Background Document

Discussion and Recommendations Regarding the Classification of NAAT-based Rapid *M. tuberculosis* Diagnostics and the Classification of Interferon Gamma Release Assays

Meeting of the CDRH Microbiology Devices Panel of the Medical Devices Advisory Committee

June 29, 2011

Gaithersburg, Maryland

Tentative Agenda

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Agenda

8:00 – 8:15	Call to Order, Announcements Shanika Craig, Designated Federal Officer, Office of Device Evaluation, CDRH
8:15 – 8:25	Introductions Sally Hojvat, Ph.D., Director, Division of Microbiology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH Alberto Gutierrez, Ph.D., Director, Office of In Vitro Diagnostic Device Evaluation and Safety, CDRH
8:25 – 9:00	Current FDA Regulation of Tuberculosis Diagnostics Steven Gitterman, M.D., Ph.D., Medical Officer, DMD/OIVD/CDRH
9:00 – 9:20	FDA Reclassification Process Marjorie Shulman, Acting Director, Premarket Notification Staff, Office of Device Evaluation, CDRH
9:20 – 10:00	Current Tuberculosis Diagnostics: The Role of Diagnostic Tests for Latent and Active Tuberculosis William Burman, M.D., Interim Director, Denver Public Health
10:00 – 10:20	**Break**
10:20 – 11:00	The Public Health Implications of Reclassification Kenneth Castro, M.D., Director, Tuberculosis Elimination Program, CDC
11:00 – 12:00	Open Public Hearing
12:00 – 1:00	**Lunch**
1:00 – 1:15	Questions to the Committee Sally Hojvat, Ph.D.
1:15 – 3:45	Committee Discussion
3:45 – 4:00	Summary and Next Steps Committee Chair and Sally Hojvat, Ph.D.
4:00	Adjourn

Table of Contents

1. Introduction 4
2. Background 7
   a. Regulation of In Vitro Diagnostic Devices 7
   b. Regulation of Currently Marketed Products for the Detection of Tuberculosis 11
   c. Regulation of Currently Marketed Products for Antimicrobial Susceptibility Testing of *M. tuberculosis* 13
3. FDA Reclassification Process 14
4. Developing Special Controls for Tuberculosis 17
   a. Special Controls Guidance for the Detection of *M. tuberculosis* complex Directly from Patient Specimens 17
   b. Considerations for a Special Controls Guidance for the Detection of Genetic Mutations Associated with Antibiotic Resistance using Nucleic Acid Amplification 29
   c. Specific Considerations for IGRAs for the Indirect Detection of *M. tuberculosis* complex 33
5. Questions for Panel Members 36
6. Attachments 39

1. Introduction

The Division of Microbiology Devices in the Center for Devices and Radiological Health at FDA has regulatory oversight of diagnostic assays for tuberculosis; this includes regulation of tests essentially as old as the first stains and culture media for the isolation of *M. tuberculosis* as the cause of consumption to state-of-the - art tests based on technology such as MALDI-TOF.[1] Although nucleic-acid based amplification assays (NAAT) for the detection of tuberculosis were first approved in the United States in 1995, no similar applications for the detection of tuberculosis directly from specimens have been submitted to FDA since 1994. More recently, however, several devices have been introduced and approved for detecting tuberculosis infection by indirect means, i.e., interferon-gamma releasing assays (IGRAs) such as the T-SPOT®.*TB* test and the QuantiFERON®-TB Gold-in-Tube (QFT) test.

FDA regulations applicable to *in vitro* diagnostic devices are based on the FDA classification of the device. The current approach to classification is a product of several laws, most prominently the 1976 Medical Device Amendments to the original Food, Drug and Cosmetic Act. How devices are classified will be described in greater detail in Section 2; however, all devices, including *in vitro* diagnostic devices, are classified on the basis of risk. Class I designation is for devices of least risk and Class III, the highest class, is reserved for devices that in general 'are of substantial importance in preventing impairment of human health' or 'for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of such device.'[2]

The purpose of this meeting is to discuss the appropriate classification of tests for several aspects of tuberculosis infection including:

1. NAAT tests for the detection of *M. tuberculosis* complex[3] directly from patient specimens. Assays approved for this use such as the Gen-Probe® Amplified Mycobacterium Tuberculosis Direct (MTD) Test are currently Class III devices.
2. Indirect tests of tuberculosis infection such as the QuantiFERON®-TB Gold-in-Tube test and the T-SPOT®.*TB* test. These assays measure the release of interferon-γ from cells *in vitro* in response to exposure to *M. tuberculosis* antigens and are approved as indirect tests for *M. tuberculosis* infection. They are also Class III devices.

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[1] Matrix-assisted laser desorption/ionization-time of flight mass spectrometry

[2] Abstracted from Code of Federal Regulations 21 CFR 860.3, Medical Device Classification Procedures: Definitions, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=860.3

[3] *M. tuberculosis* complex includes *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum, M. canetti, M. microtii, M. caprae*, and *M. pinnipedi*

3. Tests for the rapid detection of *M. tuberculosis* complex resistance mutations by nucleic-acid amplification directly from patient specimens. These tests have yet to be classified as no application for this use has been submitted to FDA.

The question of the appropriate classification of these devices was raised at the June, 2010, FDA/CDC/NIAID public workshop on *Advancing the Development of Diagnostic Tests and Biomarkers for Tuberculosis*.[4] Specifically, it was questioned whether the current Class III classification of NAAT tests for the detection of *M. tuberculosis* complex directly from patient specimens has been a deterrent for the development of new diagnostics for this disease. It was pointed out that a Class III determination for an IVD carries with it additional regulatory requirements and greater oversight than a Class II device, and may, in fact, pose a disincentive for the manufacturers to develop a test for a disease with a small market share in the US. Following this workshop, FDA agreed to consider this issue further. The purpose of the upcoming June 29th, 2011, meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee is to discuss whether FDA should consider reclassification of NAAT devices submitted for the detection of *M. tuberculosis* complex directly from patient specimens from Class III to Class II, and if FDA should consider a similar reclassification for devices for the indirect detection of tuberculosis infection. The panel is not being asked at this time to vote on whether actual reclassification should occur, or to assess whether any specific device currently under development warrants reclassification. However, depending on the discussion at this meeting, it may become apparent that reclassification is not appropriate at this time; alternatively, discussion may lead FDA to pursue the reclassification process, and possibly return to the panel with draft Special Controls Guidance documents to solicit additional discussion regarding whether they sufficiently mitigate risks associated with either type of device if reclassified.

Additional discussion at the meeting will address the initial classification of devices that detect genetic mutations associated with antibiotic resistance to *M. tuberculosis* complex. To date, no NAAT devices for this use have been submitted to FDA; therefore, by default these devices would be classified as Class III. However, a *de novo* regulatory pathway exists whereby new devices can be classified as Class II by FDA publication of a Special Controls Guidance document at the time of regulatory action on the submission. The panel will be asked to discuss the use of these devices from a perspective similar to that for reclassification of NAAT devices for the direct detection of *M. tuberculosis complex*, i.e., whether special controls can mitigate the risk associated with a Class II designation.[5]

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[4] Agenda and transcripts available at: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/UpcomingEventsonCPI/ucm203262.htm.

[5] It should be noted that devices that combine both intended uses, i.e., the rapid detection of *M.* tuberculosis complex directly from patient samples and the rapid detection of resistance

The sections below provide an overview of the following issues as background for the meeting:

- General regulation of *in vitro* diagnostic devices.
- The regulatory history of tuberculosis diagnostics.
- The FDA reclassification process.
- Issues to be addressed by special controls.

The last section contains the questions that will be posed to the panel members at the meeting. Several references are also included as attachments to this document to aid the panel, including package inserts from devices approved for the detection of *M. tuberculosis* complex directly from patient specimens and the indirect detection of tuberculosis infection.

mutations from the same specimens, would be classified as the highest class for any of the separate intended uses.

2. Background

a. Regulation of In Vitro Diagnostic Devices[6]

Per 21 CFR 809.3, *in vitro* diagnostic devices are defined as:[7]

> "Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. …for use in the collection, preparation, and examination of specimens from the human body."

