is available in 125653_09_Response.pdf located in STN 125653-0-10 folder):

RMS would like to clarify that the (b) (4) was not revised in order to reduce the invalid results; the parameters in question were changed in (b) (4) to ensure that (b) (4). This change has no impact on the sensitivity or specificity of the assay because it (b) (4)

This change could (b) (4)

Reviewer Assessment: The Sponsor has clarified that they updated the (b) (4) sub-module to ensure (b) (4)

Due to the (b) (4) update, this sample is now categorized as an invalid instead of a false negative. Hence, this change does not affect the sensitivity and specificity of the assay. ***In light of the information provided, response is Acceptable.***

2. In your Question 13 Response (provided in 125653_08_Response.pdf), you have provided information about the invalid batches and the individual invalid results. Please provide further explanation pertaining to the points listed below:
 - a. You mention in Table 2 that three instances of “invalid batch” occurred due to heat sealer defects. For some of these defects you have stated that they will be fixed in the next version of the software (SW v1.3), while the fix for the other defect is currently under development. Please explain what current resolution you have in place to ensure that while the defects fixes are being developed, the user continues to understand these errors and possibly avoid them.

Reviewer Comment: Please note that question 2a pertaining to heat sealer was not relayed to the Sponsor. The review team management stated that invalid results due to Heat Sealer hardware problem are not safety issue but user inconvenience and the Sponsor is aware of the heat sealer issues and is planning to address these issues that result in invalid batches. Hence, the question 2a was not emailed to the Sponsor.

- b. You have cited 55 occurrences of individual invalid samples due to liquid level detection error. You have listed the following mitigation for this issue: “the periodic maintenance procedure was adapted to exclude routine weekly cleaning of the sample pipettor by the operator.” It appears that you are suggesting that the revised maintenance procedure should exclude routine weekly cleaning of the pipettor. Exclusion of routine maintenance could lead to contamination and adversely affect all of the assays performance. Please provide further information about how you intend to implement this mitigation.

Sponsor Response (Amendment 10 – August 29, 2017. The entire Sponsor response is available in 125653_09_Response.pdf located in STN 125653-0-10 folder):

No negative effect is expected or has been observed by the removal of this step from the periodic maintenance procedure. It is important to note that the contamination risk is mitigated by design. The aspiration and dispensing steps are optimized that splashes will not occur. Furthermore, each sample tip contains a filter, which protects the pipettor (specifically, the stop disc) against possible splashes from

inside the sample tip. The only situation where splashes could potentially occur is with samples with clots that partially obstruct the tip; however, this is mitigated by the filter. Because of these features, and due to the fact that weekly cleaning of the pipettor is anyway an ineffective measure to limit contamination (and was found to be the root cause of the loose stop disks), the periodic maintenance was adapted to exclude the weekly cleaning.

Reviewer Assessment: *According to the Sponsor, there has been no case of adverse event or contamination that has been observed due to the removal of weekly maintenance. As described by the Sponsor, this routine weekly maintenance is the actual root cause of loose stop disks. In addition, the contamination is already mitigated by the actual instrument components (aspiration and dispensing modules) that ensure splashes do not occur in the first place. Hence, based on this clarification, the response is Acceptable.*

4 Software and Instrumentation Documentation Status and Adequacy

The table below includes the current status of the review with respect to specific documentation outlined in Agency’s software guidance document (Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices).

Version: Cobas 6800/8800 System Software: SW v1.02.13. Zika ASAP Software module: c-v10.1.0.		
Level of Concern: <i>Major LOC Provided</i>		
<i>Initial Software documentation Summaries related to cobas Zika test are provided in \blamain\other\System.pdf. The cobas 6800/8800 Systems documentation is provided in BK140195 and BK140196.</i>	Yes	No
Software Description: <i>Adequate; Further details: System.pdf, 125653_Resp to Inf Req_02May2017.pdf, 125653_09_Response.pdf.</i>	Y	
Device Hazard Analysis: <i>Adequate; Further details: System.pdf, 125653_Resp to Inf Req_02May2017.pdf, 125653_03_Response.pdf, 125653_09_Response.pdf.</i>	Y	
Software Requirements Specifications: <i>Adequate; Further details: System.pdf, 125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Architecture Design Chart: <i>Adequate; Available in System.pdf</i>	Y	

