A Médecins Sans Frontières/Doctors Without Borders Symposium supported by Howard P. Milstein and Weill Cornell Medical College's Abby and Howard P. Milstein Program in Chemical Biology

Symposium Summary

"Diagnosing and treating TB is one of the greatest challenges facing health care providers around the world," said Dr. Tido von Schoen-Angerer, the Director of MSF's Access to Essential Medicines Campaign. "The urgency for new tools could not be greater – there is no time to wait."

Doctors Without Borders/Médecins Sans Frontières Campaign for Access to Essential Medicines, with the support of Howard Milstein and Weill Cornell Medical College, convened the symposium *No Time to Wait: Overcoming the Gaps in TB Drug Development* in New York on 11-12 January 2007. Aimed at stimulating efforts to accelerate the development of effective new treatments for tuberculosis (TB), the symposium brought together more than 100 experts from around the world, including drug developers, clinical researchers, health professionals, policy makers, donors, and activists. Plenary and workshop participants discussed the inadequacy of current approaches and concrete proposals to accelerate the development of effective new treatments. These included mechanisms to stimulate basic and translational research, the expansion of global TB clinical trial capacity, and the need for serious consideration of new approaches to prioritize and fund essential medical R&D such as a global R&D treaty currently being discussed at the WHO. Participants agreed that overcoming the gaps in TB drug development requires global TB R&D leadership and a significant increase in funding. The following is a summary of key issues and recommendations arising from the conference.

Thursday January 11, 2007

Participants were first welcomed by Howard Milstein, Chairman of New York Private Bank and then Trust by Dr. Tido von Schoen-Angerer, Director of MSF's Campaign for the Access to Essential Medicines.

Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, then outlined the worldwide challenges posed by TB in a videotaped address. The disease kills almost 2 million people annually and the global burden is growing each year. About 450,000 new cases of multi-drug resistant TB occur each year, including extensively drug resistant (XDR) cases that are difficult -- and sometimes impossible -- to treat. Like HIV, he said, TB disproportionately affects young adults in their most productive years, and there is a deadly synergy between the two infections. Despite the pressing needs, health practitioners have inadequate and outdated therapeutic tools with which to manage the disease. He outlined the need to bolster TB control programs and ensure that all TB patients receive the appropriate drugs and continue to take them for the entire duration of therapy as well as to accelerate fundamental, translational and clinical science related to TB. Research and regulatory agencies, academia, industry, public health agencies, philanthropy, public-private partnerships, and activists are all vital to this effort. Research must be expanded to include the co-infections that are seen together with TB in the "real world," and to study the interactions between the medications used to treat different diseases. Dr. Fauci then described the progress made in the past decade, including a pipeline of

promising TB drugs. But this pipeline, he concluded, is shorter and thinner than will be needed and many gaps remain in the TB drug discovery, research, and development process.

The opening session, chaired by Dr. Bernard Pécoul, the Executive Director of DNDi, focused on the fact that despite the pressing needs, health practitioners have inadequate and outdated therapeutic tools with which to manage TB.

Given these challenges, Dr Mario Raviglione, Director of the Stop Tuberculosis Department at the World Health Organization (WHO) gave a global view of current approaches and targets for the control of TB, a disease he called the "biggest cause of death from a curable or preventable infectious disease." He outlined the new STOP TB strategy of the WHO including the Global Plan for 2006 to 2015 which included funds to expand DOTS programs, address TB/HIV and TB drug resistance and invest in R&D for new drugs, vaccines and diagnostic tools. At current estimates the ten year strategy budgeted at $56 billion was likely to have only half the required funds.