In vitro diagnostic devices are classified as Class I, II, or III under the authority of the Medical Device Amendments of 1976. This act established regulatory controls for medical devices and, accordingly, devices may be further distinguished by whether they are pre-amendment or post-amendment devices, (i.e., whether they were marketed before or after 1976). Although several tuberculosis diagnostics are pre-amendment devices, the device classes being discussed at this meeting are all post-amendment devices and this distinction is not discussed further. The three classes for device categorization are:

- Class I: Devices for which general controls are adequate.
- Class II: Devices which require both general and special controls.
- Class III: Devices that require premarket approval.

Class I Devices: Class I devices are primarily those devices for which general controls are determined to be sufficient to provide reasonable assurance of device safety and effectiveness. General controls are controls not unique to any specific device but controls that all device manufacturers must address for every device. Examples of general controls include:

- Prohibition against adulteration or misbranding.
- Good manufacturing practices (GMPs).
- Registration of manufacturing facilities.
- Listing of device types.
- Record keeping.

Class I devices may also be devices that do not present a potential unreasonable risk of illness or injury. For example, in microbiology, differential culture media are Class I devices as specified in the Code of Federal Regulations:

21 CFR 866.2320. Differential culture medium.

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[6] An general overview of device regulation is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm#510k.
[7] All citations or references to the Code of Federal Regulations in this document are available at: http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

(a) Identification. A differential culture medium is a device that consists primarily of liquid biological materials intended for medical purposes to cultivate and identify different types of pathogenic microorganisms. The identification of these microorganisms is accomplished by the addition of a specific biochemical component(s) to the medium. Microorganisms are identified by a visible change (e.g., a color change) in a specific biochemical component(s) which indicates that specific metabolic reactions have occurred. Test results aid in the diagnosis of disease and also provide epidemiological information on diseases caused by these microorganisms.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in 866.9.[8]

Class II Devices: Class II devices are those that cannot be classified as Class I because general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness, but where there is sufficient information to establish special controls that can provide such assurance. Examples of special controls may include:

- Specific device performance standards.
- Device labeling requirements.
- The design of clinical trials to support safety and effectiveness.
- Required *in* vitro analytical studies such as interference studies.

In microbiology, antimicrobial susceptibility tests are examples of Class II devices:

21 CFR 866.1640. Antimicrobial susceptibility test powder.

(a) Identification. An antimicrobial susceptibility test powder is a device that consists of an antimicrobial drug powder packaged in vials in specified amounts and intended for use in clinical laboratories for determining in vitro susceptibility of bacterial pathogens to these therapeutic agents. Test results are used to determine the antimicrobial agent of choice in the treatment of bacterial diseases.

(b) Classification. Class II (performance standards).

Class I and Class II applications are reviewed by FDA under what is referred to as the 510(k) premarket notification process. Under the 510(k) paradigm, a device can be cleared for marketing if it is determined to be safe and effective by

[8] Code of Federal Regulations regarding FDA classification of specific immunology and microbiology device classes are available at: http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/ CFRSearch.cfm?CFRPart=866

being 'substantially equivalent' to a preexisting 'predicate' device.[9] Substantial equivalence broadly encompasses the following:

- The new device has the same intended use as the predicate and the new device has the same technological characteristics as the predicate.

  or

- The new device has the same intended use as the predicate but the new device has different technological characteristics and the information submitted to FDA *and* the device both (a) does not raise new questions of safety and effectiveness and (b) the sponsor demonstrates that the device is at least as safe and effective as the legally marketed device.

As described on the FDA web site, "a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable." The determination of 'substantial equivalence,' is therefore a multifaceted examination of the new device focused heavily on the intended use and not whether the underlying technology is identical.[10]

Class III Devices: Class III devices are those for which insufficient information exists to determine that general and special controls can provide reasonable assurance of the safety and effectiveness, or where these devices are life sustaining or life supporting, of substantial importance in preventing impairment of human health, or present unreasonable risk of illness or injury.

Class III devices require 'pre-market applications' (PMA) for which additional materials are necessary at the time of regulatory filing by the sponsor/manufacturer, and the FDA review time is longer (180 days compared to 90 days for non-PMA devices). Other significant differences between a PMA and a 510(k) application (described below) include the following premarketing requirements: that selected sites from the pivotal clinical trials undergo FDA inspection for application integrity and sponsor quality/Good Clinical Practice; that inspections of a sponsor's manufacturing facilities occur; and that FDA review and approve the product labeling and marketing materials before approval. Post-marketing requirements for PMA versus 510(k) include submission and approval of significant labeling changes, and submission of

[9] Devices which are submitted under a 510(k) are 'cleared' for marketing by FDA; under the PMA process (described below) devices are 'approved' by FDA.

[10] More detailed information regarding pre market applications under the 510(k) process is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm, reproduced as an attachment to this document.

annual reports. In general, FDA has more control over Class III than Class II devices.[11,12]

New devices for which there is no predicate are automatically classified as Class III at the time of FDA submission; however, a '*de novo'* regulatory pathway exists whereby new devices without a predicate can be classified as Class II (and thereby qualify as a 510(k) application) when a combination of general and special controls (as defined by a Special Controls Guidance document) can offer assurance of device safety and effectiveness.[13] In such cases, FDA classifies such a device as a Class II device at the time of initial 510(k) device clearance, with publication of a Special Controls Guidance document shortly thereafter. At the time of classification, devices are placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness. Recent examples of microbiology IVD devices which have undergone a '*de novo*' process include immunoassays for the detection of norovirus and dengue virus.

There are substantial similarities in the PMA and 510(k) application processes. Numerous FDA guidance documents are available for both pathways, and FDA provides pre-submission consultation with sponsors through the pre-IDE process for both types of submissions. Requirements under both submission types include:

- Analytical Performance Data: Demonstration of the accuracy and reliability of analyte measurements over time, with different operators, and across sites, interference studies, cross reactivity studies, etc.
- Clinical Performance Data: Demonstration of clinical sensitivity and specificity.
- Proposed Labeling: Intended use, device design, directions for use, warnings/limitations, result interpretation, etc.

The distinction between the 510(k) and PMA regulatory pathways is based on the level of regulatory control that is necessary to assure safety and effectiveness. A Special Controls Guidance can require that the contents of a 510(k) application be similar to what would normally be submitted in a PMA application; for example, a 510(k) Special Controls Guidance document may include special labeling requirements, mandatory performance standards, and post market

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[11] More detailed information regarding pre market PMA applications is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm, reproduced as an attachment to this document.

[12] Application fees also differ between 510(k) and PMA applications. More information regarding current medical device application fees is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109179.htm

[13] A brief description of the de novo regulatory pathway and the pre-IDE consultation process is included as part of the 'Overview of IVD regulation' (see 'de novo classification'), available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm

studies. The data used to demonstrate analytical performance can be identical for a 510(k) or PMA application, e.g., the substances that should be tested in interference studies, the viral strains that are appropriate for a specific strain reactivity study (for a viral analyte), etc. In addition, in some situations the clinical studies that would be required for a 510(k) and PMA application may be identical, particularly if specific studies are described in a 510(k) Special Controls guidance. However, substantial differences remain in the FDA review process between the two application types, e.g., required inspection of clinical sites by FDA for PMA applications. This is discussed further below.

b. Regulation of Currently Marketed Products for the Detection of Tuberculosis

(1) Culture-based devices and/or direct staining methods.

Devices supporting the identification of *M. tuberculosis* from cultured isolates (21 CFR 866.2660) or staining reagents for use on direct specimen smears (21 864.1850 and 21 CFR 866.3370) are Class I devices. Included in this category are nucleic acid hybridization-based tests for the identification of *M. tuberculosis* from cultured isolates such as the AccuProbe Mycobacterium Tuberculosis Complex Culture Confirmation Test, which is considered functionally similar to other methods to identify cultured isolates:[14]

21 CFR 866.3370. Mycobacterium tuberculosis immunofluorescent reagents.

(a) *Identification. Mycobacterium tuberculosis* immunofluorescent reagents are devices that consist of antisera conjugated with a fluorescent dye used to identify *Mycobacterium tuberculosis* directly from clinical specimens. The identification aids in the diagnosis of tuberculosis and provides epidemiological information on this disease. *Mycobacterium tuberculosis* is the common causative organism in human tuberculosis, a chronic infectious disease characterized by formation of tubercles (small rounded nodules) and tissue necrosis (destruction), usually occurring in the lung.