Design Specifications: <i>Adequate</i> ; Further details: <i>System.pdf, 125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Traceability Analysis/Matrix: <i>Adequate</i> ; Further details: <i>System.pdf, 125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Development: <i>Adequate</i> ; <i>System.pdf.</i>	Y	
Verification & Validation Testing: <i>Adequate</i> ; <i>System.pdf, 125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Revision level history: <i>Adequate</i> ; <i>System.pdf, 125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Unresolved anomalies: <i>Adequate</i> ; <i>125653_Resp to Inf Req_02May2017.pdf.</i>	Y	
Cyber-Security: <i>Adequate</i> ; <i>Available in System.pdf.</i>	Y	

Judging from the information provided, a MAJOR level of concern is appropriate for the subject instrument/software. As explained in section 2 of this memo, the subject review primarily focuses on Assay software (also referred to as the ASAP software module) that contains the assay-specific parameters used to perform the Zika Assay on the systems. However, for better understanding of the overall system and software interaction, the reviewer did refer back to BK140195 which the Sponsor had earlier submitted for instrumentation and system software.

1. Level of Concern

+The Sponsor does provide the level of concern and the supporting rationale. Level of concern (LOC) is correctly identified as *MAJOR*. – *The LOC identified is appropriate for the subject instruments and ASAP.*

2. Software Description (SD)

+The Sponsor provides an acceptable summary of the features and software operating environment. The ASAP software module consists of all assay (test) specific software configuration and instrument operational parameters, including the following: Algorithms, Result Calculation, Result Detail View, Test & Process Definitions, Analysis Workflow Rules, Configuration Presentation. The Sponsor clarified in subsequent amendments that they intend to launch cobas Zika ASAP SW v10.1.0 which contains (b) (4) . *Hence, SD is considered Adequate.*

3. ASAP Hazard Analysis (HA)

+A Risk Analysis is performed on the ASAP software. The Sponsor has provided “cobas Zika for use on cobas 6800/8800 Systems” Risk Management Report in System.pdf (available in BL125653/0). The report provides a summary of the risk management activities, identified product risks, and implemented mitigations for the cobas Zika test. The identified risks include those associated with product safety and performance. The mitigation measures that reduce the risks related to the impacts of potential failure modes and hazards are provided and traced to the risks in the FMEA table. The Sponsor has claimed that no Risk Events concerning the cobas

Zika test have occurred during all the testing. Overall, the Risk Management and mitigating features are in place to reduce the risks posed by the ASAP software failure. In subsequent amendments, the Sponsor has clarified that Risk 64063 is not related to the instrument or software. It is related to the actual specimens collected in (b) (4)-based anticoagulants. The Sponsor's risk mitigation is to remove the claim for specimen stability for samples collected in (b) (4) anticoagulants from Zika package insert. This will notify the user not to use the samples exposed to (b) (4) anticoagulants since they will yield false negative results. The Sponsor has identified this risk and has updated their labeling accordingly to ensure that user does not use samples that are exposed to (b) (4)-based anticoagulants. *Hence, HA is Acceptable.*

4. Design Specification

+The Sponsor does provide the design specification document now in their A002. The document is labeled "cobas 6800/8800 / cobas p 680 SW 1.2 Technical Design Description Unit Analysis Package" (10784864_CON_000_00.pdf) describes the ASAP software design. This document is included for review in Attachment 6 of A002 response. – *The Sponsor has provided detailed SDS for the ASAP. Hence, SDS is considered Adequate.*

5. Software Requirements Specifications (SRS)

+The Sponsor does provide a copy of the software requirements specification document, which documents the functional parameters requirements, interface and design of the ASAP software that pertains to cobas Zika assay. The SRS are detailed in DH-04482.03-006_01.pdf and summarized in A002 / 125653_Resp to Inf Req_02May2017.pdf. Some of the requirements outlined include: "ASAP shall assign the Internal Control to channel 5", "ASAP shall report the target results for an RMC as valid or invalid", "ASAP shall be able to calculate results from raw data containing steps". The Sponsor has subsequently provided verification report to support successful implementation of these requirements. – *Hence, SRS is considered Adequate.*

6. Traceability

+The Sponsor provides a traceability matrix (TM), which details the links between the requirements, design, implementation, validation and testing. The Sponsor has provided ASAP specific TM that pertains to their Zika assay. This TM is contained in 125653_Resp to Inf Req_02May2017.pdf. – *The information provided in TM is Adequate.*

