Meeting Report
3rd Semi-annual Global TB Community Advisory Board Meeting

November 11-12, 2012
Kuala Lumpur, Malaysia

Day I | November 11, 2012

Drug Development and Registration
Mark Harrington (Treatment Action Group or TAG) provided the group with a comprehensive historical overview of the evolution of drug development and registration processes. The overview started in the 20th century when regulatory agencies were first established in response to the sale of rotten food and poisonous drugs in the United States. Mark highlighted two tragedies that resulted in laws to scale up the U.S. Food and Drug Administration's (FDA) authority and regulatory capacity– in the 1930s, following sulfanilamide-associated deaths, the Federal Food, Drug, and Cosmetic Act gave the FDA authority to oversee drug safety, and in the 1960s, following thalidomide-associated birth defects, the FDA began requiring proof of safety and well-controlled clinical trials. Mark's overview also included discussion of "the golden era" of antibiotic drug discovery and lessons from HIV that are applicable to TB. The discussion concluded with character descriptions for three regulatory authorities: the FDA, which is very structured, bureaucratic, and experienced with new TB drug reviews; the South Africa Medicines Control Council (MCC), made up of part-time academic volunteers, and poorly equipped for timely protocol and new drug application reviews; and the European Medicines Agency (EMA), which is made up of task teams, excludes drug experts from certain drug reviews, and has a history of lacking transparency.

Pediatrics
Polly Clayden's (HIV i-Base) presentation on pediatric TB began with a discussion of the need to shorten the gap between approval of drugs for adults and for children. Developers should start thinking about pediatric formulations and studies when compounds reach adult phase II studies. Polly's presentation highlighted complications in appropriately dosing for children under five years, who have variable drug absorption and metabolism; the potential flaws of weight-based dosing; the need for revised fixed dose combinations (FDCs) of first-line drugs in line with the new WHO dosing recommendations; and the need for pediatric formulations of second-line TB drugs. The hierarchy of preferred formulations is: heat stable, dispersible mini tablet (in a FDC); sprinkles; scored tablets; then liquid. Polly emphasized the need for acceptability studies and for UNITAID's involvement in pediatric MDR-TB treatment, as they currently supply ~60% of antiretroviral drugs (ARVs) worldwide.

The discussion transitioned to TB in pregnant women and regulatory authority hesitation to allow their inclusion in clinical trials of TB drugs (pregnancy is often an exclusion criterion), despite that pregnancy is a risk factor for active TB and that TB threatens the mother, the unborn fetus, and the newborn. It is actually unethical NOT to provide this population with safe treatment options. The FDA requires teratogenicity studies in mice or rats and based on these studies recommends whether the drug is safe during pregnancy (category D– strong recommendation against drug use; category X– completely contraindicated; though this classification system is changing). Pregnant women and children are often deprioritized by the private sector as they make up a smaller market, are more physiologically complex, and are perceived to bring increased risk of litigation. Prospective registries for HIV-infected pregnant women collect data on ARV adverse effects and safety and could be replicated for TB. Polly closed her presentation by pointed out the need to be less sentimental and think about the risks,

benefits, and safety data in the same way we would for a cohort of men. “Sins of omission are as great as sins of commission.”

TB Alliance

William Wells, Steven Murray, and Christophe Cooper (TB Alliance) updated the TB CAB on their phase II studies, NC002, designed to evaluate PA-824 at 100mg and 200mg daily with moxifloxacin and pyrazinamide for two months in people with DS- and MDR-TB, and NC003, designed to compare the bactericidal activity and safety of several combinations of new and existing drugs (including PA-824 and bedaquiline) given for two weeks to people with DS-TB. They are expecting data from NC002 by the end of 2013– if the results are positive, they will aim to initiate a phase III registration trial by late 2014. The presenters noted that clofazimine and linezolid might become more important in the future. The TB Alliance also discussed their hopes to develop a pediatric regimen (dispersible FDC) consistent with the ReMox regimen that attempts to shorten treatment for DS-TB to just four months by substituting moxifloxacin for isoniazid or ethambutol, as the Data Safety Monitoring Board (DSMB) have not detected any safety signal or difference in efficacy large enough to stop the study. The TB Alliance closed their presentation with highlights from a recently completed patient costing and perception study that looked at 6- vs. 4-month regimens in Tanzania and Bangladesh. The study found that while it was possible to cut down travel costs using community-based care, the remaining financial burden on patients, mainly attributable to loss of work, would be difficult to affect without the use of shorter regimens.
[Note: product development information may be outdated]