(b) *Classification.* Class I (general controls).

Devices that support the general growth of mycobacteria but are not indicated for the specific identification of mycobacteria, such as the BACTEC™ MGIT™ System, are also Class I, as are High Performance Liquid Chromatography (HPLC)-based diagnostic tests for identifying *M. tuberculosis* in culture.

(2) Amplification-based techniques for the detection of tuberculosis directly from clinical specimens.

[14] The Gen-Probe Rapid Diagnostic System for Mycobacteria is a hybridization assay used directly on patient specimens that is also Class 1, but this assay is not diagnostic for *M. tuberculosis* complex.

Amplification-based techniques, such as the Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD)® Test and the Roche AMPLICOR® Mycobacterium Tuberculosis Test, were classified as Class III devices with the initial submission of the first of these devices to FDA in 1994. The Class III designation was based on concerns raised at that time by the higher false negative rate with amplification techniques relative to culture, a concern magnified against the backdrop of a resurgence of HIV-associated tuberculosis, particularly in New York City. Other issues considered at the time included potential off-label use from the testing of AFB smear-negative patients, and a lack of data to support specimen types other than sputum. At the time of first approval, amplification-based tests from sputum were limited to patients with AFB-positive smears; this has subsequently been expanded. The current intended use for the GenProbe® AMPLIFIED™ Mycobacterium Tuberculosis Direct (MTD) Test is as follows:

> The Gen-Probe® AMPLIFIED™ Mycobacterium Tuberculosis Direct (MTD) Test is a target-amplified nucleic acid probe test for the in-vitro diagnostic detection of *Mycobacterium tuberculosis* complex rRNA in acid fast bacilli (AFB) smear positive and negative sediments prepared from sputum (induced or expectorated), bronchial specimens (e.g. bronchoalveolar lavages (BAL) or bronchial aspirates), or tracheal aspirates.
>
> The MTD test is intended for use only with specimens from patients showing signs and symptoms consistent with active pulmonary tuberculosis. The MTD test is to be used as an adjunctive test for evaluating either AFB smear positive or negative sediments prepared using NALC-NAOH digestion-decontamination of respiratory specimens from untreated patients suspected of having tuberculosis. Patients who are suspected of having pulmonary TB based on clinical evaluation and who have received no anti-tuberculosis therapy, less than 7 days of such therapy, or have not received such therapy in the last 12 months may be evaluated with this test. The MTD test should be performed only in laboratories proficient in the culture and identification of *M. tuberculosis* (Level II and III, or extent 3 and 4). The MTD Test must be performed in conjunction with mycobacterial culture.[15]

(3) <u>Indirect assays for the detection of tuberculosis</u>.

Indirect, immunologically-based assays such as the T-SPOT®*.TB* Test and the QuantiFERON® -TB Gold-In-Tube test are Class III devices. The following is representative of the intended use for these devices:[16]

[15] A copy of the current labeling for this device is included as an attachment to this document.
[16] Copies of the current labels for these devices are included as attachments to this document.

…… is an *in vitro* diagnostic test using ….. proteins to stimulate cells in heparinized whole blood. Detection of interferon-g (IFN-g) by …… is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. It is intended for use as an aid in the diagnosis of *M. tuberculosis* infection.

……. is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

c. Regulation of Currently Marketed Products for Antimicrobial Susceptibility Testing of M. tuberculosis

Devices for antimicrobial susceptibility testing of cultured *M. tuberculosis* isolates are regulated as Class II devices under 21 CFR 866.1640 as follows:

21 CFR 866.1640. Antimicrobial susceptibility test powder.

(a) *Identification*. An antimicrobial susceptibility test powder is a device that consists of an antimicrobial drug powder packaged in vials in specified amounts and intended for use in clinical laboratories for determining in vitro susceptibility of bacterial pathogens to these therapeutic agents. Test results are used to determine the antimicrobial agent of choice in the treatment of bacterial diseases.

(b) *Classification*. Class II (performance standards).

There are no FDA approved/cleared molecular-based assays testing *M. tuberculosis* for the presence of genetic mutations associated with drug resistance, either from direct specimens or from cultured isolates (although molecular assays based on gene detection have been cleared for other bacteria such as MRSA). In general, establishing susceptibility interpretive criteria (susceptible, intermediate or resistant) is based on data from multiple sources (e.g., studies of *in vitro* activity, pharmacokinetic and pharmacodynamic studies, and clinical studies).

3. FDA Reclassification Process

The FDA reclassification process follows specific steps outlined in 21 CFR 860.120. As described on the FDA web site:

> "As experience and knowledge about a device increase, the original classification can be adjusted via the process of reclassification. Changes in classification are based on FDA's receipt of new information about a device. FDA may, on its own, or in response to an outside petition, change a device's classification by regulation. A manufacturer who wishes to have a device reclassified to a lower class must convince FDA that the less stringent class requirements will be sufficient to provide reasonable assurance of safety and effectiveness.
>
> FDA notifies petitioners of determinations made on petitions for reclassification by a reclassification letter. If a determination is made to reclassify a device, FDA publishes a proposed rule to reclassify in the Federal Register which includes the scientific justification for reclassification and which affords a period for comment. Subsequently a final rule is published in the Federal Register which changes the classification."[17]

The reclassification process may be initiated by FDA, by an interested party, or by the manufacturer/importer of a device by submitting a reclassification petition. If a petition is filed, the following is required in the petition per 21 CFR 860.123(a):

(1) A specification of the type of device for which reclassification is requested.
(2) A statement of the action requested by the petitioner, e.g., 'It is requested that 'xxx' device(s) be reclassified from class III to a class II.'
(3) A completed supplemental data sheet applicable to the device for which reclassification is requested.
(4) A completed classification questionnaire applicable to the device for which reclassification is requested.
(5) A statement of the basis for disagreement with the present classification status of the device.
(6) A full statement of the reasons, together with supporting data satisfying the requirements of 860.7 [Determination of safety and effectiveness], why the device should not be classified into its present classification and how the proposed classification will provide reasonable assurance of the safety and effectiveness of the device.
(7) Representative data and information known by the petitioner that are unfavorable to the petitioner's position.

[17] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm080412.htm, included as an attachment to this document.

(8) If the petition is based upon new information under section 513(e), 514(b), or 515(b) of the act, a summary of the new information.
(9) Copies of source documents from which new information used to support the petition has been obtained (attached as appendices to the petition).
(10) A financial certification or disclosure statement or both as required by part 54 of this chapter.

For petitions to change an existing classification that are based on new information, the information submitted in support of a reclassification petition must consist of 'valid scientific evidence' as defined in 21 CFR 860.7 and includes:

- Well-controlled investigations.
- Partially controlled studies.
- Studies without matched controls.
- Well-documented case histories.
- Reports of significant human experience.

There are slightly different requirements if the petition is from the device manufacturer as opposed to another source, but requirements are generally similar. Once filed, a reclassification petition is placed on public display.

Following review of the petition, or if the process is initiated by FDA, FDA may either take action or schedule a panel meeting to discuss the reclassification proposal if necessary. If a meeting is scheduled, at the meeting FDA would request a formal recommendation from the panel regarding reclassification of the devices that are the subject of the meeting. The recommendation would include a summary of the reasons for the recommendation and a summary of the data upon which the recommendation is based. Discussion at the panel meeting would include identification of the risks to health (if any) by the devices under discussion, as well as identification of special controls for Class II (if reclassification was from Class III to Class II, as in the present discussion).

If there is a panel meeting, FDA will publish a notice of panel recommendation to reclassify these devices and propose new regulations for these devices as appropriate, with an accompanying docket for public comments. Following a complete review process, FDA may then publish a Federal Register Notice which proposes the device reclassification (referred to as the proposed rule) with the accompanying Special Controls Guidance(s). FDA will then receive and review comments in response to the proposed rule and ultimately render a final decision. Regardless of how the process is initiated, when reclassification occurs, final actions will include publication of a Federal Register Notice, proposed new regulations, under 21 CFR 866 (as in the examples above), and publication of the related Special Controls Guidance.

A relevant example of reclassification from Class III to Class II are “Fully automated short-term incubation cycle antimicrobial susceptibility systems” (21 CFR 866.1645), commonly recognized as automated antimicrobial susceptibility test (AST) systems. Originally classified as Class III, these were reclassified as Class II in 2001 after filing of a petition by manufacturing sponsors and subsequent discussion at an open public hearing.[18]

[18] The most recent version of the Special Controls Guidance document issued with this reclassification is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080564.htm.