7. Validation (including verification and testing)

+The Sponsor does provide a description of Validation and Verification activities (System.pdf) specific to Zika Assay. The Sponsor outlines testing activities that were performed to ensure that the Zika Assay on the cobas 6800/8800 conformed to the requirements defined in the documentation. The Sponsor has provided a verification report (System.pdf) that details verification / validation activities conducted. Some of the requirements tested and passed include: "the ASAP shall assign the following targets to the parameters: Target 1: ZIKA", "the ASAP shall assign the following targets to channels: Target 1: channel 3 (HEX)", "the ASAP shall report the target results for an RMC as valid or invalid". The verification reports are included in the System.pdf. The Sponsor has also conducted analytical and clinical studies that validate the system and ASAP Zika package in actual screening laboratories as well. *Hence, the*

Sponsor Validation and Verification Activities to support ASAP package implementation are Adequate.

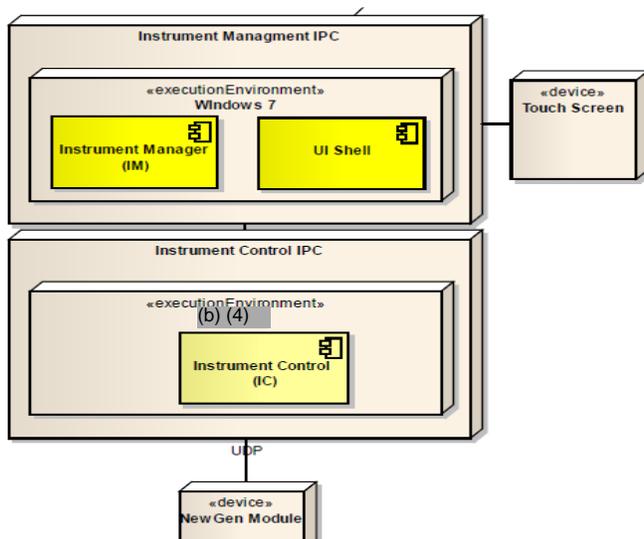
8. Architecture Design

+The Sponsor does provide a description of the software system partitioned into its functional subsystems. The Sponsor does provide a sufficient description of the role that each module plays in fulfilling the software requirements. – *Adequate Diagrams of the system units presented.*

9. Development

+The Sponsor does provide a summary of their software development life cycle plan, describing the processes that have been put into place to manage the various software development life cycle activities, including a summary of the configuration management and maintenance activities. The Sponsor states that cobas 6800/8800 systems are developed in (b) (4)

. Note that calls made to the instrument OS goes through Windows 7 OS which contains the User Interface developed in (b) (4) (as shown below). – *Adequate.*



10. Revision Level History

+The Sponsor does provide a clear revision history log, documenting all major changes to the software during its development cycle. – *Adequate.*

11. Unresolved Anomalies (bugs)

+The Sponsor states in their A002/125653_Resp to Inf Req_02May2017.pdf file that they do not have any anomalies in the cobas Zika ASAP software. – *Based on the prior agreement with the Sponsor, the reviewer has focused on ASAP package, hence notes that no anomalies are present in the ASAP package. Therefore, anomalies section is Adequate.*

12. Release Version Numbers (RVN)

+The Sponsor does provide clear software versions of the overall system components now (original and amendments). The Sponsor has now (Amendment 6) stated that they are *seeking licensure for the cobas Zika test for use with cobas 6800/8800 System Software version 1.02.13 (“SW v1.02.13”).* The Sponsor has also stated that they are planning to launch ASAP version c-v10.1.0 with the cobas Zika test. *Hence, RVNs are Adequate.*

13. Cyber-Security

+The Sponsor had discussed Cyber-Security issues in their previous submissions. Hence, ASAP related questions and issues have been addressed in previous Pre-market submissions. The Sponsor does state that Authentication (signing) of the ASAP software code has been implemented as a specific control measure. – *Cyber-security information provided in previous submissions is Adequate.*

5 Device Description

The following information contains excerpts from the submission BL125653. Software reviewer has extracted these selected passages in the memo for additional understanding of how the subject instrument/assay operates.

System Details:

cobas Zika is a qualitative test that is run on the cobas 6800 System and cobas 8800 System. cobas Zika enables the simultaneous detection of Zika RNA and the internal control in a single test of an infected, individual donation.

