

Draft Strategic Plan
Stop TB Partnership Working Group on TB Drug Development
2nd Global Plan to Stop TB 2005-2015 (GPII)
April 27, 2005

Global Plan to Stop TB: 2000 – 2005

Achievements

Current short-course (6-month) combination therapy for TB is effective when administered reliably. However, TB control has long been hindered by the lengthy and complex treatment required by current drugs, and is further complicated by the disease's deadly interaction with HIV/AIDS and the rise of multi-drug resistance (MDR-TB). These factors underscore the urgent public health need for new TB therapies.

Five years ago, the Working Group on TB Drug Development established as its goal the development of new, affordable TB drugs that would: 1) simplify or reduce the necessary duration of treatment to 2 months or less; 2) effectively treat MDR-TB; and, 3) provide treatment for patients with latent TB infection. It was recognized at the time that drug development in general was a slow process (8 to 12 years), and that TB drug development, in particular, could not rely on traditional market forces for sustainability.

For the first time in 40 years, there is a portfolio of promising new compounds poised to become the cornerstone drugs of TB control (Table 1). This remarkable achievement is the result of critical collaborations between public and private partners that have leveraged the scientific and clinical knowledge of industry, the public health sector, and world-wide academic laboratories. This portfolio would not be possible without support and funding from private foundations, governments and industry.

Table 1 – Global TB Drug Portfolio April 2005

DISCOVERY		
Cell Wall Inhibitors NIAID, Colorado State University	Methyltransferase Inhibitors Anacor Pharmaceuticals	Picolinamide Imidazoles NIAID, TAACF
Dihydrolipoamide Acyltransferase Inhibitors NIAID, Cornell University	Natural Products Explorations NIAID, TAACF, Cal. State Univ., Univ. of Auckland	Pleuromutilins GlaxoSmithKline, TB Alliance
Dipiperidines Sequella Inc.	Nitrofuranyl amides NIAID, University of Tennessee	Pyrroles TB Alliance, Wellesley College
InhA Inhibitors GlaxoSmithKline, TB Alliance	Nitroimidazole Analogs Novartis Institute for Tropical Diseases, NIAID, TB Alliance	Quinolones KRICT/Yonsei University, NIAID, TAACF, TB Alliance
Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, TB Alliance	Novel Antibiotic Class GlaxoSmithKline, TB Alliance	Proprietary Compounds AstraZeneca
Macrolides TB Alliance, University of Illinois at Chicago		Thiolactomycin Analogs NIAID, NIH

PRECLINICAL		
Diamine SQ-109 Sequella Inc.	Nitroimidazole PA-824 Chiron Corporation, TB Alliance	Translocase I Inhibitors Sequella Inc., Sankyo
	Synthase Inhibitor FAS 20013 FASgen Inc.	
CLINICAL TESTING		
Diarylquinoline R207910 Johnson & Johnson	Moxifloxacin Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins Univ., NIAID, TBRU	Proprietary Compound Otsuka
Gatifloxacin OFLOTUB-TDR, Tuberculosis Research Centre, NIAID, TBRU		Pyrrole LL-3858 Lupin Limited