4. Developing Special Controls for Tuberculosis

a. Special Controls Guidance for the Detection of M. tuberculosis complex Directly from Patient Specimens

FDA has published numerous Special Control Guidances, usually in the setting of the clearance of new products through the *de novo* regulatory pathway.[19] If reclassification of diagnostics for the direct and indirect detection of *M. tuberculosis* complex were to occur, a similar Special Controls Guidance(s) would be developed and published at the time of a reclassification action. Since diagnostics for the detection of antibiotic-associated mutations have yet to be classified (i.e., no devices for this use have been submitted for FDA approval or clearance), a Special Controls Guidance would be published shortly after the first device for this use was cleared if the device was classified as Class II under the *de novo* regulatory pathway.

The purpose of a Special Controls Guidance is to document FDA recommendations regarding the development of a device for a specific use such that adherence to these recommendations mitigates risks associated with use of the device and thereby permits review under the Class II (510(k)) paradigm rather than by a PMA application. Special control guidances are usually unique to the intended use of a specific device. For an ELISA-based diagnostic assay for a specific infectious disease, the Special Controls Guidance would likely specify the design of studies that best characterize clinical performance: device sensitivity and specificity in appropriate populations; strain reactivity and inclusivity studies (e.g., demonstrating that a test for influenza captures all possible virus strains); interference studies (what other substances may interfere with test performance, e.g., Pepto-Bismol for a device that analyzes stool samples); etc.

A Special Controls Guidance for a nucleic-acid based assay may have similar recommendations, but it could also include additional controls such as sequencing isolates from clinical trials to ensure pathogen identification, or analytical reactivity (inclusivity) studies. However, regardless of the specific Special Controls Guidance, the sole purpose of the document is to specify the

[19] All new devices submitted to FDA for which there are no predicate devices are automatically classified as Class III devices and require a PMA submission; however, devices in which the risks from use of the device can be mitigated, can be reclassified as Class II devices by the de novo regulatory pathway and the publication of a Special Controls guidance. Published Special Controls Guidances for in vitro diagnostic devices are available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm. A recent example is the guidance document for "Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection of Clostridium difficile'" available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm234868.htm

recommendations that, if followed, would offer reasonable assurance of safety and effectiveness, if the device is cleared under the 510(k) process in contrast to the PMA pathway.

The following is a discussion of the concepts that would need to be addressed in a Special Controls Guidance for the rapid detection of *M. tuberculosis* complex directly from respiratory specimens. Sections to be discussed include:[20]

(1) Introduction.
(2) Background information.
(3) Regulatory scope.
(4) Risks to health.
(5) Device description.
(6) Performance characteristics:
- Analytical performance.
- Clinical performance.

(7) Labeling.
(8) Postmarketing measures.

These are discussed in more detail below: [21]

(1) Introduction. The introduction to a Special Controls Guidance for the rapid detection of *M. tuberculosis* directly from patient specimens could include language similar to the following:

> *This draft Special Controls Guidance document was developed to support the reclassification from Class III into Class II with special controls of devices for the rapid detection of M. tuberculosis complex by nucleic acid amplification directly from patient specimens. These devices are intended to be used as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with other clinical and laboratory findings.*
>
> *When finalized, the designation of a guidance document as a Special Control means that any firm currently marketing, or intending to market, in vitro diagnostic devices for the detection of M. tuberculosis complex by nucleic acid amplification will need to address the issues covered in this Special Controls Guidance. More specifically, the firm will need to show that its device addresses the issues of safety and effectiveness identified in the guidance, either by meeting the*

[20] The discussions below do not address all the sections that would be included in a draft Special Controls Guidance.
[21] Please note that the language included in the examples below is meant only to illustrate to panel members the type of information that *could* be included in a draft Special Controls Guidance; it is not intended as a specific proposal of an actual draft guidance.

recommendations of the guidance or by some other means that provides equivalent assurances of safety and effectiveness.

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of in vitro diagnostic devices for the detection of M. tuberculosis complex directly from clinical respiratory specimens. Designation of this guidance document as a special control means that a manufacturer who intends to market a device of this type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the FD&C Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific issues of safety and effectiveness identified in this guidance document, (3) satisfy the other special controls designated in 21 CFR 866.XXXX, and (4) obtain a substantial equivalence determination from FDA prior to marketing the device.

(2) Background information regarding the rapid detection of *M. tuberculosis* complex directly from respiratory specimens.

(3) Regulatory scope. A description of the devices that would fall within the scope of the Special Controls Guidance, e.g.:

21 CFR 866.xxxx – System, Nucleic Acid Amplification, M. tuberculosis complex.

(a) Identification. Nucleic Acid Amplification systems for M. tuberculosis complex are qualitative in vitro devices intended to simultaneously detect and identify M. tuberculosis complex nucleic acids extracted from human respiratory specimens. These devices are intended to be used as an aid in the diagnosis of tuberculosis when used in conjunction with other clinical and laboratory findings.

This draft guidance is not intended to address devices for the detection of M. tuberculosis complex antigens, for assessment of host serological/immunological responses to M. tuberculosis complex infection, or for the detection of M. tuberculosis complex from non-respiratory samples. This draft guidance also does not intend to address establishing the performance of non-M. tuberculosis complex components of multi-analyte or multiplex devices, although the concepts described here may be helpful for this use. Those seeking guidance for devices which fall outside of this scope should contact the Agency.[22]

[22] This is only for illustrative purposes; the use of rapid tests from non-respiratory samples is an issue where panel discussion is anticipated.

(4) Risks to health: A discussion of the issues of safety and effectiveness/risks to health that would require special controls. This section describes the risks from use of the device that the Special Controls Guidance is designed to mitigate, i.e., more specifically, those risks associated with use of the device that are of sufficient concern such that in the absence of a Special Controls Guidance, a PMA application would be necessary. For in vitro diagnostic devices these risks are failures of the device to perform as indicated, leading to inaccurate results or lack of results, and incorrect interpretation of results, that may result in incorrect patient management decisions.

For a molecular diagnostic device for the rapid detection of tuberculosis directly from clinical specimens, the following proposed risks have been identified:

(a) False positive test results
- Risks: False positive test results may lead to unnecessary treatment with concomitant individual and public health costs, such as contact investigations, potential adverse effects from treatment and drug interactions; and possible unnecessary patient confinement.[23]

(b) False negative test results:
- Risks: False negative test results could pose the risk of disease progression, and for patients who are 'smear positive' (if a smear is not performed), a higher risk of transmitting disease to contacts.[24]

(c) Bio-safety and risks to laboratory workers handling test specimens and control materials
- Risks: Depending on the specific device used there may be additional biosafety hazard concerns with potential health-care worker infection with false negative NAAT results.

Panel members will be asked to discuss whether all of the risks of false positive and false negative NAAT results have been identified, and whether these risks can be adequately mitigated.

[23] It is anticipated that discussion of the risks of false positive test results will be an important part of the panel discussion regarding possible reclassification of molecular diagnostics for rapid detection of *M. tuberculosis.*. It is assumed that all samples tested by a NAAT device would also undergo traditional mycobacteriology culture as a risk mitigation. Whether AFB smear is also recommended should be discussed by panel members. Other possible mitigation strategies for false-positive results include repeating NAAT positive/smear negative results with a second NAAT test at the time of diagnosis or at a fixed time into treatment for NAAT positive/culture negative results.

[24] It is anticipated that the panel will discuss the risks of false negative test results. Although 'false-negative' NAAT results may be considered similar to current standard of care while awaiting culture results, risk may be different depending on whether AFB-smear is routinely performed. The higher sensitivity of NAAT assays relative to AFB-smears may yield a higher level of false assurance that a patient is uninfected in the setting of a false-negative result.