The Sponsor states that the cobas 6800/8800 Systems Software provides basic functionality such as a Graphical User Interface (GUI), instrument management, database functionality, report engines, and LIS interfaces. These basic functions do not change when a new ASAP is added onto the system. The ASAP 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.

For users that have installed cobas Synergy Software to manage pooling for other RMS tests (such as cobas MPX and WNV), Synergy can also be used to communicate individual donor testing results for cobas Zika to an LIS, in a similar fashion to commonly-available middleware used for result management. Note that cobas Synergy Software has been cleared by CBER under BK160113.

Differences between 6800 and 8800: The Processing Module, where the extraction of nucleic acids from sample material occurs, as well as the subsequent setup for PCR including sealing of the Amplification and Detection (A/D) plate. The cobas 6800 System contains one Processing Module, and the cobas 8800 System contains two Processing Modules. The cobas 6800 System contains one Analytic Module with one Analytic Cyler (thermal cycling and detection unit), and

the cobas 8800 System contains two Analytic Modules with a total of four Analytic Cyclers. The design of the Analytic Module is the same for both the cobas 6800 and cobas 8800 Systems, except that the AD-Plate Handler has a broader range of movement in the cobas 8800 System to be able to load AD-Plates into all four Analytic Cyclers.

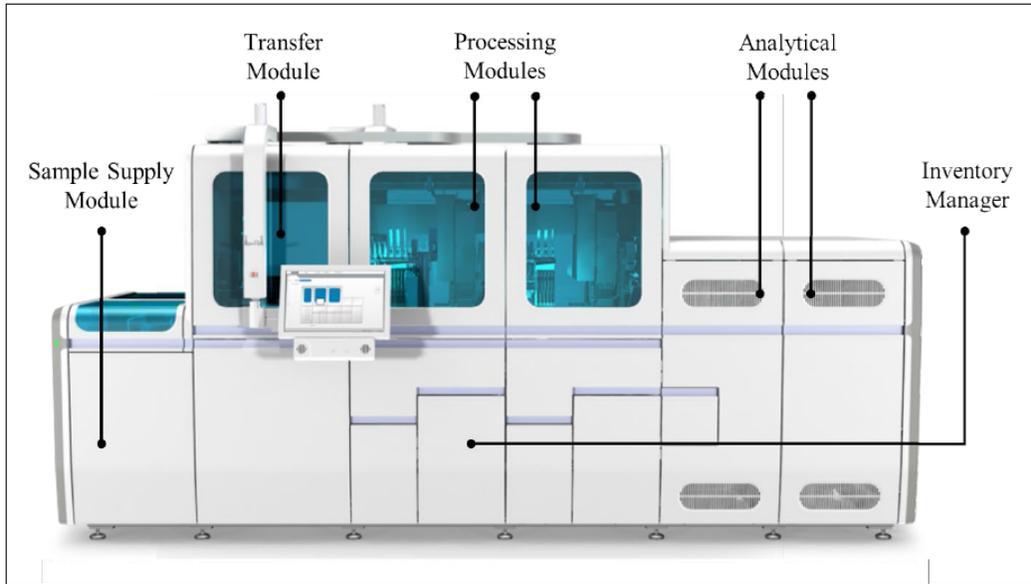


Figure 1: cobas Zika 8800 System.

