September 23, 2013

Re: Customer reports of higher than expected rates of mitogen indeterminate results using the QuantiFERON®-TB Gold (QFT) test.

Dear Valued Customer;

We have received a number of inquiries from users of the QuantiFERON®-TB Gold (QFT) test who observed an increase in the rate of mitogen indeterminate results. We recognize that this has inconvenienced some customers, and raised concerns about the quality of QFT test results. We hope that by providing further information, including the likely cause and recommended handling of mitogen indeterminate tests, we will more effectively address your questions and concerns.

The purpose of the mitogen tube in the QFT assay is to serve as a positive control, providing both information about correct blood sample handling and potential information about the immune status of the patient. The mitogen control is independent and not considered in the determination of a positive result. A negative QFT result requires both a TB antigen tube value of < 0.35 IU/mL and a mitogen control value of ≥ 0.5 IU/mL. The rate of indeterminates should generally be low, although may vary depending on the immune-competence of the population tested.

The increased rate of indeterminate tests observed by our customers correlated with the introduction of a new lot of phythaemagglutinin-P (PHA), the stimulating agent used in the mitogen tube. Although manufactured according to our specifications, we recognize that there has been a shift in the distribution of mitogen control values, such that they are lower than that observed in previous mitogen tube lots. However, given that the mitogen tube acts as a qualitative control this would normally not have been a reason for concern. The increase in indeterminate results observed by customers was not expected as our quality control procedures and donor blood testing did not identify any increase. Further, testing of retention tube lots and customer returned tubes did not yield indeterminate tests.

The number of indeterminate results reported does appear to vary from customer to customer; and some users have reported a significant increase (i.e. outside the range in the QuantiFERON®-TB Gold package insert). Our observation is that this is typically associated with more variability in blood sample handling. The current lots of mitogen tubes may be more sensitive to handling errors and require more caution in handling. We recognize that technique may not be the only factor and we accept that mitogen values are currently not in a range that customers have previously observed.

Where an indeterminate result is obtained, we direct physicians to our package insert and the 2010 CDC Guidelines for Interferon Gamma Release Assays (IGRAs) for appropriate guidance:

> *A low response to Mitogen (<0.5 IU/mL) indicates an Indeterminate result when a blood sample also has a negative response to the TB antigens. This pattern may occur with insufficient lymphocytes, reduced lymphocyte activity due to prolonged specimen transport or improper*

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specimen handling, including filling/mixing of blood tubes, or inability of the patient's lymphocytes to generate interferon gamma (IFN-gamma). If technical issues are suspected with the collection or handling of blood samples, repeat the entire QFT test with new blood specimens. Indeterminate tests that result from low Mitogen values would not be expected to change on repeat unless there was an error with the ELISA testing. Indeterminate results should be reported as such. Physicians may choose to redraw a specimen or perform other procedures as appropriate. (QuantiFERON®-TB Gold Package Insert. Cellestis. Doc. No. US05990301L March 2013)

CDC provides the following guidance for indeterminate results;

Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate and a reason for testing persists. A second test also might be useful when assay measurements from the initial test are unusual, such as when the Mitogen value is lower than is expected for the population being tested (e.g. the mitogen response by QFT is <0.5 IU/mL). If an IGRA is to be repeated, a new blood sample should be used. In such situations, repeat testing with another blood sample usually provides interpretable results. (Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection – United States, 2010. Centers for Disease Control and Prevention MMWR June 25, 2010; Vol. 59. No.RR-5)

As with any diagnostic test for TB infection, QFT is an aid to assist clinicians in their diagnosis and should be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

We remain fully committed to providing products of the highest quality and thank you for your patience, understanding and partnership. We will continue to rely on your feedback to ensure that we meet your expectations in terms of product quality and customer service. Lastly, we would like to express our sincere gratitude to our customers for promptly bringing this matter to our attention, providing data and assisting us in our investigations.

Sincerely,

Mark Boyle

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