(5) Device description: A Special Controls Guidance could require that the sponsor include and clearly describe the following:

(a) Intended use: The intended use of the device; the clinical popluations for which the device is indicated; if there are limtiations such as disease stage and/or patient characteristics such as age, gender, immune-compromise, etc.; the types of specimens that can be tested; and, the specific conditions of use.
(b) Reagents and test methodology: The reagents used by the device and the specific methodolgy, e.g., primers used in the assay and the specificity for *M. tuberculosis* complex. Test methodology should include a description all equipment/instrumentation used as part of the assay, software, design controls to minimize contamination, validation of methods for nucleic acid extraction, etc.[25]
(c) Controls: Appropriate controls should be run every day of testing during analytical and clinical studies. These include positive, negative, internal, and extraction controls.
(d) Ancillary reagents: A description of any reagents specified in device labeling as "*required but not provided*." Included in this section is a risk assessment of any risks associated with ancillary reagent quality or consistency, instructions provided with the ancillary reagent, etc. It is expected that the sponsor will provide appropriate user labeling, stability studies, material specifications, etc. that insure appropriate use of ancillary reagents with the device.
(e) Test procedure: A description of the principles of operation applicable to the device for its intended use, including testing conditions, procedures and controls designed to safeguard against conditions that may yield false positive or false negative results, or present a bio-safety hazard. These include, but are not limited to, procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.
(f) Specimen storage and shipping conditions: The firm should include appropriate studies that validate recommended storage and shipping conditions included in product labeling.
(g) Interpreting test results/reporting: The submission should include how positive, negative, equivocal (if applicable), or invalid results are determined and how they should be interpreted or treated. Cut-off values for all outputs of the assay should be discussed as applicable. If equivocal or invalid test results can be reported, recommendations regarding retesting (e.g., whether from the same or a new sample) should be included.

[25] Specific FDA guidance regarding the validation of software used in diagnostic devices has been published, e.g., "General Principles of Software Validation; Final Guidance for Industry and FDA Staff," available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm.

(6) Performance studies: A description of the studies recommended for submitting an application to FDA for the detection of *M. tuberculosis* complex. Sponsors should include all study protocols and/or reference to CLSI standards, if applicable.

(a) General study recommendations: A brief introductory statement should include detailed descriptive information regarding the studies conducted to establish the device's performance characteristics.

(b) Analytical Studies:

- Nucleic acid extraction studies
  - An evaluation of the effect of different nucleic acid extraction methods on the performance of the assay with respect to satisfactory MTB-complex nucleic acid quantity and quality for the intended use of the assay.
- Analytical sensitivity:
  - *Limit of Detection* (LOD) determination, using serial dilutions of well characterized *M. tuberculosis* and *M. bovis* isolates.
  - *Analytical Reactivity* (inclusivity) studies, i.e., *in vitro* test performance against susceptible and resistant *M. tuberculosis* strains, *M. bovis*, *M. africanum*, *M. canetti*, *M. microti*, *M. caprae*, and *M. pinnipedi*. Analytical reactivity studies would also address geographical diversity of *M. tuberculosis* complex strains.[26]
- Analytical specificity:
  - *Cross-reactivity* studies would include other mycobacteria (e.g., *M. intracellulare, M. kansasii*, *M. gordonae*, *M. avium*), mycobacteria known to cross react with *M. tuberculosis* complex targets (*M. celatum*, *M. kumamotonense*), common oral/respiratory commensal and pathogenic bacteria (e.g., *S. pneumoniae*, *H. influenzae*, *Neisseria spp.*, *P. aeruginosa, Nocardia spp., Actinomyces*), fungi (e.g., *C. albicans,* Aspergillus spp.), respiratory viruses (e.g., RSV, rhinovirus), and human DNA.[26]
  - *Interference* studies, including endogenous substances such as blood and mucus, and exogenous substances and nasal and throat medications e.g., decongestants and bronchodilators, and common antibiotics.
- Cut-off and equivocal zone (if appropriate):

[26] This is an incomplete list as other organisms would likely also be tested.

- An explanation of how the assay cut-off was determined and how the cut-off values were validated.

- Precision studies:
  - Within-Laboratory Precision testing within a single facility for a minimum of 12 days (not necessarily consecutive), with 2 runs per day, and at least 2 replicates of each specimen per run. Several *M. tuberculosis* complex strains spiked in relevant specimen matrix or simulated specimen matrix should be tested at different concentrations that span the device measuring range and also near the cutoff of the new device (e.g., negative, low positive, high negative, moderate positive, high positive), with different test operators and different lots as appropriate.
  - Between-laboratory precision (reproducibility), testing across several (usually 3) sites over several days, with at least 2 runs per day using samples similar to those used in the within-laboratory precision studies above.
- Specimen collection, storage and shipping studies:
  - If there are recommended collection, storage, or shipping conditions for device specimens, appropriate studies should be conducted to demonstrate that performance is not altered within these conditions.
- Carry-over and cross-contamination studies:
  - Carry-over and cross-contamination studies should be conducted with high positive specimens used in series alternating with negative samples in patterns dependent on the operational function of the device. At least 5 runs with alternating high positive and negative specimens should be performed.
- Fresh vs. frozen samples:
  - If options for the testing of fresh or frozen samples exist, studies to document the effect of freezing/thawing of the specimens should be conducted.

(c) Clinical studies:

It will be important to identify very early in protocol development the appropriate reference methods to be used for ascertaining ‘clinical truth.’ For studies of *M. tuberculosis* complex this should include *M. tuberculosis* culture, and may include comparison with either an FDA cleared/approved NAAT assay or another well-characterized NAAT assay. Bi-directional sequencing should always be performed to confirm the identification of *M. tuberculosis* complex.

It should be noted that for devices intended for 'point-of-care' use, i.e., where it is intended to test specimens at the site of collection (e.g., in an Emergency Room setting), clinical studies are required that specifically support this use. This is in contrast to the studies described below where it is assumed that testing occurs in a moderately complex clinical laboratory. Tests that seek point-of-care use as part of the intended use should have specimen analysis performed at the site of collection, by multiple operators, and by operators with a skill level similar to those who would perform the test at the anticipated point-of-care setting. Reference testing and all other issues discussed below would need to be addressed for traditional use as well as point-of-care use.

Documenting the sensitivity/specificity of a NAAT test for *M. tuberculosis* complex from direct sputum specimens should include a prospective study (or studies) that include patients at risk for tuberculosis in populations similar to those likely to be tested in the US. Study protocols should include the following:

i. Reference assays

- The protocol should include a description of all quality control measures used for the investigational device and references assays, including smears and cultures, and tests for identification of *M. tuberculosis* complex in cultured isolates. If a central laboratory is not used during the study, it is expected that the protocol will describe the permissible comparative assays that can be used in the study and the quality control measures to be used at each site.
- When describing the reference method (or 'clinical truth') to be used for assessing study results, the protocol should describe how each result will be categorized. For example, if culture alone is used as the reference method, investigational device positive/culture negative results should be considered false positive results for the investigational device. If a composite reference method that incorporates results from culture and a well-characterized NAAT test, outcomes should be reported by comparing the investigational device against culture alone and against the combined reference method (i.e., culture with NAAT) separately.[27,28]
- If a NAAT assay is used as part of the composite reference it is recommended that this include a well-characterized PCR assay or comparable NAAT assay followed by bi-directional sequencing

[27] CLSI Standards for Nucleic Acid Sequencing (MM9-A) and Molecular Diagnostic Methods (MM3-A2) should be followed. If the study includes a second NAAT assay as a reference assay, full documentation regarding the performance of the assay (including LOD and reactivity) should be included in the submission.

