Federal TB Task Force
April 8, 2013, **Report of the Diagnostics Workgroup**
Cochairs: Peter Kim and Michael Iademarco

Since December 2011, substantial activity has resulted from previous efforts of the workgroup, including the establishment of an FDA and NIH co-sponsored frozen trial bank, the NIH-sponsored TB Diagnostics Research Forum, bilateral CDC-NIH joint activity on improvements to diagnostic testing for pyrazinamide resistance, CDC and NIH coordination with WHO on moving R&D to field demonstrations for the molecular detection of drug resistance, and FDA policy efforts related to devices to detect *M. tuberculosis* and related drug resistance.

Guided by the workgroup's recognition of the importance of biomarkers for TB treatment efficacy and resulting workshops (Yasinkaya Y, et al, IJLD, 2011; Nahid et al, AJRCCM 2011) the FDA and NIH are sponsoring a clinical-trial specimen bank (Frozen Trial Initiative) to aid in biomarker discovery. The Consortium for TB Biomarkers is currently comprised of the TB Alliance, the AIDS Clinical Trial Group, and the TBTC, and efforts are underway to store prospectively collected specimens from TB Clinical trials.

Similarly, the workgroup's prioritization of molecular diagnostics has led to a number of coordinated and collaborative activities between U.S. agencies and other partners. Much of this activity has focused around improving the diagnosis of pyrazinamide (PZA) resistance because of its unique and essential role in both current and future TB drug regimens. Ongoing efforts include improving PZA phenotypic testing, development of pncA sequencing as eligibility criteria for clinical trials, improving understanding of *pncA* mutations and their role in PZA resistance, enlarging a database of PZA resistant isolates, and heightening understanding and cooperation between developers of new molecular diagnostics and the TB drug development field.

FDA has continued reexamination of the regulation of nucleic acid TB diagnostic assays following a 2011 FDA Microbiology Devices Panel meeting devoted to this issue. Draft guidance regarding reclassification of Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens was published March, 2012. Reclassification has been affected by passage of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), and there are efforts at many levels to move forward with reclassification in the context of the new law.

Concerns have been expressed regarding regulatory challenges for the clearance of devices that detect the presence of resistance mutations for drugs that are not FDA approved for the treatment of TB, e.g., quinolone drugs. This issue is also the subject of vigorous internal discussion.

Future priorities of the workgroup include the use of important drugs besides PZA (e.g., fluoroquinolones and new drugs) for drug-susceptible and drug-resistant TB, the use of molecular detection of drug resistance for drug resistance surveillance, and pediatric diagnostics.

In the Task Force, Xpert MTB/RIF rollout is being addressed largely by the International Workgroup.

References

FDA

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM260828.pdf

PZA

Early data from studies presented at three national meetings show the importance of PZA for any regimen that might use a new anti-tuberculosis drug. All three meetings are well documented on the website of the Stop TB Partnership's Working Group on New TB Drugs, including the study presentations.

In May 2011, the National Institutes of Health (NIH) hosted a workshop, "Essentiality of PZA." The gathering laid the groundwork for exploring the subject further in-depth. Richard Hafner (Division of Acquired Immunodeficiency Syndromes (DAIDS)) concluded that "PZA has potent sterilizing activity and is a highly important drug in current anti-tuberculosis combination therapy. Unfortunately, while PZA-resistant TB has been increasing worldwide, rapid and reliable diagnostic tools for the detection of PZA-resistant TB are still unavailable. This presents a major barrier for treatment, especially for multidrug-resistant and extensively drug-resistant disease. PZA is the least understood anti-TB drug due to its complex mechanisms of action and obstacles in establishing animal models for PZA testing."

http://www.newtbdrugs.org/meetings/pza-workshop.php

In December 2011 in Atlanta, CDC hosted a meeting to review in detail our research activities related to PZA in order to enhance alignment with NIH and Food and Drug Administration (FDA) goals and priorities. The Global Alliance for TB Drug Development was also in attendance. CDC presented information on the surveillance of PZA resistance, experience in providing clinical microbiologic service, and preliminary results on approaches to improve drug susceptibility testing for PZA. A series of concrete actions steps were laid out for the various federal agencies to strengthen internal U.S. government interaction. The goal was to facilitate ongoing partner planning and efforts to advance PZA drug susceptibility testing in both the short-term and long-term. Assistant Surgeon General Kenneth G. Castro, USPHS and co-chair of the Federal TB Task Force remarked on the importance of ongoing inter-agency discussion tied to concrete tracking of action.

http://www.newtbdrugs.org/downloads/resource-docs/2011-12-25-Summary-PZA-Day-at-CDC.pdf

In September 2012 in Baltimore, in follow-up, NIH and Johns Hopkins University hosted a broader, partner workshop: "Demystifying PZA—Challenges and Opportunities." Topics included mechanisms of action; drug resistance and associated testing; combination therapy; and toxicity. In-depth presentations in these four areas led to lively and stimulating discussion, capitalizing on previous meetings and contributing significantly to the growing momentum needed to tackle the issues. The next step was announcement of a NIH-sponsored "TB

Diagnostics Research Forum," designed to facilitate future dialog and collaboration; this will be the subject of a future report to TB Notes.

http://www.newtbdrugs.org/meetings/pza-workshop-2012.php

Frozen Trial Initiative www.fda.gov/downloads/.../CriticalPathInitiative/.../UCM289182.doc

The **last two formal meetings**, sponsored by the TB Federal Task Force Diagnostics Workgroup have been documented and productive. Please see a May 2012 supplement in JID, http://jid.oxfordjournals.org/content/205/suppl_2.toc

1) Clinical Research and Development of Tuberculosis Diagnostics: Moving From Silos to Synergy
2) Opportunities and Challenges for Cost-Efficient Implementation of New Point-of-Care Diagnostics for HIV and Tuberculosis
3) Perspectives on Introduction and Implementation of New Point-of-Care Diagnostic Tests
4) Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel
5) Evaluation of Tuberculosis Diagnostics in Children: 2. Methodological Issues for Conducting and Reporting Research Evaluations of Tuberculosis Diagnostics for Intrathoracic Tuberculosis in Children. Consensus From an Expert Panel
6) New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise, and Prospects for the Future
7) Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis
8) Viewpoint: Challenges and Opportunities in Tuberculosis Research

And most recently, "Alignment of new tuberculosis drug regimens and drug susceptibility testing: a framework for action," in Lancet Infect Dis. 2013 Mar 22.