After decades of standstill, initiatives in the last five years have ensured that the drug development pipeline has begun to fill. Dr Maria Freire, President and CEO of the Global Alliance for TB Drug Development, described the four major goals of the TB Alliance: 1. to shorten and/or simplify treatment of active, drug-susceptible TB; 2. to improve treatment of MDR-TB; 3. to improve treatment of TB/HIV; 4. to improve treatment of latent TB infection. She outlined the approach taken by the Alliance to create and advance candidate drugs through discovery, pre-clinical, and clinical phases. The current TB pipeline consists of 7 compounds in basic research, 26 in the discovery phase, 6 at the pre-clinical stage, and 13 compounds at the clinical stage. As of today, there are plans to have combination trials in 2007-8, the registration of a shorter (3-4 month) regimen by 2011, a sustainable pipeline and regular delivery of new drugs available for use in combination by 2015, and a breakthrough regimen (1-2 month) in trials by 2015 based on rational combinations.

The present-day reality of inadequate therapeutic tools was highlighted by Dr. Francis Varaine, Chairman of the Médecins Sans Frontières TB Working Group, who presented a field perspective of addressing TB in 102 programs run by MSF in 44 countries. The history of three patients in Abkhazia described the nearly insurmountable challenges of TB treatment and infection control with the current tools. Even the best TB treatment available still leads to high death, failure and default rates, and inevitably leads to XDR TB even under optimal conditions and strict Direct Observation Therapy. (An alarming 10% of MSF's patients with MDR TB develop XDR TB.) Delayed diagnosis causes an unacceptable delay in appropriate treatment and makes infection control a nearly impossible task, raising the risk of nosocomial and community infections. With the tools currently available, Dr. Varaine did not see the situation improving.

Dr. Ying Zhang of Johns Hopkins University concluded the session with lessons learned from persisters and the persister drug PZA. All of today's TB drugs are only active against actively growing bacilli, except PZA and RIF, thus they cannot kill persisters/dormant bacilli. Drugs that can kill persisters/dormant bacilli could shorten the therapy. So new drugs active against drug-resistant TB need to be active against dormant/persistent bacilli and shorten the therapy from 6 months to a few weeks.

Gaps in TB Drug Discovery

Despite some progress, participants in the second session chaired by Novartis' Dr. Paul Herrling, acknowledged that these initiatives are insufficient for bringing improved treatment to patients in the next few years. Dr. Ken Duncan, of the Bill and Melinda Gates Foundation, identified weaknesses in the pipeline including the limited number of new chemical entities, a lack of depth (meaning development is sensitive to attrition), insufficient activity at early stages of discovery to fuel the pipeline, and the lack of focus on the problem of "persistence" in TB. Dr. Duncan illustrated the initiatives launched by the Gates

Foundation aimed at tackling these limitations, including the Grand Challenges in Global Health and the more recent TB Drug Accelerator program.

Scott Franzblau and Alan Kozikowski of the University of Illinois in Chicago described how the lack of access to proper medicinal chemistry expertise in academic settings represented a critical bottleneck in TB drug discovery. “What is missing in the acceleration of cures for diseases is quality medicinal chemistry to expand on a lead,” said Alan Kozikowski. He proposed an International Drug Discovery Institute as a way to assemble expertise in publicly-funded centers to optimize lead compounds.

Amy Kapczynski, of Yale University, then discussed ways to manage intellectual property in academia to ensure future access to products. Currently, patenting and licensing practices sometimes impede research, while university technology transfer offices have been slow to address access issues in low and middle income countries. Recent developments to address these problems include the Philadelphia Consensus Statement in November 2006. Commons-based solutions include calling on universities and public sector institutions to adopt access-first patenting and licensing policies. To this end, there should be no patents on TB research tools, and negotiations with partners to ensure low-cost access to resulting drugs and diagnostics in target countries.

Clinical Trial Capacity

A second critical gap in the drug development pipeline discussed by participants was the shortage of funds that prevented the development of candidate drug compounds through to clinical trials. Clinical trials for drugs and combinations that could be done today are being held back because of a lack of funding, a lack of capacity, and regulatory barriers. These points were raised in a session chaired by Professor Wafaa El-Sadr of Colombia University’s Mailman School.

