

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Manufacturing and Product Quality

MEMORANDUM

Recommendation to Waive Pre-License Inspection

From: Cecily Jones, OCBQ/DMPQ/MRB1

To: BLA File – STN 125653/0

Subject: Recommendation to waive the pre-license inspection for Roche Molecular Systems Inc., located in (b) (4), for the manufacture of the Zika Test for use on the cobas[®] 6800/8800 Systems

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/MRB1

Concurrent Clearance Routing

_____CONCUR/ DO NOT CONCUR Date: _____

John A. Eltermann, Jr., R.Ph., M.S.
Director, Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

_____CONCUR/ DO NOT CONCUR Date: _____

Hira Nakhasi, Ph.D.
Director, Division of Emerging Transfusion Transmitted Diseases
Office of Blood Research and Review
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Summary:

This memorandum recommends that a pre-approval inspection be waived for the Biologics License Application, STN 125653/0 from Roche Molecular Systems, Inc., (here after referred to as RMS) submitted to CBER April 7, 2017, to provide for the

manufacturer of the cobas[®] Zika, Nucleic acid kit (hereafter referred to as cobas[®] Zika) for use on the cobas[®] 6800/8800 Systems at their (b) (4) location (b) (4)). Concurrence for this recommendation is requested.

Brief History:

In response to FDA recommendations, **cobas[®] Zika**, a qualitative PCR NAT assay, was developed to detect ZIKV RNA in plasma from donors of whole blood and blood components. The **cobas[®] Zika** was approved under IND16926 on Mar. 30, 2016 to screen blood donations. On August 26, 2016, the US FDA expanded the requirement for screening of blood donations with a NAT or using PRT to extend to all blood donations collected in all the 50 U.S. states, as of November 18, 2016. Twelve US testing sites are currently enrolled under IND16926. The approval of the **cobas[®] Zika** BLA will enable the use of a licensed test for screening blood donations.

Manufacturing for all cobas 6800/8800 test kits and components takes place at the following location:

Roche Molecular System, Inc.

(b) (4)
 (b) (4)
 (b) (4)

The manufacturing suite where each in vitro product is manufactured is listed below.

Table 1: cobas[®] Zika Test Kit Manufacturing Information

Kit	Manufacturing Site
cobas Zika test kit (480T)	(b) (4)
cobas Zika Control Kit	(b) (4)

Table 2: cobas[®] Zika Test Kit Component Manufacturing Information

Kit	Component	Manufacturing Site
cobas Zika test kit	Master Mix R2 Master Mix R2 (Bulk)	(b) (4)
	RNA Internal Control RNA Internal Control (Bulk)	
cobas Zika Control Kit	Zika (+) C (Vial) Zika (+) C (Bulk)	(b) (4)

Table 3: cobas omni Reagent and Common Component Manufacturing Information

Kit	Component	Manufacturing Site
Assay Specific Test Kits	Protease Protease (Bulk)	(b) (4)
	Elution Buffer Elution Buffer (Bulk)	
	Master Mix R Master Mix R1 (Bulk)	
Wash Reagent	Wash Reagent (Bottle) Wash Reagent (Bulk)	
Specimen Diluent	Specimen Diluent (Bottle) Specimen Diluent (Bulk)	
Lysis Buffer	Lysis (Bottle) Lysis (Bulk)	
MGP Reagent	Magnetic Glass Particles (Bulk) Magnetic Glass Particles (Buffer)	
Negative Control	Negative RMC (Vial) Negative RMC (Bulk)	

Building (b) (4), 6800/8800 Fill Suite: The building contains laboratories for the PCR IVD Quality Control and Operations Technical Support Departments and an area used for the manufacture of stocks and components of in vitro diagnostic test kits and non-diagnostic PCR products for research use. The 6800/8800 filling suite is considered a (b) (4) area, lowest risk in the manufacturing facility, dedicated to the manufacturing of the cobas 6800/8800 line of products, which also include the CDRH approved cobas® HBV (P150014) and cobas® HCV (P150015) tests (approval date October 14, 2015). Activities in the 6800/8800 filling suite include the filling of Magnetic Glass Particle (MGP), Master Mix (MMX), and Elution Buffer (EB) reagents, and subsequent labeling. The product contact equipment in the 6800/8800 filling and labeling suite is single use, disposable, and autoclaved before use.