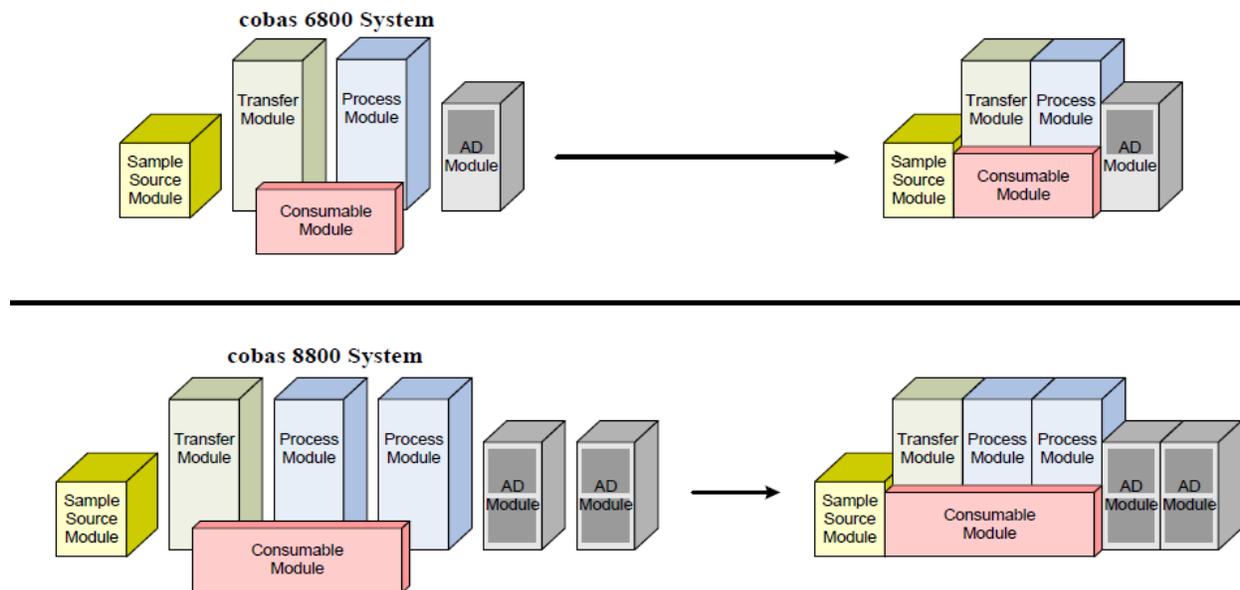


Figure 2: Modular Construction of the cobas 6800\8800 Systems Instrumentation.

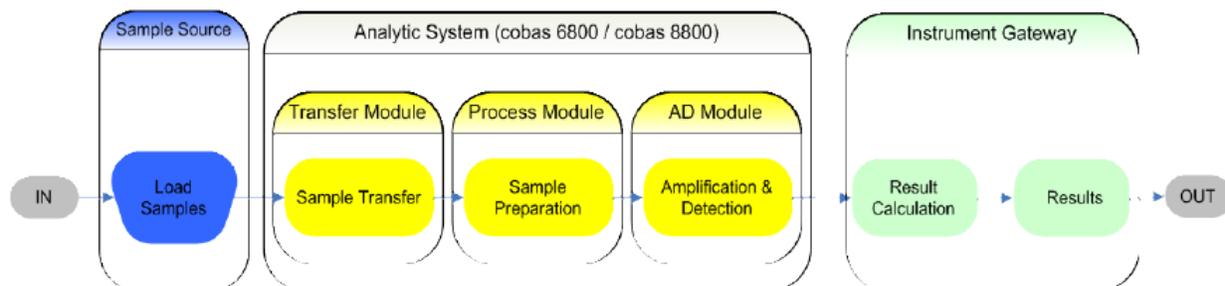
Sample supply: Samples are placed onboard the sample supply module using standard 5-position racks and supporting rack trays. Each sample is then moved automatically into the transfer module. Sample racks hold 5 primary or secondary sample tubes. Each rack tray holds 15 sample racks, for a total of 75 sample tubes per tray.

Sample transfer: The transfer module automatically moves samples into the System for barcode scanning and subsequent transfer from primary or secondary tubes onto the cobas omni Processing Plate.

Sample preparation: Extraction and purification of nucleic acids from input samples takes place in the processing module. The purified nucleic acids are then transferred to amplification plates, along with test-specific amplification master mixes to prepare the plates for amplification and detection in the analytical module. The inventory manager houses all reagents, controls and consumables necessary to achieve complete automation.

Amplification and detection: The analytical module performs the automated amplification and detection of target nucleic acids using real-time PCR technology.

