DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

August 17, 2016

Estela Raychaudhuri
President
InBios International, Inc.
562 1st Avenue S., Suite 600
Seattle, WA 98104

Dear Ms. Raychaudhuri:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of InBios International, Inc.'s ("InBios"), ZIKV *Detect*™ IgM Capture ELISA for the presumptive detection of Zika virus IgM antibodies in human sera collected from individuals meeting the Centers for Disease Control and Prevention (CDC) Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated), by laboratories in the United States that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories,[1] pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3). Where there are presumptive Zika positive, possible Zika positive, or presumptive other flavivirus positive results from the ZIKV *Detect*™ IgM Capture ELISA, confirmation of the presence of anti-Zika IgM antibodies or other flavivirus IgM antibodies requires additional testing, as described in the Scope of Authorization of this letter (Section II) and in the authorized Instructions for Use document, and/or consideration alongside test results for other patient-matched specimens using the latest CDC guideline for the diagnosis of Zika virus infection.

On February 26, 2016, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C), the Secretary of Health and Human Services (HHS) determined that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves Zika virus.[2] Pursuant to section 564(b)(1) of the Act (21 U.S.C. § 360bbb-3(b)(1)), and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or

[1] For ease of reference, this letter will refer to "laboratories in the United States that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories" as "authorized laboratories."

[2] As amended by the Pandemic and All-Hazards Preparedness Reauthorization Act, Pub. L. No. 113-5, under section 564(b)(1)(C) of the Act, the Secretary may make a determination of a public health emergency, or of a significant potential for a public health emergency.

diagnosis of Zika virus infection, subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).[3]

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(c)) are met, I am authorizing the emergency use of the ZIKV *Detect*™ IgM Capture ELISA (as described in the Scope of Authorization section of this letter (Section II)) in individuals meeting CDC Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated) (as described in the Scope of Authorization section of this letter (Section II)) for the presumptive detection of Zika virus infection by authorized laboratories, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the ZIKV *Detect*™ IgM Capture ELISA for the presumptive detection of Zika virus-specific IgM antibodies in the specified population meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. The Zika virus can cause Zika virus infection, a serious or life-threatening disease or condition to humans infected with the virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the ZIKV *Detect*™ IgM Capture ELISA may be effective in diagnosing Zika virus infection, and that the known and potential benefits of the ZIKV *Detect*™ IgM Capture ELISA for diagnosing Zika virus infection outweigh the known and potential risks of such product, when, for presumptive Zika positive, possible Zika positive, and presumptive other flavivirus positive results, additional testing (as described in the Instructions for Use document) is performed and/or test results for other patient-matched specimens (using the latest CDC guideline for the diagnosis of Zika virus infection) are considered; and

3. There is no adequate, approved, and available alternative to the emergency use of the ZIKV *Detect*™ IgM Capture ELISA for diagnosing Zika virus infection.[4]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized ZIKV *Detect*™ IgM Capture ELISA by authorized laboratories for the presumptive detection of Zika virus-specific IgM antibodies in individuals meeting CDC Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological

[3] HHS. *Determination and Declaration Regarding Emergency Use of In Vitro Diagnostic Tests for Detection of Zika Virus and/or Diagnosis of Zika Virus Infection.* 81 Fed. Reg. 10878 (March 2, 2016).

[4] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

criteria for which Zika virus testing may be indicated) when, for presumptive Zika positive, possible Zika positive, and presumptive other flavivirus positive results, additional testing (as described in the Instructions for Use document) is performed[5] and/or test results for other patient-matched specimens (using the latest CDC guideline for the diagnosis of Zika virus infection) are considered.

The Authorized ZIKV *Detect*™ IgM Capture ELISA

The ZIKV *Detect*™ IgM Capture ELISA is an IgM antibody capture enzyme-linked immunosorbent assay for the *in vitro* presumptive detection of Zika virus-specific IgM antibodies in human sera and other authorized specimen types from individuals meeting CDC Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated). The test procedure is based on capturing human IgM antibodies from the patient specimen on a microtiter plate using anti-human-IgM antibody followed by the addition of Zika virus specific antigen and detector conjugate.

One of the limitations of this test is the possibility of false positive results in patients with a history of infection with other flaviviruses. For presumptive Zika positive, possible Zika positive, and presumptive other flavivirus positive specimens, additional testing (as described in the Instructions for Use document) and/or consideration of test results for other patient-matched specimens, using the latest CDC guideline for the diagnosis of Zika virus infection, is therefore required to confirm Zika virus infection.