Cepheid

Ellen Jo Barron (Cepheid) updated the TB CAB on the rollout of GeneXpert, a molecular diagnostic test that can detect TB and resistance to one of the key first-line TB drugs, rifampicin, in just two hours. As of September 30, 2012 5,000 Xpert modules and 1,482,550 cartridges have been procured– as well as Cepheid’s plans for registration in the US. The FDA’s Pre-Market Approval process, now necessary for TB and HIV viral load tests, requires more stringent quality assurance and high application fees (USD 800,000). Cepheid will only register GeneXpert in the U.S. if they can use an alternative track, as they can’t afford the existing pre-market approval application fees and additional requirements– if registration is successful, they will sell Xpert in the US at $75 per cartridge. Ellen also discussed challenges given the need for centralized module recalibration, and development plans for a site based calibration kit and cloud based integrated data system. Ellen closed her presentation by expressing Cepheid’s interest in developing cartridges to test for resistance to other TB drugs if given the money to do so. She estimated that it would cost $2 million to internally develop such a cartridge from scratch. More funding would be required to support optimization testing ($1 million) and clinical trials. Cepheid would also need access to resistant TB strains from all different sites to ensure geographical representation, as strains can differ by site and region. Also mentioned were Cepheid’s CEOs plan to eventually have Xpert developing facilities in Brazil and India.
[Note: product development information may be outdated]

TB in India

An expert on TB in India presented an overview of the TB situation in India, where over 100 people die of TB each day. The presentation highlighted the story of Radha, who lost her mother

to TB, despite her mother's diligence in completing her TB treatment. Also detailed were difficulties with diagnosis and empowering patients. A majority of the discussion centered on access to quality assured medicines– India uses Global Fund money to buy locally-made TB drugs. The catch is that these same manufacturers, supplying poor quality drugs to their own nationals, provide WHO pre-qualified drugs to other countries. The presenter expressed the need for Indian activists trained on TB issues to bring these concerns forward and to hold manufacturers and the government accountable for these injustices.

Day II | November 12, 2012

Ethics Training

Jerome Singh, the head of Ethics and Law at the Center for the AIDS Program of Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, University of KwaZulu-Natal (UKZN), led a half-day training in ethics surrounding clinical trials. The training covered the difference between therapeutic and non-therapeutic trials, legal vs. moral obligations, and the potential for variable standards of care in national vs. local contexts. The training also covered various international doctrines that can be used to protect trial participants, including: the Helsinki Declaration (1996), the International Harmonization Guidelines for Good Clinical Practice, the Council for International Organizations of Medical Sciences Guidelines (1993, 2002), and the UNESCO Universal Declaration on Bioethics and Human Rights (2005). The ethics training ended with a discussion of drug sponsor obligations both during and post trial, the ethics of administering multiple novel drugs in combination studies, and differing country mechanisms and processes for expanded access/ compassionate use.

TB Diagnostics Training

For the second half of day two Maunank Shah (Johns Hopkins University) conducted training on existing TB diagnostic tools. Maunank discussed the benefits, shortcomings, and cost-effectiveness from both the provider and laboratory perspective of each diagnostic technology. The training covered tools currently in use for screening both latent and active disease, including: tuberculin skin tests (TSTs), interferon gamma release assays (IGRAs), x-ray, smear microscopy, sputum culture, drug-susceptibility testing (DST), lipoarabinomannan antigen tests (LAM), and molecular assays. Maunank highlighted difficulties in diagnosing patients with smear-negative and extra-pulmonary disease and the need for ensuring that diagnosis actually leads to treatment and cure.