Clinicians involved in TB clinical trials, like Dr. Neil W. Schluger, Steering Committee Chair of the Tuberculosis Trials Consortium (TBTC) and Associate Professor of Medicine and Public Health at Colombia University and Dr Amina Jindani of St. George’s Hospital Medical School in London, outlined the current capacity and future needs for evaluating new drugs through clinical trials. Both described how the lack of funds prevented clinical trials with existing candidates (to reduce treatment time, for example) from occurring. Dr Schluger reinforced this point by providing estimates that only $20-30 million is spent annually for clinical trials for TB drugs worldwide compared to nearly $300 million for HIV drugs in the US alone.

Christian Leinhardt, Director of Research at the International Union Against Tuberculosis and Lung Diseases identified the importance of running multi-center TB trials in countries where the greatest needs are, and the need therefore to develop clinical trial capacities in resource poor settings by investing in training and the upgrade of sites to ensure that they conformed to GCP/GLP standards.

During the discussion period that followed, Dr. Ezio Santos Filho of Brazil’s TB/HIV Community Advisory Committee stressed the need to include people suffering from TB in the planning stages of clinical trials and development.

This point was supported by others, including Lawrence Geiter in the panel discussion. He added that doing so would help educating – rather than simply training – people who would be assisting in running clinical trials. Ann Ginsberg of the Global Alliance for TB Drug Development said that an overall assessment of sites around the world was nearly completed, and with some capacity building, there could be several sites readied to conduct GCP/GLP registration trials. During this panel, Margareth dal Colmo, of the Brazilian Society of Respiratory Diseases, stressed that in her experience there is a strong connection between good clinical care and good clinical trials. Hannu Laang, representing the European Commission, described plans to fund the increase in clinical trial capacity in Africa.

Accelerating Clinical Development
In a session chaired by Dr. Ken Castro of the Centers for Disease Control and Prevention, Dr Leonard Sacks of the U.S Food and Drug Administration provided a perspective on the difficulties in shortening TB clinical development through regulatory options, because of the problems associated with the selection of appropriate study end points and the demonstration of activity within a multi-drug regimen.

The challenges of conducting meaningful clinical trials for TB candidate therapies were debated by participants following presentations by Karel De Beule of Tibotec and by Anuradha Kulasekaran of Lupin Ltd, who presented preliminary data on two candidate drugs in clinical trials for TB developed by their companies - TMC 207 and LL-3858.

Dr William Burman, Study Chair of the Tuberculosis Trials Consortium at Denver Public Health discussed the specific context of clinical trials for MDR-TB. Clinical trials for MDR-TB are necessary in order to avoid the empiric introduction of new drugs in the regimen (i.e. introduction of fluoroquinolones as second-line drugs). Dr. Burman also discussed the utility of running comprehensive preclinical studies of new drugs and new drug combinations before starting tests in human patients. Studies in animal models could help saving time by providing useful information on dosage range, dosage frequency, and drug combinations that would speed up the identification of effective regimens

TB and the Global R&D Framework
The final session of the day, chaired by Ellen 't Hoen, Policy and Advocacy Director of MSF's Campaign for Access to Essential Medicines, was opened by Mark Harrington, from Treatment Action Group (TAG), who presented a report about global expenditures on TB R&D. TAG found that the current funding needs to be increased at least five-fold in order to devote sufficient resources to properly address the emergency of TB. The TAG report also revealed that R&D for TB diagnostics was largely under funded, and did not reflect the existing urgent need for improved diagnostic tools. This lack of resources for tackling TB was just another striking example of the failure of a R&D paradigm based on market-driven incentives rather than on global health priorities. James Love, Director of the Consumer Project on Technology, and Dermot Maher, of the World Health Organization, gave an update from the WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property that is currently discussing ways to prioritize, create incentives, and increase funding for essential medical R&D worldwide and to improve access to resulting therapies.

Friday January 12, 2007

Working Group Discussions/Workshops
Day two of the conference was devoted to participants breaking out into three specific working groups to develop concrete proposals and recommendations on ways to address the gaps in the TB drug development pipeline identified the previous day: 1. Filling the Gaps in TB Drug Discovery; 2. Building Clinical Trial Capacity; 3. Accelerating Clinical Development: MDR TB Trial Design as a Possible Way Forward.