The assay uses a purified antibody specific for human IgM that is immobilized on a test plate to capture IgM antibodies from a human specimen. A serum specimen from a patient and positive and negative controls are added to the test plate, and incubated to allow the IgM antibodies from the specimen to bind to the immobilized antibody. After washing, Ready-To-Use Zika virus antigen (Zika Ag), a Cross-reactive Control Antigen (CCA), and a Normal Cell Antigen (NCA) are added separately to appropriate locations on the ELISA plate and allowed to incubate. During incubation the Zika Ag binds to any Zika virus-specific IgM antibodies captured on the plate. Following a washing step, a flavivirus specific monoclonal antibody conjugated to horseradish peroxidase is then added which binds to any immobilized Zika Ag and generates a colorimetric optical signal upon addition of a chromogenic substrate that can be measured by a spectrophotometer or other instruments that may be authorized. Any signals generated in the wells exposed to CCA and NCA are analyzed as part of the test procedure and used to aid in the interpretation of the ELISA results.

The ZIKV *Detect*™ IgM Capture ELISA includes the following materials, or other authorized materials:

- **Coated Microtiter Test Strips for IgM:** ELISA plate strip holder with 96 (12x8 strips) polystyrene microtiter wells pre-coated with capture antibodies specific for human IgM.

[5] As discussed in the Instructions for Use document, the additional testing for presumptive Zika positive and possible Zika positive results is to be performed using the latest CDC guideline for the diagnosis of Zika virus infection, and the additional testing for presumptive other flavivirus positive results is to be performed with FDA-cleared Dengue and West Nile virus IgM devices.

- **ZIKV Sample Dilution Buffer:** The buffer solution is used to dilute all serum specimens and controls prior to testing in the ZIKV *Detect*™ IgM Capture ELISA.

- **Ready-To-Use ZIKV Recombinant Antigen for IgM (Zika Ag):** The Zika Ag comprises the Zika envelope glycoproteins and is used in the ZIKV *Detect*™ IgM Capture ELISA.

- **Cross-reactive Control Antigen for ZIKV IgM (CCA):** The CCA cocktail is used to aid in the interpretation of the ELISA results.

- **Normal Cell Antigen for ZIKV IgM (NCA):** The NCA is used to aid in the interpretation of the ELISA results.

- **100X Conjugate for ZIKV IgM:** This is horseradish peroxidase-labeled monoclonal anti-Flavivirus antibody used to generate the optical signal measured by the ELISA spectrophotometer.

- **Conjugate Diluent for ZIKV:** This solution is used to dilute the 100X Conjugate for ZIKV IgM solution during the ELISA procedure.

- **10X Wash Buffer:** Concentrated wash buffer used during the ELISA procedure.

- **Liquid Tetramethylbenzidine Substrate:** Chromogenic substrate that reacts with the horseradish peroxidase conjugate to generate the optical signal measured by the ELISA spectrophotometer.

- **Stop Solution:** Used to terminate the reaction between the chromogenic substrate and the horseradish peroxidase conjugate.

The ZIKV *Detect*™ IgM Capture ELISA requires the following control materials or other authorized control materials provided with the kit:

- **ZIKV IgM Positive Control:** The positive control aids in verifying the validity of the kit.
- **ZIKV IgM Negative Control:** The negative control aids in verifying the validity of the kit.

Controls listed above must be included on each 96-well plate. Controls must generate expected results in order for a plate to be considered valid.

The ZIKV *Detect*™ IgM Capture ELISA also requires the use of additional materials and ancillary reagents commonly used in clinical laboratories and that are described in the authorized ZIKV *Detect*™ IgM Capture ELISA Instructions for Use.

The above described ZIKV *Detect*™ IgM Capture ELISA, when labeled consistently with the labeling authorized by FDA entitled "ZIKV *Detect*™ IgM Capture ELISA Instructions for Use"

(available at http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm), is authorized to be distributed to and used by authorized laboratories under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law. This labeling may be revised by InBios in consultation with, and with concurrence of, the Division of Microbiology Devices (DMD)/Office of In Vitro Diagnostics and Radiological Health (OIR)/Center for Devices and Radiological Health (CDRH).