[28] A composite result could be 'reference method positive' if either culture or the reference NAAT assay are positive and 'reference method negative' if both culture and reference NAAT assay are negative.

analysis. Sequencing should be performed on both strands of the amplicon (i.e., bi-directional sequencing), should demonstrate that the generated sequence is at least 200 base pairs of an acceptable quality (e.g., a quality score of 40 or higher as measured by PHRED or similar software packages), and should demonstrate that it matches the reference or consensus sequence.

ii. Study protocol

- Clinical study protocols should be finalized prior to study initiation. At a minimum, protocols should include complete patient inclusion and exclusion criteria, study procedures, and a detailed statistical analysis plan that includes performance measures to be used, statistical analysis methods, and statistical justification of sample size. Copies of the original study protocols, protocol modifications, all deviations from the study protocol, copies of IRB approvals and informed consent and any other relevant study information should be included in the 510(k) submission. Study protocols can be reviewed by FDA during development as part of the pre-IDE review process. The study protocol must also explicitly state that if test results will be used for patient management, an approved IDE will be necessary.
- The protocol should include a description of where tests will be performed (i.e., on site, at a clinical laboratory or central facility). It is expected that a non-amplification based method for the rapid detection of mycobacteria (e.g., AFB-smear) and liquid culture will be performed on every specimen.
- Study masking procedures for both clinicians and laboratory personnel should be described.

iii. Specimen types

- The protocol should include a description of the specimen types that can be included in the study, including the minimum number of specimens to be collected per patient. Patients should be representative of the intended use population. There should be a description of the methods of specimen collection, transport, and storage (if appropriate). This should include possible aliquotting of samples, any processing prior to testing, and the location where these steps will be performed. The protocol should contain maximum acceptable times for transport and storage, and the timing of each step should be captured in the case report form. The protocol should also outline safety precautions for handling, processing, and testing samples that will be used during the study.

iv. Study sites

- The experimental test should be performed at a minimum of three different geographical sites representing environments where the device will ultimately be used (e.g., clinical laboratories) and by

laboratory personnel likely to perform the test in clinical practice. (These testing sites may be different from the sites where subjects are enrolled.) At least two of the study sites should be located in the United States. Study sites should document all quality control results and repeat tests for runs with out-of-range quality control values.

v. Study population

- Patients enrolled in clinical studies should be those patients who meet the study inclusion and exclusion criteria for suspected active, untreated tuberculosis. Study inclusion criteria should match the intended use population of the assay. A minimum set of demographic characteristics including age, gender, date of symptom onset, HIV status (CD4 count/viral load if available), the presence of other relevant medical conditions and/or medications, the presence/absence of cardinal signs/symptoms of tuberculosis, and radiographic results should be captured. AFB smear results and TST results, if collected, should be provided.[29]
- All age groups should be represented in your clinical studies; if possible, including clinical sites that focus on certain patient populations (e.g., pediatric care clinics). Pediatric patients should be analyzed separately.

vi. Statistical analysis plan

- A complete statistical analysis plan (SAP) should be included with each study protocol. This should include:
  - For sputum, the target sensitivity and specificity to be achieved in clinical studies with associated confidence intervals; sample sizes should be adjusted to achieve these targets. The analysis of AFB-negative smears should clearly identify whether results are based on an analysis of a single specimen or from a serial strategy of more than one sample, e.g., if a strategy of repeating the test on a second sample is used (if testing of the original sample is negative), and whether concentrated specimens should be used.[30]
  - For matrices other than sputum, the protocol should include the anticipated number of specimens to be captured.[31]

[29] Enrollment of subjects with active tuberculosis infection may be challenging for studies without international sites and enrichment may be necessary. Panel members may wish to address whether only untreated subjects should be enrolled or there is an acceptable duration of prior treatment.

[30] Panel members will be asked to discuss device standards that could be recommended in a Special Controls Guidance, i.e., the lower bound of the 95% confidence interval for sensitivity and specificity appropriate for these devices. Sensitivity may differ for AFB-positive and AFB-negative specimens.

[31] It is recognized that reliably estimating sensitivity and specificity for matrices other than sputum (e.g., BAL or CSF) may be difficult, and that samples from prospective clinical trials may be

- Any planned interim analyses or administrative examinations of the study data should be described in the clinical protocol.
- Any subgroup analyses should be specified in advance, particularly if assay performance will be described separately in adults and pediatrics.

vii. Presentation of clinical study results

- Analyses should account for all patients enrolled and samples collected. Comparisons of device performance against the reference method should be included in an appropriate comparison table format. Additional analyses should be included for device performance relative to pre-defined patient characteristics, e.g., subject age. Depending on the experimental protocol, non-sputum respiratory samples such as BAL fluid, and/or non-respiratory samples such as CSF or joint fluid may be captured in a clinical trial. Panel members may wish to discuss the appropriate inclusion of non-sputum respiratory samples in the primary analyses; non-respiratory samples should be analyzed separately from respiratory samples.
- All study data should be included in the 510(k) submission in an acceptable electronic format. Data files should include appropriate annotations or separate codebooks and should include all primary and derived variables, e.g., the result of the clinical reference algorithm for determining the presence of norovirus.[32] Description of the statistical methods applied to the data set should be sufficiently detailed to allow FDA to reproduce from the data files the results reported in the submission.

(7) Labeling

IVD devices for the detection of *M. tuberculosis* complex, like all other *in vitro* diagnostic devices, are subject to statutory requirements for labeling (sections 502(a), 201(n) of the Act; 21 USC § 352(a), 321(n)). These IVD devices must provide adequate directions for use and adequate warnings and precautions (section 502(f); 21 USC § 352(f)). Specific labeling requirements for all IVD devices are set forth in 21 CFR 809.10; also see 21 CFR 801.119 where it is stated that IVDs labeled in accordance with 21 CFR 809.10 are deemed to satisfy section 502(f)(1).

FDA recommends that labeling for devices for the detection of *M. tuberculosis* complex include information similar to that below to mitigate the risks identified previously in this guidance to ensure safe and effective use of these

insufficient for regulatory action. The sponsor should discuss alternative means for obtaining specimens (e.g., banked/retrospective specimens) for other sample types.

[32] Separate data files for the analytical studies should also be included in the 510(k) submission.

devices. Requirements in 21 CFR 809.10 must be addressed in device labeling, as described below.

(a) Intended use

- The intended use should clearly specify the intended use of the device, the population to which it is applicable, and other significant aspects of use as appropriate, e.g., whether the test should be used with concomitant culture and AFB-smear. The statement of intended use should be qualified that the device is to serve only as an aid in diagnosis and that false-negative results may occur. Additional qualifications may be appropriate based on the results of clinical trials.
- The following guideline should be included prominently immediately below the intended use statement:

  "*For use in laboratories with experienced personnel who have training in the principles and use of mycobacteriology culture and identification methods and infectious disease diagnostics, and with appropriate bio-safety equipment and containment*"

(b) Directions for use

- The directions for use should provide clear instructions that delineate the procedures for using the device and any controls that can minimize the risk of yielding inaccurate results. Instructions should encourage the use of additional control measures and testing of control materials to ensure use in a safe and effective manner.
- Directions should be specific regarding processing of each possible specimen type included in the intended use.
- Guidance for bio-safety precautions with specimen handling and testing procedures should be provided as appropriate. It should be specified at which procedural step the test is non-infectious.

(c) Warnings, contraindications, precautions, and limitations

- Warnings, contraindications, precautions, and limitations relevant to the specific device should be included as applicable. At a minimum this should include discussion of certain populations where device performance may be affected, e.g., pediatrics (if applicable). Specific precautions regarding the use of matrices other than sputum should be included if these have not been studied.
- If positive or negative interference has been reported for any commonly used collection materials or substances that may be endogenously or exogenously introduced into a specimen prior to testing, users should be advised under limitations of the possibility of false negative or false positive results due to such interference.

(d) Specimen collection

- We recommend that you state that inadequate or inappropriate specimen collection, storage, number of freeze/thaw cycles and transport are likely to yield false negative test results. It should also be noted in labeling that samples should be collected as soon as possible after symptom onset.

(e) Interpretation and reporting of test results

- How the operator should interpret each of the possible device results, e.g., positive, equivocal, and negative, should be described. Recommendations for retesting or reporting of samples that are 'indeterminate' (if this is a possible device output) or where sample processing fails should be described (e.g., whether another aliquot of the same sample or a fresh sample is necessary should be specified). Clinical circumstances where immediate or delayed retesting is indicated should also be included.
- Photographs and/or diagrams to indicate how to interpret results for tests with a qualitative result, if appropriate, should be included.
- Labeling should include a statement that tuberculosis is a nationally notifiable disease that must be reported to public health authorities in accordance with state and local law. Users should verify reporting requirements in their area, and notify their state or local public health laboratory, the Centers for Disease Control and Prevention, and any other agency specified by their accreditation guidelines, if *M. tuberculosis* is detected or tuberculosis infection is suspected.

(f) Performance characteristics

- Labeling should include a summary of the study designs and study results described in Section 6 and 7 that would aid users in interpreting test results; this should include both clinical and analytical performance results.

