Fact Sheet for Healthcare Providers: Interpreting DPP® Zika IgM Assay System Results

September 27, 2017

Dear Healthcare Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Chembio Diagnostic Systems, Inc. (Chembio) DPP® Zika IgM Assay System. This assay provides *in vitro* qualitative detection of human IgM antibodies to Zika virus. The DPP® Zika IgM Assay System is intended for use with serum (plain or separation gel) and fingerstick whole blood, EDTA venous whole blood, or EDTA plasma (each collected alongside a patient-matched serum specimen) specimens of individuals meeting CDC Zika clinical and/or epidemiological criteria for testing (see www.cdc.gov/zika/hc-providers/index.html) by laboratories in the U.S. that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high or moderate complexity tests, or by similarly qualified non-U.S. laboratories. Specimens used with the DPP® Zika IgM Assay System should not be collected prior to 8 days after onset of symptoms or risk of exposure. This test should be performed according to CDC's algorithm for Zika testing (see http://www.cdc.gov/zika/laboratories/lab-guidance.html).

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the DPP® Zika IgM Assay System (see http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm).

Why is this test needed at this time?

Public health officials have determined that Zika virus poses a potential public health emergency. Current information on Zika virus infection for healthcare providers, including case definitions and information about signs and symptoms, is available at www.cdc.gov/zika/hc-providers/index.html. All information and guidance, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (www.cdc.gov/zika/index.html).

At this time, there are no FDA approved/cleared tests available that can detect Zika virus infection in clinical specimens in the US. Therefore, Chembio has developed the DPP® Zika IgM Assay System to detect evidence of Zika virus infection.

The U.S. Secretary of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of in vitro diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate

when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

When should the DPP® Zika IgM Assay System test be performed?

Anti-Zika IgM is typically detectable starting soon after onset of symptoms and is reliably detectable for approximately 12 weeks following infection. If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the DPP® Zika IgM Assay System may be ordered for patients whose blood specimen was collected after 8 days from likely risk of Zika virus exposure or post-onset of symptoms and should be performed according to the CDC-issued guidance (http://cdc.gov/zika/laboratories/lab-guidance.html). The algorithms included within the guidance illustrate the appropriate Zika testing approach based on the presence of signs and symptoms, pregnancy status, and the time between onset of symptoms or suspected exposure and specimen collection.

As disease manifestations of dengue and chikungunya virus infections can resemble those of Zika virus infection, additional testing for these viruses should be considered in the context of the epidemiological setting to aid in differentiating dengue and chikungunya virus infections from Zika virus infections. Please contact your state or local health department to facilitate testing.

The DPP® Zika IgM Assay System has been authorized for use with human serum (plain or separation gel), fingerstick whole blood, EDTA venous whole blood, and EDTA plasma specimen types. However, confirmatory testing requires the use of serum samples as of September 27, 2017. Therefore, if fingerstick whole blood, or EDTA venous whole blood, or EDTA plasma specimens are used with the DPP® Zika IgM Assay System, a patient-matched serum specimen should also be collected, or if this is not possible, an additional serum specimen should be collected soon after the original specimen.

Specimens tested with DPP® Zika IgM Assay System should be collected after 8 days post-onset of symptoms or likely risk of Zika virus exposure. If a specimen is collected prior to 8 days post-onset of symptoms or likely risk of Zika virus exposure the patient should be asked to return and provide a second sample at least 7 days after the initial blood specimen was collected. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device, handling, and storage. Serum should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis. Venous whole blood and plasma should be collected in tubes containing EDTA. Fingersticks should be tested immediately. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: https://www.cdc.gov/zika/laboratories/test-specimens-bodyfluids.html.

How should results from the DPP® Zika IgM Assay System be interpreted?

This test may give one of two possible results: (1) reactive, or (2) non-reactive.

- **Specimen tests positive with the DPP® Zika IgM Assay System (i.e., reactive)**
  A positive test (i.e., reactive) result from the DPP® Zika IgM Assay System indicates that anti-Zika IgM antibodies were detected in the patient's specimen. Confirmation of DPP® Zika IgM Assay System reactive results requires additional testing by CDC or by qualified laboratories designated by CDC and in consultation with CDC, using the CDC-issued algorithm published in the CDC laboratory guidance found at:
  http://cdc.gov/zika/laboratories/lab-guidance.html.