The above described ZIKV *Detect*™ IgM Capture ELISA is authorized to be accompanied by the following information pertaining to the emergency use, which is authorized to be made available to health care providers, pregnant women, and other patients:

- Fact Sheet for Health Care Providers: Interpreting ZIKV *Detect*™ IgM Capture ELISA Results
- Fact Sheet for Pregnant Women: Understanding Results from the ZIKV *Detect*™ IgM Capture ELISA
- Fact Sheet for Patients: Understanding Results from the ZIKV *Detect*™ IgM Capture ELISA

Other Fact Sheets developed by InBios in consultation with, and with concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and DMD/OIR/CDRH may be authorized to accompany the above described ZIKV *Detect*™ IgM Capture ELISA and to be made available to health care providers, pregnant women, and other patients.

As described in Section IV below, InBios is also authorized to make available additional information relating to the emergency use of the authorized ZIKV *Detect*™ IgM Capture ELISA that is consistent with, and does not exceed, the terms of this letter of authorization.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized ZIKV *Detect*™ IgM Capture ELISA in the specified population, when used for presumptive detection of Zika virus-specific IgM antibodies and used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of such a product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized ZIKV *Detect*™ IgM Capture ELISA may be effective in the diagnosis of Zika virus infection, when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the authorized ZIKV *Detect*™ IgM Capture ELISA, when used to diagnose Zika virus infection in the specified population (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized ZIKV *Detect*™ IgM Capture ELISA under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the ZIKV *Detect*™ IgM Capture ELISA described above is authorized to diagnose Zika virus infection in individuals meeting CDC Zika virus clinical criteria (e.g., a history of clinical signs and symptoms associated with Zika virus infection) and/or CDC Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika transmission at the time of travel, or other epidemiological criteria for which Zika virus testing may be indicated).

This EUA will cease to be effective when the HHS declaration that circumstances exist to justify the EUA is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

III. Waiver of Certain Requirements

I am waiving the following requirements for the ZIKV *Detect*™ IgM Capture ELISA during the duration of this EUA:

- Current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the ZIKV *Detect*™ IgM Capture ELISA.

- Labeling requirements for cleared, approved, or investigational devices, including labeling requirements under 21 CFR 809.10 and 21 CFR 809.30, except for the intended use statement (21 CFR 809.10(a)(2), (b)(2)), adequate directions for use (21 U.S.C. 352(f)), (21 CFR 809.10(b)(5), (7), and (8)), any appropriate limitations on the use of the device including information required under 21 CFR 809.10(a)(4), and any available information regarding performance of the device, including requirements under 21 CFR 809.10(b)(12).

IV. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

InBios and Its Authorized Distributor(s)

A. InBios and its authorized distributor(s) will distribute the authorized ZIKV *Detect*™ IgM Capture ELISA with the authorized labeling only to authorized laboratories. InBios may request changes to the authorized labeling. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

B. InBios and its authorized distributor(s) will provide to authorized laboratories the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Health Care Providers, the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Pregnant Women, and the

authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Patients, and any additional ZIKV *Detect*™ IgM Capture ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

C. InBios and its authorized distributor(s) will make available on their websites the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Health Care Providers, the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Pregnant Women, and the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Patients, and any additional ZIKV *Detect*™ IgM Capture ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize.

D. InBios and its authorized distributor(s) will inform authorized laboratories and relevant public health authority(ies) of this EUA, including the terms and conditions herein.

E. InBios and its authorized distributor(s) will ensure that authorized laboratories using the authorized ZIKV *Detect*™ IgM Capture ELISA have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[6]

F. Through a process of inventory control, InBios and its authorized distributor(s) will maintain records of device usage.

G. InBios and its authorized distributor(s) will collect information on the performance of the assay. InBios will report to FDA any suspected occurrence of false negative results and significant deviations from the established performance characteristics of the assay of which InBios becomes aware.

H. InBios and its authorized distributor(s) are authorized to make available additional information relating to the emergency use of the authorized ZIKV *Detect*™ IgM Capture ELISA that is consistent with, and does not exceed, the terms of this letter of authorization.

InBios

I. InBios will notify FDA of any authorized distributor(s) of the ZIKV *Detect*™ IgM Capture ELISA, including the name, address, and phone number of any authorized distributor(s).

J. InBios will provide its authorized distributor(s) with a copy of this EUA, and communicate to its authorized distributor(s) any subsequent amendments that might be made to this EUA and its authorized accompanying materials (e.g., fact sheets, instructions for use).

K. InBios may request changes to the authorized ZIKV *Detect*™ IgM Capture ELISA Fact

[6] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that InBios and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition (see http://www.cdc.gov/zika/).