A workflow defines how the system processes the samples designated for a specific test, including any required user interactions. This workflow is shown below:



The system identifies the orders, and manages the process automatically. The system workflow is centered on the batch process and linked to the design of the Processing plate (P-Plate 48) and Amplification\Detection plate (AD-Plate 96):

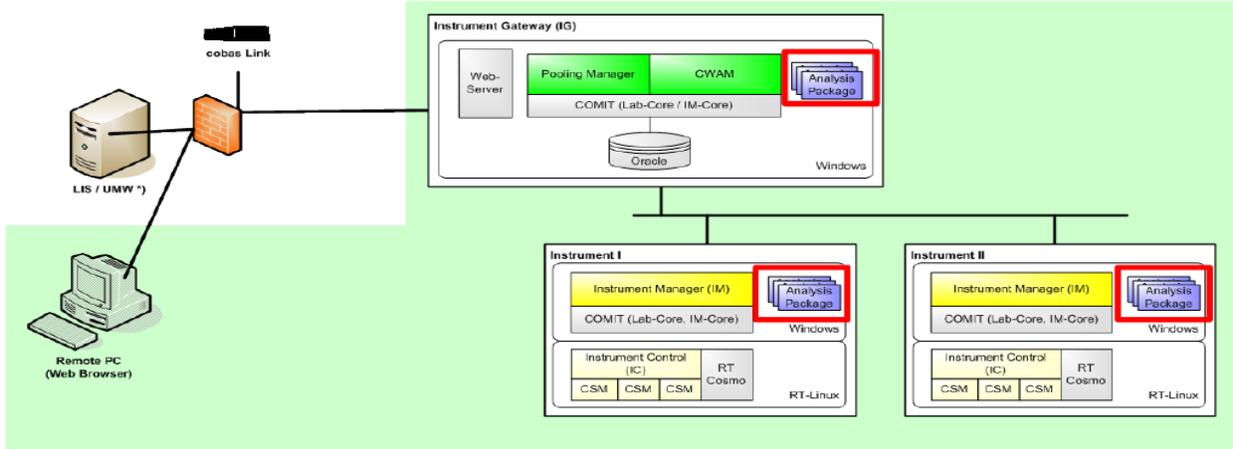
- The P-Plate 48 has 48 wells
- The system has two 48 channel process heads which can process 96 test orders in parallel, using two Process plates
- The AD-Plate 96 has 96 wells

As stated in the BK140195 submission, the ASAP consists of all assay (test) specific software configuration and instrument operational parameters, including the following:

- Algorithms
- Result Calculation
- Result Detail View
- Test & Process Definitions

- Analysis Workflow Rules
- Configuration Presentation

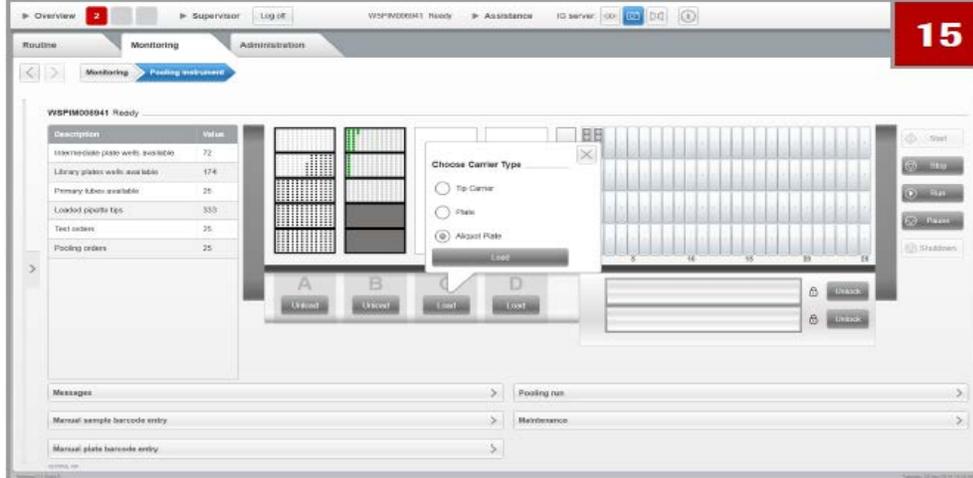
ASAP are deployed on the Instrument Gateway (IG) and on the Instrument Manager (IM) for each instrument, which ensures that the Analysis Packages are deployed consistently in the cluster.