Figure 1 – TB Drug Development Pipeline

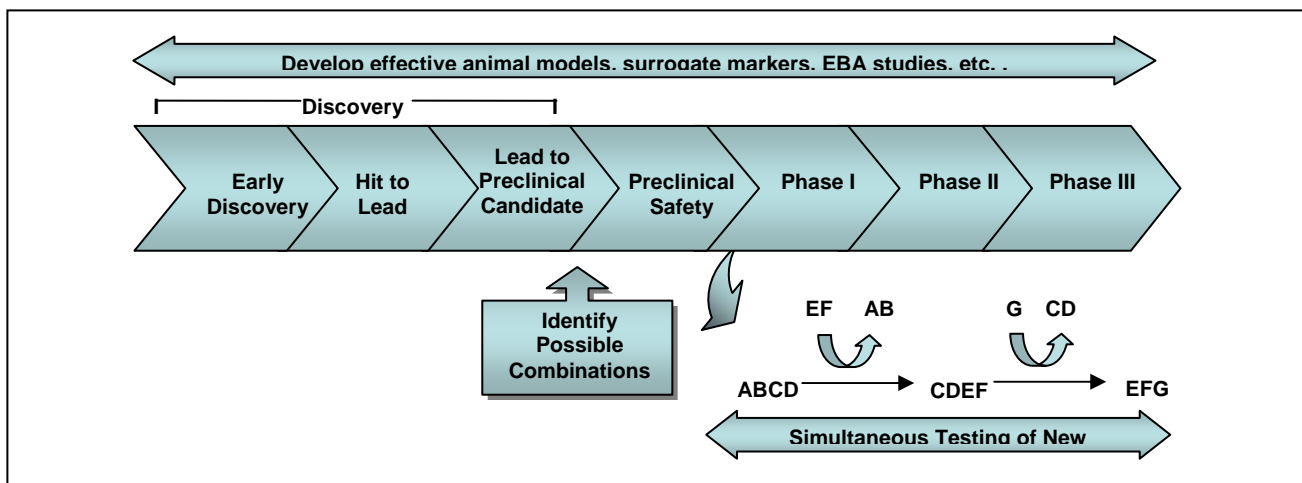


Figure 1 and Table 1 show research and development (R&D) activity in virtually all stages of TB drug discovery and development – from early discovery projects through to phase clinical testing. The drug candidates in the portfolio originate from two sources: 1) novel chemical entities; and 2) compounds from existing families of drugs, where innovative chemistry helps to optimize compounds. Examples of category 1) include molecules like the nitroimidazole PA-824, the diarylquinoline R207910, and the pyrrole LL-3858. Included in category 2) are molecules in the quinolone and macrolide families, compounds that are derivatives of various first-line drugs (e.g. ethambutol and isoniazid) and newer fluoroquinolone antibiotics (e.g. moxifloxacin and gatifloxacin) all of which have shown potent activity in vitro against *M. tuberculosis*. These compounds, their respective developers and the projected timetable of activities are shown in Table 2. Still to come are the expected products of rational drug design based on mycobacterial genetics and pharmacogenomics. These products should further enrich this promising group of candidate drugs.

Global Plan to Stop TB: 2005 – 2015:

a. Strategic Vision

The Working Group on TB Drug Development (WGDD) envisions an environment by 2015 that will allow for the sustained development of new TB drugs that can ultimately be combined into completely novel and revolutionary TB regimens. The lessons learned since the introduction of the existing anti-TB drugs are that continued worldwide commitment, research and vigilance toward a consistent pipeline of new antimicrobials are required to eradicate tuberculosis within the 21st century.

Specifically, the WGDD's goal is to have a new TB regimen that will cure in 1-2 months or less, will be effective against MDR-TB, will be compatible with anti-retroviral treatments and will be effective against latent TB infection. In addition, the new regimen must be affordable and easily managed in the field. It is recognized that this goal is exceedingly challenging but is imperative if we are to change the face of TB therapy. It is conceivable, should continued progress be made in the basic understanding of the biology of *Mycobacterium tuberculosis* (*M Tb*), that the course of therapy could be reduced even further, to 10-12 days, before 2050.

To achieve this vision, the WGDD has identified the following areas of strategic importance: i) basic discovery biology to identify new targets and candidate compounds using creative medicinal chemistry; ii) drug development R&D; iii) more effective clinical trial planning and execution, including identification of improved biomarkers and methods of assessing latent disease; and iv) clear and efficient regulatory guidance and processes. Sections (b) and (c) of this document outline the goals and objectives set forth for the next 10 years.

The WGDD recognizes that affordability, adoption and access to new drugs and the implementation of new regimens are intimately linked to manufacture and production of medicines, alone or in combination, and to the adoption of such therapies as international standards. The WGDD therefore will continue to work closely with the other Working Groups of the Stop TB Partnership, ministries of health, international health agencies and in-country field workers to understand these needs thereby ensuring rapid and successful introduction and adoption of the new regimens.