Building (b) (4), Bioprocessing Suite or Manufacturing Suite (b) (4): The building is used for the manufacture of components of test kits and contains manufacturing suites, a kit packaging area, a staging warehouse, and office space. The office space is separated from the manufacturing suites. The manufacturing facility in Building (b) (4) is sub-divided into (b) (4) manufacturing suites that are connected by a central corridor running through the facility dividing the suites. Manufacturing suites for Central Weigh, Oligonucleotide and Positive Control are situated on the North side of the main corridor and the Bioprocessing

(Enzyme), Bulk Manufacturing, and Filling and Labeling suites are situated on the opposite (South) side of the corridor.

Kit packaging, a staging warehouse containing room temperature and refrigerated storage areas, and a shipping/receiving area are adjacent to the manufacturing core on the west side. The office suite is adjacent to the manufacturing core on the east side of the facility.

Basis for the Waiver:

This waiver is based on criteria outlined in CBER SOPP 8410 “Determining When Pre-Licensing/Pre-Approval Inspections (PLI/PAI) are necessary.” As stated in the aforementioned SOPP, it is CBER’s policy that a pre-license or pre-approval inspection will generally be necessary for a supplement if any of the following criteria **in bold** are met:

The facility does not hold an active US license.

RMS holds a U.S. License 1636. **cobas**® Zika is run on the **cobas**® 6800/8800 Systems which have been cleared by CBER. The **cobas**® 6800/8800 Systems also support licensed **cobas**® MPX (BL 125576) and **cobas**® WNV (BL 125575) tests at the (b) (4) facility. Common reagents and components shared between **cobas**® Zika and **cobas**® MPX and **cobas**® WNV tests.

The facility has not been inspected in the last two years by the FDA.

The (b) (4) facility was last inspected (b) (4). The inspection was classified VAI and all inspectional issues have been resolved. The current Team Biologics led EI was conducted as a CP 7342.008, Inspection of Licensed *In-Vitro* Diagnostic (IVD) Devices Regulated by CBER ((b) (4)) and the OBPO/Team Biologics Staff FY 2017 Workplan. System coverage included the Corrective and Preventive Action and Production Systems.

The previous establishment inspection (EI) was conducted as a Level 1 QSIT (Quality System Inspection Technique) and Postmarket PMA inspection of Class II, III and licensed IVD medical devices from (b) (4) per FACTS Assignment (b) (4), Operation Identification (b) (4), eNSpect Operation Identification (b) (4).

The inspection covered the **cobas** (b) (4) Test. CAPA, Production & Process Controls (P&PC) subsystems were covered. Limited coverage was given to the Design

Control subsystem. The firm's final response to the 2015 inspection was collected.

The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.

The areas and equipment used to manufacture the approved **cobas**[®] MPX (BL 125576) and **cobas**[®] WNV (BL 125575) tests at the (b) (4) facility are the same as the areas and equipment used for the manufacturing of the **cobas**[®] Zika Tests Kit.

No new equipment types were purchased specifically for the manufacture of the **cobas**[®] Zika Test Kit, and no new processing areas were employed distinct from those used to manufacture **cobas**[®] Zika Test Kit.

The previous inspection revealed significant GMP deficiencies in areas related to the processes in the application/supplement (similar processes) or systemic problems, such as QC/QA oversight.

The current Team Biologics led EI was conducted as a CP 7342.008, Inspection of Licensed *In-Vitro* Diagnostic (IVD) Devices Regulated by CBER ((b) (4)) and the OBPO/Team Biologics Staff FY 2017 Workplan.

The (b) (4) facility was last inspected (b) (4) . The inspection was classified VAI and all inspectional issues have been resolved.

The manufacturing process is sufficiently different (new production methods), specialized equipment or facilities) from that of other approved products produced by the establishment.

The manufacturing process is not sufficiently different from that of other licensed products, including the **cobas**[®] MPX (BL125576) and **cobas**[®] WNV (BL125575) tests.

Waiver Recommendation:

Based on the information provided in the Original Biologics License Application and the previous inspection reports supporting the overall compliance status of the license holder, I recommend waiving the pre-license inspection for the facility associated with this application.