*) The following configurations are foreseen:
 - UMW
 - LIS
 - UMW + LIS

- Instrument Gateway SW
- Instrument Management SW
- Instrument Control SW
- Framework / external Tools
- Assay Tools, Service Tools

Screenshots below from cobas 6800/8800 monitor:



Hid	Flags	Sample type	Overall result	Target 1	Target 2	Target 3	Control Batch ID	Creation datetime	Retest	Status	Instrument
Q02		MPX O (+) C	Invalid	Invalid			20	11-Nov-2013 19:34:43	No	Not released	WSIM100
CD2H1		(-) C	Invalid	Invalid	Invalid	Invalid	20	11-Nov-2013 19:34:42	No	Not released	WSIM100
PP1	MPX Non-Reactive	MPX Non-Reactive	HIV Non-Reactive	HBV Non-Reactive	HCV Non-Reactive		18	08-Nov-2013 19:57:44	No	Not released	WSIM100
PP1	MPX Non-Reactive	HIV Non-Reactive	HBV Non-Reactive	HCV Non-Reactive			18	08-Nov-2013 19:57:43	No	Not released	WSIM100
PP1	MPX Reactive	HIV Reactive	HBV Reactive	HCV Reactive			18	08-Nov-2013 19:57:42	No	Not released	WSIM100
PP1	MPX Reactive	HIV Reactive	HBV Reactive	HCV Reactive			18	08-Nov-2013 19:57:40	No	Not released	WSIM100
PP1	MPX Non-Reactive	HIV Non-Reactive	HBV Non-Reactive	HCV Non-Reactive			18	08-Nov-2013 19:57:39	No	Not released	WSIM100
PP6	MPX Reactive	HIV Reactive	HBV Reactive	HCV Reactive			18	08-Nov-2013 19:57:32	No	In Workflow	WSIM100
PP6	MPX Non-Reactive	HIV Non-Reactive	HBV Non-Reactive	HCV Non-Reactive			18	08-Nov-2013 19:57:27	No	Not released	WSIM100
PP6	MPX Reactive	HIV Reactive	HBV Reactive	HCV Reactive			18	08-Nov-2013 19:57:26	No	In Workflow	WSIM100
PP6	MPX Non-Reactive	HIV Non-Reactive	HBV Non-Reactive	HCV Non-Reactive			18	08-Nov-2013 19:57:24	No	Not released	WSIM100
PP6	MPX Reactive	HIV Reactive	HBV Reactive	HCV Reactive			18	08-Nov-2013 19:57:22	No	In Workflow	WSIM100