Drug development is an expensive enterprise. The momentum achieved in the past five years has only been possible because of the financial commitment made by public and private entities. To implement the vision set forth by the WGDD, substantial additional resources will be needed over the next 10 years. These are further detailed in Section (d).

b. Objectives, target and indicators:

i. Discovery biology and chemistry

The current standard "short-course" treatment regimen requires at least 6 months to eliminate persisting *M. tuberculosis* that remain a viable threat to health for long periods of time despite daily treatment. By 2015, the objective of the WGDD is to have identified and validated drug targets for persistent bacilli and latent disease. This requires a concerted international effort to develop a comprehensive understanding of the basic biology of persistence and latency so that new agents in development can effectively eliminate this organism phenotype rapidly.

Targets

- Inclusion of related goals in the research funding opportunities announced by major research funders (e.g., NIH, MRC, INSERM, Wellcome Trust, etc)
- Identification of novel drug targets and specific inhibitors
- Publication of 10 validated drug targets
- Broad access to validated bioassays including high throughput screening to identify new drug candidates in a timely fashion.

Indicators

- Number of candidate targets validated by molecular biology and animal experiments
- Number of developed country research funders who have announced funding opportunities
- Number of relevant announcements offering at least \$5 million in total awards

A second objective is to understand fully the mode of action of all compounds under development. This objective is important to devise novel and enhanced molecules for specific drug targets thereby maximizing their bactericidal and sterilizing activity. The WGDD further recognizes that there is a unique opportunity to select proactively and combine a new generation of TB drugs to obtain maximum therapeutic impact by putting together rational combinations of these compounds. Specifically, the target by 2015 is to ascertain the mechanisms of action of the drugs in the global portfolio to generate complementary or even synergistic combinations effective against the mycobacteria.

Targets

- Elucidate modes of action

- Validate combinations

Indicators

- Number of new drugs with mode of action identified
- Confirmed laboratory data for effective new combination regimens in vitro and in vivo
- Number of new mechanism-based regimens in at least 1 clinical trial
- Number of new candidate targets for which at least 1 compound has entered pre-clinical testing

ii. Drug development R&D

The objective by 2015 is to have a sustainable portfolio of new drug candidates under development that meet the drug profile criteria required for the 1-2 month therapy outlined in the new strategic vision of the WGDD.

As shown in Table 1, there are 9 compounds with novel modes of action that are currently in or approaching clinical development. Some of these compounds, as is the case for moxifloxacin, have been shown to reduce treatment time in animal models. The target, by 2010, is the introduction of a new drug or combination of drugs that can reduce time of treatment to 3-4 months.

There are new *in vitro* data suggesting that compounds under development can reduce treatment duration even further. Genomic and microbiological research from some of our members on novel targets against latent organisms provides optimism that a one-month treatment for TB may be attainable and could be in clinical trials in the 2015 timeframe of this report. Combining agents that attack different targets in a new regimen maximizes the therapeutic effectiveness. Therefore, the target for 2015 is the clinical testing of a rational drug combination therapy that can reduce the required time of treatment to 1-2 months or less.

Targets:

- Sustained pipeline of new drug candidates
- Introduction of a new drug or combination by 2010
- Development of rational combination to reduce treatment to 1-2 months by 2015

Indicators:

- Number of clinical trials initiated evaluating a shortened TB treatment regimen
- Number of candidates in discovery phase, e.g. 10 in lead identification stage
- Published data supporting shortened treatment using in vitro and in vivo models
- Number of drugs or formulations in development with once-daily dosing
- Number of candidates with minimized side effects
- Documented tolerance of candidate therapies in human volunteers
- Number of candidate drugs with minimal effects of food on bioavailability
- Number of candidates with no significant impact on cytochrome P450 isoenzyme activities to help ensure compatibility with HIV/AIDS therapies

Successful drug development is predicated on strong pre-clinical and clinical testing, careful monitoring and strong portfolio management. If a compound is to fail in development, it is preferable that it does so early. Animal models that can predict compound activity and side effects as well as validated surrogate markers that are broadly adopted by TB drug developers are urgently required.