(8) Postmarket measures

- If appropriate, information should be included with the 510(k) submission that describes how to assure that the performance characteristics of the test remain unchanged over time..

b. Considerations for a Special Controls Guidance for the Detection of Genetic Mutations Associated with Antibiotic Resistance using Nucleic Acid Amplification

A Special Controls *de novo* Guidance for the detection of genetic mutations associated with antibiotic resistance using nucleic acid amplification could likely contain elements similar to a Special Controls Guidance for the detection of *M. tuberculosis* complex directly from patient specimens. The

following section discusses only issues unique to the detection of mutations/genetic markers of resistance directly from patient specimens.

Antimicrobial susceptibility test systems are currently classified as Class II by a Special Controls Guidance; this guidance, however, is not applicable to test systems for mycobacteria or for rapid tests based on direct specimens (i.e., non-culture based systems).[33] Culture-based methods for mycobacteria susceptibility determination are classified as Class II under 21 CFR 866.1640:

> 21 CFR 866.1640. Antimicrobial susceptibility test powder.
>
> (a) *Identification*. An antimicrobial susceptibility test powder is a device that consists of an antimicrobial drug powder packaged in vials in specified amounts and intended for use in clinical laboratories for determining in vitro susceptibility of bacterial pathogens to these therapeutic agents. Test results are used to determine the antimicrobial agent of choice in the treatment of bacterial diseases.
>
> (b) *Classification*. Class II (performance standards).

In general, establishing interpretive criteria for susceptibility (e.g., susceptible, intermediate, or resistant) is based on information from multiple sources, including *in vitro* activity, pharmacokinetic and pharmacodynamic analyses, and clinical studies. For antitubercular therapy, an innovative approach, referred to as the method of proportion, has been used where critical concentrations of the antimycobacterial agent are used to define resistance as growth of >1% of the inoculum in the presence of a given concentration of the drug. The agar proportion method is currently considered the reference method; however, final results can take up to 3 weeks to be reported after the initial recovery of the organism in culture (although earlier reporting of results may be possible if the isolate is resistant).

Liquid-based phenotypic assay systems based on the same principles as the agar proportion method but with shorter incubation times have been cleared by FDA under the 510(k) mechanism for the testing of isoniazid, rifampin, ethambutol, and pyrazinamide susceptibility.[34]

Although a correlation between phenotypic resistance and detection of a mutation or a genetic element that confer resistance may be well established,

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[33] Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080564.htm

[34] Devices/assays for testing drug susceptibility cannot be cleared or approved for drugs that are not FDA-approved for the treatment of tuberculosis, even if the drugs are approved for other uses.

it should be recognized that these are separate concepts and that the converse may not be true: negative results for assays that detect mutations associated with drug resistance do not necessarily assure drug susceptibility. Similarly, depending on the strength of the relationship or the presence of mixed populations, detection of a 'resistance' mutation or a biomarker may or may not provide assurance of phenotypic/clinical resistance.[35] These issues need to be addressed when considering devices for the rapid detection of resistance based on mutations.

For devices intended for the direct detection of resistance biomarkers in *M. tuberculosis* complex directly from clinical specimens, the following risks and clinical mitigation strategies are proposed.

(1) Safety and effectiveness:

The following risks and potential clinical mitigation strategies have been identified for a NAAT device intended for the direct detection of resistance biomarkers in *M. tuberculosis* complex directly from clinical specimens. It is assumed when considering these risks that all samples would also undergo mycobacterial culture with traditional susceptibility testing of cultured isolates.

(a) False positive test results (i.e., false detection of a mutation/genetic biomarker associated with drug resistance).

- Risks: Erroneous detection of a molecular marker of resistance may lead to treatment with a potentially less effective or less well-studied antibiotic, with potentially less effectiveness and a different adverse event profile. There is also an increased possibility of additional infection control measures being implemented to prevent spread of a drug resistant isolate.[36]

(b) False negative (false susceptible) test results:

- Risks: A false-susceptible test result based on a negative NAAT result for the biomarker may lead to initiation of inadequate antimicrobial drug therapy. This would be especially true in areas where drug resistance may be prevalent, thus increasing the risk to the patient. The risk in this setting would be of inadequate treatment, possible emergence of resistance to other components of a multi-drug regimen, and possible spread of a resistant isolate.

[35] Panel members may wish to discuss circumstances where the presence of resistance mutations is confirmed but phenotypic sensitivity is also observed.
[36] It is anticipated that discussion of the risks of false positive test results by the panel would include these risks in the setting of the low probability of drug resistance in the US, as well as possible mitigations such as confirmation of the presence of a resistance mutation by a second NAAT assay.

For both false-negative or false positive results, the risk of an inaccurate NAAT result cannot be mitigated if an isolate cannot subsequently be cultured. It is also assumed that tests for the detection of genetic mutations associated with resistance on direct specimens would only be reported for patients with positive results on highly specific rapid tests for the detection of *M. tuberculosis* complex from direct specimens.

(2) Performance studies: Performance studies similar to those required for the direct detection for *M. tuberculosis* complex would be necessary. Unique aspects of analytical studies for the detection of mutations/genetic markers associated with drug resistance include the need for analytical reactivity (inclusivity) studies using a diverse panel of *M. tuberculosis* complex isolates where phenotypic status has been determined by reference culture methods and bidirectional sequencing has documented the presence or absence of specific mutations associated with resistance. Limit of detection studies should include specimens spiked with varying proportions of drug-susceptible and drug resistant isolates.[37]

(a) Clinical studies:

The greatest difference between development of special controls for the direct detection of *M. tuberculosis* complex and genetic mutations associated with antibiotic resistance is likely to be the studies of clinical performance. The low frequency of phenotypically resistant *M. tuberculosis* in the US likely precludes prospective study of device sensitivity. Alternative approaches could include:

- Prospective studies in areas of greater prevalence, e.g., ex-US.
- Spiking studies using a panel of well-characterized *M. tuberculosis* isolates specimens. Such studies could involve spiking into artificial matrices, sputum (or other matrices) samples from uninfected individuals, possible mixing studies (where samples from patients infected with *M. tuberculosis* regardless of drug sensitivity are spiked with resistant isolates). These studies would be expected to test a large sample of resistant isolates obtained from geographically diverse sources where there has been complete characterization of all isolates. Resistant isolates should include singly-resistant and both MDR/XDR isolates. When multiplex assays are studied (e.g., assays that may detect mutations conferring resistance to INH and/or rifampin simultaneously), overall performance by specimen as well as for each mutation individually should be reported.[38]

[37] Analytical studies in other mycobacterial species with known resistance mutations may be required as appropriate.
[38] This is also true for specificity when defined as the false-positive detection of mutations in the setting of *M. tuberculosis* complex detection. Even a relatively large prospective study in the US

(3) Labeling:

The discussion of labeling in a Special Controls Guidance would likely parallel that for the direct detection of *M. tuberculosis* complex; however, additional discussion regarding assay limitations based on the overall sensitivity for detecting phenotypic resistance (rather than just the presence of specific mutations) would need to be carefully described in labeling. Warnings regarding interpretation in the setting of low prevalence and the need for confirmation of positive results by other assays may also be needed.

(4) Post-marketing monitoring

A request for information regarding the sponsor's plans for post marketing monitoring for the emergence of new mutations (and a possible change in expected assay performance) should also be described in the Special Controls Guidance.

c. Specific Considerations for IGRAs for the Indirect Detection of M. tuberculosis complex

Interferon-gamma releasing assays (IGRAs) are 'indirect tests for *M. tuberculosis* infection (including disease) intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.' As noted by Horsburgh and Rubin, "There is no way to directly detect the presence of latent *Mycobacterium tuberculosis* in an individual patient. Instead, the assessment of latent infection relies on measurement of host immune responses as a surrogate for the presence of viable bacteria, an imperfect approach".[39] Accordingly, there is no *direct* means to establish the sensitivity and specificity of assays for latent tuberculosis infection (LTBI) absent large prospective clinical studies that follow patients for the development of active tuberculosis. The absence of these data has led to differences of opinion regarding the recommended use of IGRAs.[40]

Accordingly, a Special Controls Guidance for an IGRA assay may present more challenges than for the direct detection of *M. tuberculosis* complex. The following could be considered in a Special Controls Guidance:

(1) Safety and effectiveness:

The following proposed risks have been identified for devices intended for the indirect detection of *M. tuberculosis* infection.