Control ID: C161420284080480097581

Sample ID: C161420284080480097581

Tests: MPX

Test results: Invalid, Invalid, Invalid

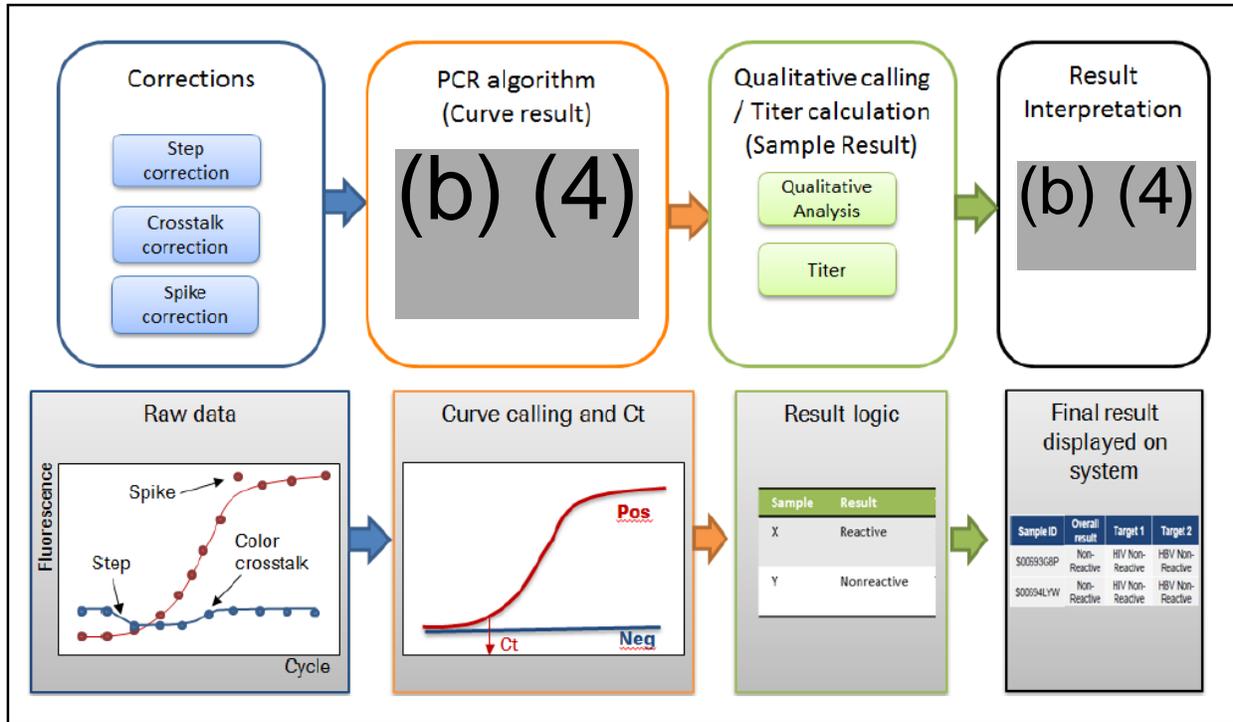
Valid: No

Status: Not released

Flag	Description	Severity
CD2H1	Data for target 1 cannot be analyzed.	Critical
CD2H2	Data for target 2 cannot be analyzed.	Critical
CD2H3	Data for target 3 cannot be analyzed.	Critical

The Sponsor explains that the (b) (4) approximates the fluorescence measurement data with an analytical Model Function to calculate the characteristic numerical values. The most important characteristic values are the relative fluorescence increase (RFI) value, the F value as a measure from the deviation of a line, the maximal relative slope (MRS), the endpoint relative increase (ERI) and the threshold cycle (C_T). They are used as discriminators between positive and negative curves and as a measure for quantification.

The (b) (4) uses the (b) (4) algorithm that iteratively looks for the best model fit. If one of the stopping criteria is reached the (b) (4) algorithm proceeds with the best model function parameter set which has been found in the iteration process.



cobas 6800/8800 Systems Assay Algorithm Process Flow.

6 Review

Please refer to “Reviewer Summary of Software and Instrumentation” and “Software and Instrumentation Documentation Status and Adequacy” section of this memo.

7 Reviewer Notes and Recommendations

Please refer to “Reviewer Summary of Software and Instrumentation” section of this memo.

8 Appendix 1: Interactive Review

The Sponsor was asked on May 2, 2017 to submit software documents to fulfil Major Level of Concern requirements. The Sponsor responded on May 19, 2017 by submitting an Amendment (A002) that contained the specific documents. Request for information, and brief Sponsor response are shown below:

FDA COMMENT 5 FROM MAY 02, 2017: DESCRIPTION OF ASAP FUNCTIONALITY:

Regarding the software, you have stated that the ASAP (Zika specific software package) includes assay (test) software configuration and instrument operational parameters. It also includes test and process definitions, algorithms, and result calculation. You have also associated a Major level of software concern (LOSC) to your entire system. However, we could not locate information pertaining to your ASAP package that satisfies the Major LOSC documentation criteria described in our software guidance

<https://www.fda.gov/RegulatoryInformation/Guidances/ucm089543.htm>. Therefore, please submit the following documents specific to ASAP: Software Design Specifications, Software Requirements, List of Anomalies, Software Release Management, cyber security assessment. Please also include detailed description of ASAP controlled instrument operational parameters, process definitions, algorithms in ASAP, and result calculation flowchart. Please email this information by May 12, 2017.

RMS Response to FDA Comment 5 (A002: 125653 Resp to Inf Req 02May2017.pdf - May 19, 2017): The ASAP software for all assays run on the cobas 6800/8800 Systems share a common design that consists of generic and assay-specific packages. The software design specifications, requirements, and other documentation requested by FDA which defines the functionality of the cobas Zika ASAP software is summarized.

RMS Amendments August 2017:

The Sponsor submitted numerous Amendments (5 – 9) that contained responses to the review team questions that were relayed to the Sponsor in July of 2017. The software reviewer (Mr. Syed) evaluated software responses and judged several of them to be adequate. However, he did have clarification questions pertaining to maintenance routine, (b) (4) package and heat sealer. These clarification questions were relayed to the Scientific Lead (Dr. Caren Chancey) in an August 18, 2017 email.

RMS Amendments September 2017:

The Sponsor submitted (August 29, 2017) Amendment 10 that contained the responses to the clarification software questions related to Amendments 6 to 9. The software reviewer (Mr. Syed) evaluated the responses and judged them to be adequate. Software reviewer recommended Instrumentation and Software Approval on September 14, 2017.