Targets

- Development of a standard animal model that reliably predicts efficacy in humans
- Development of 1 or more surrogate markers to give confidence of sterilization within 6 months

Indicators

- Number of animal models developed
- Number of animal models with demonstrated reliability in prediction of efficacy

- Number of animal models that reliably predict tolerability
- Number of surrogate markers reliably demonstrated to predict outcome at 2 years
- Percent reduction in required follow-up period

iii. Clinical Trial Planning and Execution

The objective is the timely start and conduct of clinical trials according to appropriate regulatory requirements and highest ethical standards. This demands clinical trial sites with trained personnel, sound infrastructure and appropriate procedures for patient recruitment, compliance and retention. Proof of cure in TB will require lengthy clinical trials. Thus, biomarkers and surrogate endpoints must be developed as part of a translational research strategy to speed future clinical development programs. Testing programs that enable more rapid and precise dose selection and optimization of complementary drug combinations are also needed.

Targets

- Clinical trial capacity to evaluate 3 promising and complementary candidate drugs for treatment of active TB up to Phase 3 within 5 years
- Clinical trials capacity to evaluate 2 promising candidate drugs for treatment of latent TB infection up to Phase 3 within 5 years
- Establish an effective one/two month regimen for the treatment of tuberculosis by 2015
- Establish a network of trial sites capable of an annual enrolment capacity of at least 5,000 cases
- Clinical trials capacity sufficient to enrol up to 2,000 patients for each Phase 3 trial
- Timely registration of compounds

Indicators

- Mapping project to identify trial sites and data centers with appropriate microbiology, staff, and ICH 6 Good Clinical Practice guidelines in place
- Expansion of global TB clinical trials enrollment capacity to 5,000 patients annually with active TB disease
- Expansion of global TB clinical trials enrollment capacity to 5,000 patients annually with latent TB infection
- Outcomes in pre-clinical and early (Phase I and II) clinical trials for each drug tested
- Sites with an annual incidence of new cases of greater than 200
- Sites with laboratories capable of carrying out microscopy, culture and susceptibility tests
- Sites with GCP to international standards

iv. Regulatory approval and registration

There has been a hiatus in TB drug development of over 40 years and there are not TB-specific regulatory guidelines for drug development. Therefore, as portfolio compounds enter into clinical development it is imperative that harmonized regulatory guidelines, including fast-track approval, become available for TB drug developers world-wide. This will require open and active dialogue during the next decade among the drug development groups, the regulatory agencies and external experts to define and agree on novel trial approaches and registration criteria for TB drugs.

Targets

- Approval of surrogate markers for conditional registration of therapies for treatment of TB disease
- Expansion of global expertise in monitoring of clinical trials
- Approval of new drugs, singly and in combination

Indicators

- Number of surrogate markers approved by at least one developed country regulatory agency
- Number of agencies approving each proposed surrogate marker
- Number of drugs completing registration process
- Number of entities with trained and funded clinical trial monitors

c. Activities, timelines and milestones:

Discovery biology and chemistry.

Many promising discovery activities are on-going in 2005 by Working Group partners and are likely to bring forth several new lead candidates by 2015 (Tables 1 and 2). Novartis Institute for Tropical Diseases/TB Alliance/NIAID has an ongoing collaboration on the nitroimidazole analog class. GlaxoSmithKline/TB Alliance is assessing candidates in the classes of pleuromutilins, isocitrate lyase inhibitors, and InhA inhibitors. Astrazeneca Pharmaceuticals, the Gates Grand Challenge awardees, investigators at St. George's Hospital Medical School, and university researchers supported by the U.S. National Institutes of Health are exploring the nature of the *M. tuberculosis* proteasome in persistence and developing assays and strategies to attack slowing replicating mycobacteria. The Tuberculosis Structural Biology Consortium and individual investigators continue to decipher the large *M. tuberculosis* genomic sequence and purify specific proteins for docking new inhibitors into enzyme active sites. The Institute for Tuberculosis Research, University of Illinois/TB Alliance is exploring the biology and chemistry of newer macrolide antibiotics. Several discovery programs are testing natural products from plants and ocean sources, performing combinatorial and focused chemistry around known antituberculars, synthesizing analogs to attack novel targets (such as methyl transfersase, complex lipid transporters), and screening new libraries of proven antibiotics (quinolones, oxazolidinones, quinolines, etc.). NIAID TB drug development contractors (www.taacf.org) provide services to screen new chemical entities from laboratories throughout the world and to objectively assess and compare candidates in animal model efficacy tests. Key milestones in discovery include factors such as drug-likeness (solubility, medicinal chemistry, metabolic stability), structure-activity relationships for specific target, selectivity for the target, cell-based toxicity assessments, molecular mode of action, and efficacy in an appropriate animal model of disease. The WGDD will support meetings and other information sharing activities to inform partners on global activities and progress towards number of preclinical candidates entering development.

