Potential *M. tuberculosis* (TB) Interferon Gamma Release Assays (IGRAs) Device Reclassification

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Potential reclassification of M. tuberculosis Interferon Gamma Release Assay (IGRA) in vitro diagnostic devices from Class III to Class II with special controls

What is the Purpose of This Panel Session?

- The purpose of this meeting is to discuss the potential future reclassification of *Mycobacterium tuberculosis* (TB) cell mediated immune reactivity *in vitro* diagnostic devices such as interferon gamma release assays (IGRAs).
- FDA is seeking recommendations from the Panel members and the public on whether sufficient information exists such that the development of special controls (which along with general controls) could mitigate the risks from these devices such that the devices would provide a reasonable assurance of safety and effectiveness and therefore, can be eligible for a Class II designation.

Clinical Aspects: Public Health Burden of TB

- TB case counts and incidence rates have steadily decreased in the U.S. over the last 30 years
  - 8,300 reported TB cases in 2022 (2.5 cases per 100,000 persons)
  - Case counts are returning to pre-pandemic levels following declines in reporting during the previous two years
  - CDC estimates that up to 13 million people in the U.S. could have latent TB
- Worldwide TB burden estimated at 10.6 million persons
  - Globally, 1.6 million people died from TB in 2021

Interferon Gamma Release Assays (IGRAs)

- IGRAs are in vitro blood tests which measure T-cell release of IFN-γ following stimulation with TB antigens (e.g., ESAT-6, CFP-10) to aid in the diagnosis of TB.
- The commonly used ESAT-6 and CFP-10 IGRA peptide antigens are specific to organisms in the *Mycobacterium tuberculosis* complex (MTBC) but absent from BCG strains and most nontuberculous mycobacteria
- IGRAs are useful in bacille Calmette-Guérin (BCG) vaccinated persons and in clinical scenarios where a single patient visit is advantageous

M. tuberculosis (TB) IGRAs: Intended Use

- TB cell mediated immune reactivity assays:
  - **[Assay Name]** is an in vitro diagnostic test using a cocktail of **[TB antigens]** to stimulate cells in **[sample type, e.g., whole blood]**. Detection of interferon-γ (IFN-γ) by **[technology, e.g., ELISA, CLIA, ELISpot]** is used to identify in vitro responses to these antigens that are associated with *Mycobacterium tuberculosis* infection.
  - **[Assay Name]** is an indirect test for *M. tuberculosis* infection and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

PMA Approved TB IGRAs

Manufacturer	Device	PMA Number	Date of Approval	PPA* [95% CI)]	NPA** [95% CI]
Qiagen	QUANTIFERON-TB GOLD-IN-TUBE QUANTIFERON TB GOLD QUANTIFERON-TB GOLD PLUS	P010033	11/28/2001	88.7% [77.4-94.7%] 81.0% [69.2-89.1%] 88.7% [77.4-94.7%]	99.06% [96.63 – 99.74%] 99.2% [97.65-99.8%] 98.11% [95.25-99.26%]
Oxford Immunotec, Ltd.	T SPOT-TB TEST	P070006	7/30/2008	95.6% [91.6-98.1%]	97.1% [94.5-98.7%]
DiaSorin, Inc.	LIAISON QuantiFERON - TB Gold Plus, LIAISON Control QuantiFERON - TB Gold Plus, and LIAISON QuantiFERON Software	P180047	11/26/2019	78.6% [69.77-85.45%]	96.9% [94.2-98.3%]

* Estimated sensitivity as compared to culture confirmed TB disease

** Estimated specificity in subjects with low risk (no known risk factors) for tuberculosis infection

Clinical Aspects: Risks to Health of Inaccurate Results

- False negative results, incorrectly operating device causing false negative results, and incorrectly interpreting results as negative results can lead to:
  - Progression of active or reactivation of latent TB disease in individuals
  - Spread of disease in the community
  - Missed opportunity for diagnosis of underlying disease (HIV)
- False positive results, incorrectly operating device causing false positive results, and incorrectly interpreting results as positive results can lead to unnecessary:
  - Treatment with associated drug toxicities
  - Patient isolation
  - Radiologic imaging and laboratory testing
  - Contact tracing and wasted healthcare resources

Considerations for IGRA Devices

- Clinical performance study populations:
  - Patients at low risk for previous TB infection (absence of risk factors)
  - Patients with culture-confirmed or FDA cleared NAAT-confirmed active TB infection
  - At high risk for LTBI
  - History of nontuberculous mycobacterial infection or colonization

- Performance estimates
  - Estimated specificity/sensitivity vs. expected result for low risk and active TB
  - PPA/NPA to TST, existing IGRA

- Labeling would focus on the limitations of studies conducted in the absence of a true reference standard

Additional Considerations

- Increased opportunities for innovative diagnostic devices
- Reduced regulatory requirement for sponsors and manufacturers
- PMA specific requirements would be removed but the risks can be mitigated by special controls

Questions for the Panel

1. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by *M. tuberculosis* assays.

   Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of *M. tuberculosis* assays.

2. Please discuss potential mitigation measure(s)/control(s) that FDA should consider that could mitigate each of the identified risks.

3. Based upon the information presented and future discussion at panel meeting, please discuss whether, based on the available information, the Panel believes FDA should initiate the reclassification process for this device from Class III to Class II, subject to special controls.


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