Working group 1: Filling the Gap in TB drug discovery
Among the critical obstacles that are still hampering the field of TB drug discovery, the need to drastically improve access to information and tools emerged as a major theme during the working group discussion. Professor Carl Nathan, of Weill Cornell Medical College identified the failure of current financing mechanisms to align innovation, incentives, and access as the structural reason for the problems in the TB drug development pipeline. He identified the limitations with current approaches including donations, PPP, public and philanthropic institutions to overcome the structural barrier and discussed the concept of "open access drug companies" as a possible way forward.

The attempt to build fruitful collaboration among academia and industry can be hampered by cumbersome legal procedures related to technology transfer issues. Academic technology transfer offices should distinguish between “for profit” and “not-for profit” activities of the pharmaceutical industry and apply different procedures for each.

The transfer of compounds from industry libraries to academia has also been complicated by legal and intellectual property issues. Some pharmaceutical companies are giving access to a small subset of compound collections, but this usually requires lengthy negotiations and legal agreements are often defined on a case by case basis.

Moreover, academic scientists underscored that access to optimized compound libraries for screening of anti-infectives, access to medicinal chemistry and pharmacology expertises, remained critical bottlenecks despite some current initiatives in the filed of TB drug discovery. These existing bottlenecks do not allow for the great increase in activities that is urgently required to respond to the TB emergency.

Possible solutions discussed by participants included:

Empowering public and not-for-profit sector to run drug discovery programs.

This requires public sector access to appropriate compound libraries as well as to medicinal chemistry and pharmacology expertises. Suggestions were made for scientific funding agencies to finance projects aimed at creating and maintaining optimized compound libraries for the screening of anti-infectives.

With regard to the access to medicinal chemistry and pharmacology expertises (usually found the pharmaceutical industry), the possibility of creating medicinal chemistry resource centers was discussed. What emerged from the discussion is that this approach would face the difficulty of attracting and retaining talented chemists in the public sector.

The discussion ended up evaluating whether investing so much time and resources in re-inventing the expertises in drug discovery outside industry would be a successful strategy. The way forward might instead be represented by exploiting the different capabilities of the parties involved (academia, biotech, pharmaceutical, etc.).

Governments should create incentives for pharmaceutical and biotech companies to run in house phenotypic screens for anti-TB drugs with all available existing compound libraries.

Besides the inadequacy of typical compound collections for this purpose, another obstacle is that there is limited expertise in the private sector in working with *Mycobacterium tuberculosis*

Open access drug discovery entities and reform of current R&D financing mechanisms

The failure of current financing mechanisms to align innovation, incentives, and access can be seen as the structural reason for the problems in the TB drug development pipeline. Two structural reforms could allow for the development of a better R&D where innovation, incentive, and access would be mutually reinforcing: 1) the implementation of alternative incentive mechanisms to stimulate R&D to be applied in parallel to current market incentives; 2) the development of “open access drug companies” implementing a new model for academic-industry collaborations. Alternative patent tracks and/or incentive mechanisms would stimulate R&D not through high pricing of medicines, but rather through rewarding the impact of inventions on health care outcomes.

The establishment of "open access drug discovery entities" within traditional pharmaceutical companies might offer an interesting alternative to encourage close collaboration between academia and the pharmaceutical industry. "Open access drug discovery entities" can be envisioned as contract-based frameworks and sites for collaborations between academics and industry and among companies. Pharmaceutical companies would be enlisted as hosts in several geographic regions and, on a fee for service basis, open sectors of their R&D facilities to approved scientists from academia or other drug companies. This would offer a crucial logistic solution, allowing close collaboration among academic and industry scientists and eliminating the drawbacks of managing virtual drug discovery within large international consortia.

Open access "drug discovery entities" should also play the important role of generating and maintaining novel chemical libraries likely to be rich sources for anti-infectives.