  Laboratory test results should always be considered in the context of clinical observations, epidemiological information, and travel history in making a final diagnosis and patient management decisions. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

  Positive DPP® Zika IgM Assay System results are not definitive for diagnosis of Zika virus infection and must be confirmed with additional testing and/or consideration using the latest CDC testing algorithms for the diagnosis of Zika virus infection before making healthcare management or treatment decisions for the patient. It is possible that the DPP® Zika IgM Assay System may generate reactive results in patients with a history of non-Zika flavivirus infections or in patients who have received yellow fever or Japanese encephalitis vaccination, which may make it difficult to identify which flavivirus is causing the patient's current illness. In the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true source of symptoms; in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy; or other unintended adverse effects.

  Due to cross-reactivity of anti-dengue IgM and IgG antibodies in tests to detect recent Zika virus infection, it may be difficult to determine the specific flavivirus causing the recent infection in patients with a history of flavivirus infection or in those who reside in areas where Zika and/or dengue virus have been known to circulate. Due to this limitation, plaque reduction neutralization test (PRNT) is not currently routinely recommended for confirmation of DPP® Zika IgM Assay System results in Puerto Rico. Please refer to CDC guidance, including the CDC laboratory guidance (http://www.cdc.gov/zika/laboratories/lab-guidance.html) for additional information about diagnostic testing recommendations in the U.S. and its territories.

  In the U.S. and its territories, Zika virus infection and disease (non-congenital and congenital) are nationally notifiable conditions and should be reported to the local or state health department. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

While there is an established association between Zika virus infection during pregnancy and microcephaly, detection of anti-Zika IgM antibodies in specimens collected from a pregnant woman does not provide definitive information about the health of her fetus and does not indicate imminent harm to her fetus. If a pregnant woman is diagnosed with Zika virus infection based on detection of anti-Zika IgM antibodies, issues such as timing of infection during the course of pregnancy, presence of symptoms and other factors may help determine the risk to her fetus.

- **Specimen tests negative with the DPP® Zika IgM Assay System (i.e., non-reactive)**
  A negative DPP® Zika IgM Assay System (i.e., non-reactive) result does not rule out Zika virus infection, particularly if testing is conducted prior to 8 days post-onset of symptoms (before anti-Zika IgM antibodies levels are expected to become detectable by the assay) or more than 12 weeks after the infection is thought to have occurred (as anti-Zika IgM antibodies levels are expected to drop). As with any test, providers must consider the patient's likelihood of exposure and the possibility of false laboratory results when making treatment or other patient management decisions.

  Absence of laboratory evidence of Zika virus infection cannot definitively rule out Zika virus infection in persons with epidemiological risk factors. All results should be considered in the context of clinical signs and symptoms, exposure risk and time since symptom onset, or in the absence of symptoms, time since exposure. Conversely, an on-reactive result in an asymptomatic patient with a lower likelihood of exposure (e.g., a short term traveler to an affected area) may suggest the patient is not infected.

Guidance for healthcare providers, including those caring for pregnant women and women of reproductive age with possible Zika virus exposure, is available on the CDC website: http://www.cdc.gov/zika/hc-providers/index.html.

Reporting Adverse Events

You should report adverse events, including problems with test performance or results, to MedWatch at http://www.fda.gov/Safety/MedWatch/default.htm, by completing and submitting the online FDA Form 3500 for Health Professionals (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) or by calling 1-800-FDA-1088.

All patients should receive the Fact Sheet for Patients: Understanding Results from the DPP® Zika IgM Assay System.

Contact Information for the Manufacturer:
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Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the DPP® Zika IgM Assay System will be made available at www.chembio.com/.

References

1) Rasmussen, S.A., Jamieson D.J., Honein M.A., and Petersen L.R. Zika Virus Birth Defects—Reviewing the Evidence for Causality. NEJM (April 12, 2016). DOI: 10.1056/NEJMsr1604338.

2) CDC Website. http://www.cdc.gov/zika.