(a) False positive test results

may not yield an acceptable number of *M. tuberculosis* complex infected patients for determining specificity with narrow confidence intervals.

[39] Horsburgh R and Rubin E. Latent Tuberculosis Infection in the United States. New England Journal of Medicine 2011;364:1441-8, included as an attachment to this document.

[40] Alexander T and Miller M. Point-Counterpoint: Should Interferon Gamma Release Test become the standard method for screening patients for *Mycobacterium tuberculosis* infections in the United States? Journal of Clinical Microbiology; epub April 6, 2011, included as an attachment to this document

- Risks: An erroneous positive result may lead to unnecessary treatment for latent tuberculosis infection, with potential adverse effects from treatment.

(b) False negative test results:

- Risks: A false negative result would result in a patient not being administered treatment for LTBI and thereby having a greater risk of reactivation disease relative to a treated patient. An additional risk is transmission to contacts prior to diagnosis in patients with reactivation disease.

(2) Performance studies:

(a) Clinical studies: Clinical studies similar to those required for previous IGRA applications would be necessary. This would include studies in patients: (1) at low risk for previous tuberculosis infection, defined by the absence of risk factors, (2) patients at high risk for LTBI defined by CDC guidelines for screening of risk groups, (3) patients with culture-confirmed active tuberculosis infection, and (4) patients with a history of non-tuberculosis mycobacterial infection and/or colonization (e.g., with MAI, *M. kansasii*, or *M. gordonae*). Each study would need a comparison to TST and likely to an existing IGRA assay. Results would be presented and reported as currently shown in approved labeling.[41]

(3) Labeling:

The discussion of labeling in a Special Controls Guidance for IGRAs would likely focus on the fundamental limitations of studies conducted in the absence of a true reference standard. For example, current assays contain the following limitations:

- Results from IGRA testing must be used in conjunction with each individual's epidemiological history, current medical status, and the results of other diagnostic evaluations.
- A diagnosis of LTBI requires that tuberculosis disease must be excluded by medical evaluation including an assessment of current medical and diagnostic tests for disease as indicated.

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[41] Current CDC recommendations regarding diagnostic testing for tuberculosis (including links to MMWR reports and expert panel reports) is available at: http://www.cdc.gov/tb/topic/testing/default.htm. Specific updated CDC guidelines on the use of IGRAS to detect *Mycobacterium tuberculosis* Infection (MMWR, 59(RR-5), June 25, 2010) are available at: http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf; updated CDC guidelines on the use of NAAT in the diagnosis of tuberculosis (MMWR, 58(1); pages 7-10. January 16, 2009) are available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm. Copies of the IGRAS and NAAT guidelines are included as attachments to this document.

- A negative result does not exclude the possibility of infection with *M. tuberculosis*.

5. Questions for Panel Members:

The reclassification process for down-classifying a device from Class III to Class II depends on being able to mitigate the risks associated with use of the diagnostic device such that there is reasonable assurance of safe and effective use. Similar considerations exist for deciding whether a new device class is appropriate for the de novo regulatory pathway, i.e., whether Class II designation is appropriate at the time a 'first-in-class' application is filed. As described earlier, in both instances FDA is mandated to publish a Special Controls Guidance that outlines what a sponsor should follow for developing a new diagnostic device. In this context, please discuss the following:

a. For nucleic acid amplification assays that detect *M. tuberculosis* complex directly from respiratory samples:

(1) Please discuss the risks associated with inaccurate test results for *M. tuberculosis* complex detection (i.e., false-positive and false-negative results).

(2) Regarding special controls that could mitigate each of these risks, please discuss the following:

i. The types of clinical studies that should be recommended for demonstrating clinical performance. Please address appropriate patient populations to be studied and the role of both prospective studies and archived/banked patient samples.
ii. The appropriate reference method for use in clinical studies, e.g., is an alternative NAAT test required, and how results positive for the investigational device but negative for traditional culture should be interpreted.
iii. Minimum device performance standards (e.g., sensitivity and specificity) that should be recommended in the guidance.
iv. Device use recommendations that should be included in labeling to minimize risks, e.g., requiring AFB smears (and/or other antigen-based detection methods) routinely for all specimens or just for NAAT-positive results.
v. Any additional special controls that should be considered for these devices.

(3) Based on the above considerations, please discuss if sufficient risk mitigation is possible for FDA to initiate the reclassification process from Class III to Class II devices for this use through drafting a Special Controls Guidance.

i. If reclassification is possible for sputum samples, please discuss the clinical performance validation that would be necessary for device use with other respiratory specimens (such as BAL fluid), and/or extra-pulmonary matrices such as CSF or joint fluid.

b. For nucleic acid amplification assays that detect genetic mutations associated with antibiotic resistance to *M. tuberculosis* complex directly from respiratory specimens:[42]

(1) Please discuss the risks associated with inaccurate results for the detection of genetic mutations associated with antibiotic resistance to *M. tuberculosis* complex.

(2) Please discuss all possible special controls to mitigate each identified risk, including the following:

i. Clinical studies that would be appropriate for assessing device performance. Considering the relative infrequency of antibiotic resistance mutations in different populations, please discuss the appropriate role of prospectively collected samples, archived/banked samples, and spiked samples in determining device performance.
ii. The appropriate reference method(s) for determining antibiotic resistance, e.g., Agar Proportion Method.
iii. Minimum device performance standards (e.g., sensitivity and specificity) that should be recommended in the guidance.
iv. Device use recommendations that should be included in labeling to minimize risks, e.g., requiring specimens that are positive for the presence of resistance mutations to be confirmed by an alternative assay at a reference laboratory.
v. Any additional special controls that should be considered for these devices.

(3) Based on the above considerations, please discuss if sufficient risk mitigation is possible for FDA to consider classifying these devices as Class II by drafting a Special Controls Guidance through the *de novo* regulatory pathway.

i. If Class II designation is possible, please discuss if there are any unique risks or possible mitigations for devices used to simultaneously detect *M. tuberculosis* complex and resistance mutations.

c. For immunologically-based tests, such as IGRAs, intended for the detection of tuberculosis infection by indirect means:

(1) Please discuss the risks associated with inaccurate test results for the detection of tuberculosis infection (i.e., false-positive and false-negative results).

(2) Please discuss possible special controls to mitigate each of these risks, including the following:

[42] Please note that diagnostic assays for anti-tuberculous drug resistance can only be approved or cleared for antibiotics that are FDA-approved for the treatment of tuberculosis.

i. Clinical studies that would be appropriate for documenting device performance.
ii. The appropriate reference method for use in clinical studies.
iii. Minimum device performance standards (e.g., sensitivity and specificity) that should be recommended in guidance.
iv. Device use recommendations that should be included in labeling to minimize risks.
v. Any additional special controls that should be considered for these devices.

(3) Based on the above considerations, please discuss if sufficient risk mitigation is possible for FDA to initiate the reclassification process from Class III to Class II devices for this use through drafting a Special Controls Guidance.

6. Attachments

(1) A description of the FDA 510(k) Premarket process. From the FDA Web Site at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.

(2) A description of the FDA PMA process. From the FDA Web Site at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm.

(3) GEN-PROBE® AMPLIFIED™ Mycobacterium Tuberculosis Direct (MTD) package insert. (Available at: http://www.gen-probe.com/pdfs/pi/IN0014.pdf.)

(4) QuantiFERON® -TB Gold In-Tube package insert. (Available at: http://www.cellestis.com/IRM/Company/ShowPage.aspx?CPID=1171.)

(5) T-SPOT®.TB package insert. (Available at: http://www.oxfordimmunotec.com/USpageInsert.)

(6) A description of the FDA Reclassification process. From the FDA Web Site at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ ClassifyYourDevice/ucm080412.htm.

(7) Horsburgh R and Rubin E. Latent Tuberculosis Infection in the United States. New England Journal of Medicine; 364:1441-8, 2011.

(8) Alexander T and Miller M. Point-Counterpoint: Should Interferon Gamma Release Test become the standard method for screening patients for Mycobacterium tuberculosis infections in the United States? Journal of Clinical Microbiology; epub April 6, 2011.

(9) Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010. MMWR; 59(RR-5), June 25, 2010. (Available at: http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf.)

(10) Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. MMWR, 58(1),7-10, January 16, 2009. (Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/ mm5801a3.htm.)