Representatives of Novartis and GSK explained that their facilities in Singapore and Tres Cantos, respectively, are already open to close collaboration with academia and hosting academic scientists to carry out focused projects. Initial pilot experiments of this new model for R&D for neglected diseases could therefore expand on the existing base already in place.

Conclusions:
An efficient and effective strategy to solve the gap in TB drug discovery should consider the need to assign complementary roles to and make optimal use of the expertise of each of the key sectors involved (academia, not-for-profit, and biotech and pharmaceutical industries). One solution might be the development of new ways to foster academic and industry collaboration and allow efficient public sector contribution to drug discovery. It was questioned whether the attempt to replicate industry's expertise in drug discovery in separate entities within the public sector can represent a viable strategy to address existing problems on the necessary scale.

In this sense, the "open access drug discovery entities" model was considered as an interesting solution worth to explore. Participants broadly recognized that the need to develop new R&D financing paradigms would also be of primary importance.

Working Group 2: Building clinical trial capacity in high-burden countries

Dr Christo van Niekerk of the Global Alliance for TB Drug Development outlined the importance of assessing the capabilities of trial sites and the accessibility of this information for trial sponsors. He described a global capability assessment project being undertaken to assess 51 sites in 25 countries and the entry of the outcomes of this assessment in a public database. Dr Alwyn Mwinga of CDC Zambia noted, the involvement of high burden settings in clinical trials carried with it many important ethical and regulatory issues and required that capacity for ethical review and regulatory approval were developed at the same time. Dr Renata Guerra of the Hospital Universitario Clementino Fraga Filho of Rio de Janeiro, Brazil discussed the experience of TB trials in Brazil to show that, provided human capacity was developed, TB clinical trials in high burden regions could be conducted with adequate quality.

The working group recommended that capacity for high quality clinical trials in resource-limited settings needs to be developed. Members estimated that 3,000-5,000 patients per year need to be enrolled in phase 2 and 3 clinical trials if TB treatment is to be substantially improved in the next 5-10 years. Carrying out such a clinical trials agenda will require funding of $200-300 million annually. The working group favored a capable, prepared and adequately resourced clinical trials network of TB clinical trial sites rather than a product by product approach, with stable funding for clinical staff, education/training, laboratory, data/biostatistics, ethics, and community engagement.

Working Group 3: Accelerating clinical development; MDR-TB trial design as a possible way forward

Dr Leonard Sacks of the FDA discussed ways to address some of the key barriers to shortening clinical development times and reviewed various approaches to clinical trial design including superiority vs. non-inferiority trials, and determination of sterilizing activity. He argued that the setting of MDR-TB was one in which superiority could be much more easily demonstrated than in drug sensitive disease (which is 95% curable, thus raising a high bar for a superiority study), and the likelihood that a superior MDR regimen would produce early bacteriological and clinical endpoints when compared with standard of care in a randomized, controlled trial. In addition to improving cure rates, the potential demonstration of a reduction in infectiousness would have significant public health implications. From a regulator's perspective he argued that a multi-pronged approach was the best way to expedite the development of new agents, but recognised the need for significant increases in TB clinical development activity and investment.

Following breakaway discussions on ways to address these challenges, the working group concluded that it was time to move forward with randomized, controlled trials for MDR-TB, and presented consensus parameters for design of such trials. The first goal of an MDR-TB treatment trial would be to improve cure rates; that having been achieved, a follow-up goal would be to shorten therapy. It is possible that both goals could be achieved in the same clinical trial if it were designed with a suitable combination of rigor and flexibility. The proposed trial would seek to demonstrate superiority of a new agent by comparing an optimized background regimen (OBR) against OBR plus the new agent. The trial could have broad inclusion criteria being all patients with rifampicin resistance. The OBR could be based on a given site or country's standard of care, and different OBRs would be acceptable as long as the sample size was sufficient to demonstrate clear superiority of the new treatment if such superiority was truly the case. For example countries such as Peru which individualize MDR treatment regimens after determination of drug sensitivity patterns could utilize ITR (individualized treatment regimen) as OBR, while other countries using standardized regimens could continue to do so.

