May 18, 2013

Colleen Daniels
Director TB/HIV
Treatment Action Group
261 Fifth Avenue, Suite 2110
New York, NY 10016-7701

RE: Marketing and Use of QuantiFERON-TB Gold for active TB in India and high TB burden countries

Dear Ms. Daniels,

I want to reassure you that we are all on the same side and have the same goals. The improper use of QIAGEN's QuantiFERON (QFT) assay in India or anywhere in the world is a major concern to us for obvious reasons, as it can affect patient outcomes and individual lives. To be precise however, QFT® is approved as an in vitro diagnostic aid for detection of *Mycobacterium tuberculosis* infection and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations. And as you well know, like the tuberculin skin test, QFT results alone cannot distinguish active TB disease from latent infection. As such, we cannot say it is only a LTBI test, because in truth, it isn't. However, it is best used as a screening tool, (as you would the tuberculin skin test) along with a symptom review and targeting populations with the highest rates of TB or individuals at high risk of disease progression such as persons with HIV, diabetes, end stage renal disease, or on immunosuppressive therapies. We fully agree with the RNTCP that IGRAs should not be used for diagnosis of symptomatic pulmonary TB and have been vigilant in spreading the message that QFT should never be used as a stand-alone test for the diagnosis of disease. We promote sputum collection or tissue biopsy (for extrapulmonary TB), and not QFT, when active TB is suspected because of symptoms or physical findings. Our primary company focus has been on the private sector, promoting it as a screening tool for high risk populations that can lead to early detection of asymptomatic TB and prevention that can help accelerate the decline. The attached study supported by the Bill and Melinda Gates Foundation shows that accelerated decline cannot happen without addressing LTBI and prevention and as now recognized by the WHO, passive case finding is not adequate. We would like IGRAs to be a tool that creates private-public partnership in the coming years. That said however, once our product is sold to a lab or researcher, we cannot control what happens after, unless there is feedback. As discussed on Thursday with you, we kindly request the reporting of any and all information on misuse of our products directly so that we can take swift corrective action.

We have been actively addressing the issue of misuse. After Cellestis-QIAGEN team was notified about it by the WHO in early September, we communicated directly with the RNTCP (see attached). I personally went to India to assess the situation first hand. I met with ~25 Indian TB experts and clinical microbiologist in the Delhi area to assess current QFT use at their facilities, understanding of the strengths and limitations of QFT, and to determine QIAGEN's next action steps. Our team found that the use of QFT as a replacement for the recently banned serologic tests had occurred in some instances but was not widespread. Our current sales figures since the ban continue to confirm this. Appropriate use of QFT has been happening as well. This includes the screening of patients being placed on anti-rheumatic biologic agents and as an adjunctive test in extrapulmonary TB where definitive diagnosis with tissue biopsy or culture are not helpful, accessible or possible. The medium and larger laboratories reported that physicians seemed to be in an inquiry stage to find out whether QFT can be used as replacement for the serologic tests. Most laboratories were aware that QFT, as a diagnostic aid, should never be used as a sole diagnostic for active TB (pulmonary or otherwise) but often, they were unclear as to when and in what situations to use QFT because of their lack of familiarity of latent TB infection and targeted TB screening. During my 2 visit to India last fall and in March, I have personally

provided CME training, round table discussions, grand rounds and seminars to well over 300 doctors from Delhi, Chennai, and other selected cities. Our QIAGEN team has retrained our commercial partner on appropriate use and have taken the following steps to curb the misuse of QFT:

1. Placing a caution label on all boxes of QFT product sold in India with messaging that states that QFT is a diagnostic aid that cannot distinguish between active TB disease and infection.
2. Informing all laboratories running the QFT assay to use the cautionary message on all laboratory reports going to providers. In addition, we also recommended that the RNTCP require such messaging on QFT laboratory reports as a direct form of education and warning to providers and labs.
3. Working closely with our commercial partner, Alere to educate customers and providers on the topic. All of Alere's staff assigned to QFT have been trained.

In summary, our three main goals at QIAGEN are the appropriate use of the QFT, high quality laboratory results and greatest impact. We are focused on the private setting and not working against the WHO guidelines intended for high-burden, low & middle income, public care setting. The RNTCP is rightly focused on active pulmonary TB, based on their limited resources and we fully support that. We disagree however, that a lack of an RNTCP LTBI program is justification to impose WHO guidelines on all practitioners in India as it would deny the appropriate use and clinical interventions that are going on today. Rather, we hope that QFT can be used as a catalyst to educate and create the synergy needed for the private sector to help advance TB control in India. Our true enemy is India's unregulated system and ignorance. QIAGEN should not be its scapegoat when there are other IGRAs on the market that are actively promoting misuse or not engaged in dispelling it. Our shared commitment with TAG and the RNTCP on the issue of misuse should instead be put into action through partnership. There is much education that is needed in India. As a small example, the Babu survey you included shows that misuse of the skin test as a sole basis of TB diagnosis was actually worse than IGRAs (21% vs. 16%). However, to address the larger issue of misuse from India's unregulated system, all stakeholders with the RNTCP at the lead, need to work together. We at QIAGEN welcome the opportunity to collaborate with you at TAG, the RNTCP and the India Community Advisory Board with full transparency and open communication.

Respectfully yours,

L Masae Kawamura MD

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cc: Peer Schatz, CEO, QIAGEN, Hilden, Helge Lubenow, Senior Vice President, Medical Diagnostics, QIAGEN, Hilden, Dr Mario Raviglione, Director, Stop TB Department, WHO, Geneva, Dr. V. M. Katoch, Director General, Indian Council of Medical Research, Dr GN Singh, Drug Controller General of India, New Delhi, Dr RS Gupta, Deputy Director General – TB, Central TB Division, Ministry of Health and Family Welfare, New Delhi, Dr KS Sachdeva, Chief Medical Officer, Central TB Division, Ministry of Health and Family Welfare, New Delhi, Dr Reba Kanungo, President, Indian Association of Medical Microbiologists, Dr Ram Gopalakrishnan, President, Clinical Infectious Diseases Society of India, Dr K Vijayakumar, President, Indian Medical Association