Sheet for Health Care Providers, the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Pregnant Women, and the authorized ZIKV *Detect*™ IgM Capture ELISA Fact Sheet for Patients. InBios may also request that InBios develop new ZIKV *Detect*™ IgM Capture ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients, if appropriate, and may request changes to such Fact Sheets. All such requests listed in this condition of authorization will be made by InBios in consultation with, and require concurrence of, OCET/OCS/OC and DMD/OIR/CDRH.

L. InBios may request the addition of other instruments for use with the authorized ZIKV *Detect*™ IgM Capture ELISA. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

M. InBios may request the addition of other ancillary reagents for use with the authorized ZIKV *Detect*™ IgM Capture ELISA. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

N. InBios may request the addition of other specimen types for use with the authorized ZIKV *Detect*™ IgM Capture ELISA. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

O. InBios may request the addition of other control materials for use with the authorized ZIKV *Detect*™ IgM Capture ELISA. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

P. InBios may request substitution for or changes to the authorized materials used in the detection process of the human anti-Zika IgM in the specimen. Such requests will be made by InBios in consultation with, and require concurrence of, DMD/OIR/CDRH.

Q. InBios will track adverse events and report to FDA under 21 CFR Part 803.

R. InBios will evaluate the performance of the ZIKV *Detect*™ IgM Capture ELISA with a FDA-recommended or established panel(s) of characterized clinical specimens, and will submit that performance data to FDA. After DMD/OIR/CDRH's review of and concurrence with the data, InBios will update its labeling, in consultation with, and with concurrence of, DMD/OIR/CDRH, to reflect the additional testing.

Authorized Laboratories

S. Authorized laboratories will include with reports of the results of the ZIKV *Detect*™ IgM Capture ELISA the authorized Fact Sheet for Health Care Providers, the authorized Fact Sheet for Pregnant Women, and the authorized Fact Sheet for Patients, and any additional ZIKV *Detect*™ IgM Capture ELISA Fact Sheets for Health Care Providers, Pregnant Women, and Patients that OCET/OCS/OC and DMD/OIR/CDRH may authorize. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.

T. Authorized laboratories will perform the ZIKV *Detect*™ IgM Capture ELISA on serum or

with other authorized specimen types.

U. Within the United States and its territories, authorized laboratories will report all presumptive Zika positive, possible Zika positive, and presumptive other flavivirus positive results to InBios.

V. Authorized laboratories will have a process in place to assure that, for presumptive Zika positive, possible Zika positive, and presumptive other flavivirus positive results, additional testing (as described in the Instructions for Use document) is performed and/or test results for other patient-matched specimens, using the latest CDC guideline for the diagnosis of Zika virus infection, are considered.

W. Authorized laboratories will have a process in place for reporting test results to health care providers and relevant public health authorities, as appropriate.[7]

X. Authorized laboratories will collect information on the performance of the assay and report to InBios any suspected occurrence of false negative results and significant deviations from the established performance characteristics of which they become aware.

Y. All laboratory personnel using the assay should be appropriately trained in performing and interpreting immunoassays techniques, use appropriate laboratory and personal protective equipment when handling this kit, and use the test in accordance with the authorized labeling.

InBios, Its Authorized Distributor(s), and Authorized Laboratories

Z. InBios, its authorized distributor(s), and authorized laboratories will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

Conditions Related to Advertising and Promotion

AA. All advertising and promotional descriptive printed matter relating to the use of the authorized ZIKV *Detect*™ IgM Capture ELISA shall be consistent with the authorized Fact Sheets and authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

BB. All advertising and promotional descriptive printed matter relating to the use of the authorized ZIKV *Detect*™ IgM Capture ELISA shall clearly and conspicuously state that:

- This test has not been FDA cleared or approved;
- This test has been authorized by FDA under an EUA for use by authorized laboratories;

[7] For questions related to reporting Zika test results to relevant public health authorities, it is recommended that InBios and authorized laboratories consult with the applicable country, state, or territory health department(s). According to CDC, Zika is a nationally notifiable condition (see http://www.cdc.gov/zika/).

- This test has been authorized only for the diagnosis of Zika virus infection and not for any other viruses or pathogens; and

- This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

No advertising or promotional descriptive printed matter relating to the use of the authorized ZIKV *Detect*™ IgM Capture ELISA may represent or suggest that this test is safe or effective for the diagnosis of Zika virus infection.

The emergency use of the authorized ZIKV *Detect*™ IgM Capture ELISA as described in this letter of authorization must comply with the conditions and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of *in vitro* diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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Robert M. Califf, M.D.
Commissioner of Food and Drugs

Enclosures