For such a trial to take place several pre-conditions would be necessary including 1) the proper training and GLP/GCP certification of clinical trial sites within, for example, existing Green Light Committee (GLC) approved or other high quality MDR treatment programs, and 2) the proper drug-drug interaction studies involving the new drug plus all first- and second-line TB drugs likely to be used in the randomized study. Preclinical activity studies of various combinations in the mouse model would also be useful. The group also felt that longer (7-14 day) early bactericidal activity (EBA) studies might be appropriate but did not come to a strong consensus on the safe length of EBA monotherapy studies in drug naïve TB cases. Mario Raviglione, from WHO Stop TB, also said that donors who support MDR programs – such as UNITAID or Global Fund – should be approached to consider contributing financial resources to such trials.

Regarding endpoints, it was felt that a combination of bacteriological and clinical endpoints would suffice, providing that there was regular, external quality assurance of bacteriology. Dr. Sacks argued for the time-to-durable-sterilization (culture confirmed repeated negative sputum smear and/or tissue samples) as a good potential endpoint which would be acceptable to the regulatory agency.

The group discussed compassionate use (expanded access to investigational new dugs) noting that in some circumstances XDR TB is an immediately life threatening disease for which conventional therapies are unsuitable or have failed and for which some drugs are under development that can potentially be effective. Therefore "compassionate use" must be considered. As there seems to be little if any experience with expanded access to investigational new drugs in developing countries, WHO should provide guidance to countries and potential users.

Conference conclusions

The conference concluded with recommendations from working groups being presented and discussed jointly by participants. Based on these discussions a consensus developed as to the critical areas where steps need to be taken to address gaps in TB drug development and these are listed below.

Participants call upon governments, intergovernmental agencies, researchers, drug and diagnostic developers, nongovernmental organizations, and funders to take action in five key areas.

1. Accelerate drug discovery
   - The public and not-for-profit sector needs to be guaranteed access to professional pharmaceutical services, which mostly exist in the private sector, to develop diagnostics and drugs. Mechanisms must be established to ensure public access to compound libraries and to build appropriate libraries with potential to exhibit anti-TB properties, particularly novel and natural products

2. Expand clinical trial capacity and accelerate clinical development
   - Worldwide, only $20 million is spent annually for clinical trials for TB drug compared to around $300 million for HIV drugs in the US alone. Funding bodies should support the creation of a TB clinical trial platform and the massive expansion of clinical trial capacity, particularly in developing countries
   - There is an immediate priority to shorten the time of clinical drug development. Criteria for compassionate use must be established by the WHO and regulatory authorities for important candidate drugs
   - In particular, trials for (M)DR-TB drugs must be prioritized because of the explosive spread of drug resistance and the potential of these trials to show efficacy rapidly
   - Drug trials should seek to integrate studies of potential new diagnostics

3. Support new approaches to R&D
   - The lack of TB drug development is a result of the failure of current profit-driven drug research and development model. The TB community must engage in the World Health Organization's Intergovernmental Working Group on Innovation, Intellectual Property and Public Health to establish a global R&D framework to help design new ways of setting R&D priorities and financing.
   - With respect to TB drug development, participants of the New York symposium support current discussion at the WHO for a treaty on essential health R&D that addresses the question of who pays for essential medical R&D and de-links incentives from drug prices, instead rewarding the impact of inventions according to health care outcomes.

4. Commit to global TB R&D leadership
   - Strong political leadership is required to improve collaboration among scientists, drug developers, care providers, and affected individuals, in both developed and developing countries, and develop a global priority research agenda for TB.

5. Increase funding for TB R&D activities
   - There is a critical funding gap for TB R&D. Around $900 million needs to be invested annually in the development of new tools for TB, but only $206 million was invested in 2005, and the funding gap is expected to widen over time. A dramatic funding increase is needed to support drug research and development activities. This is above all a matter of political prioritization.

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