Drug Development R&D

At least 7 compounds are in clinical or advanced preclinical development (Table 2.) in 2005 by several sponsors. The key milestones for these efforts will be achieved when lead compounds meet sponsor criteria set for advancement of leads into advanced preclinical development. Most of the go/no go decisions are driven by the development plan and are predicated by how the new drug will be used clinically. Thus, criteria may differ in parameters for milestones between a drug to be added to existing regimens with daily dosing for many months versus a drug that may be used for prophylaxis with intermittent dosing. Animal safety tests, pharmacokinetic and pharmacodynamic characterizations, spectrum of microbial activity including resistant-TB strains, chemical synthesis routes, and cost of goods factor into the decision for entry into Good Laboratory Practice (GLP) animal safety studies. These tests are lengthy, expensive and require large amounts of purified compound. These formal reports are included into submissions to regulatory agencies for Investigational New Drug Applications (IND). A critical milestone is IND submission as it indicates that a candidate has passed the sponsor's go/no go decision processes with objective data generated by a GLP-certified laboratory. A second critical milestone is approval by regulatory agencies for entry into Phase I human safety trials, followed by initiation of Phase II and III trials leading to a New Drug Application (NDA). If the compiled data from all these studies are convincing to the regulatory agencies, a new drug or new indication will be launched and registered.

It must be acknowledged that drug candidate attrition throughout R&D in drug development is a significant risk for sponsors both in terms of time and funds. Only about 10% of candidates that enter the advanced pipeline actually make it to the next phase, mostly due to safety concerns. Thus, the robust pipeline of new candidates and back-up discovery programs is absolutely essential to success. As new drug entities arise as candidates, the WGDD will assist in early communication among partners to begin modeling for drug compatibility and complementarities in efficacy. The Working Group for Drug Development serves as a venue for interaction between partners to increase efficiencies and decrease risk for the process as a whole.

Table 2. Drugs in development and timetable towards launch

Compound/Project (Developer)	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Gatifloxacin (OFLOTUB/TDR, TB Research Centre, NIAID, TBRU)	II	II	II/III	III	III	III/NDA					
Moxifloxacin (Bayer, CDC TBTC, Johns Hopkins Univ. NIAID, TB Research Centre, TBRU)	II	II	II/III	III	III	III/NDA					
Diarylquinoline R207910 (Johnson & Johnson)	I	I/II	II	II/III	III	III	III	NDA			
Proprietary Compound (Otsuka)	I	I/II	II	II/III	III	III	III	NDA			
Pyrrole LL3858 (Lupin Limited)	I	I/II	II	II/III	III	III	III	NDA			
Nitroimidazole PA-824 (Chiron Corporation, TB Alliance)	I	I	I/II	II	II/III	III	III	III	NDA		
Diamine SQ-109 (Sequella Inc.)	I	I	I/II	II	II/III	III	III	III	NDA		
Quinolones (KRICT/TB Alliance)	D	D	PC	PC	I	I/II	II	II/III	III	III	III
Nitroimidazole Analogs (NITD, NIAID, TB Alliance)	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
Macrolides (Univ. of Illinois, TB Alliance)	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
Pleuromutilins (GlaxoSmithKline, TB Alliance)	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
Methyltransferase Inhibitors (Anacor)	D	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III
Isocitrate Lyase Inhibitors (ICL) (GlaxoSmithKline, TB Alliance)	D	D	D	D	PC	PC	I	I/II	II	II/III	III
Pyrroles (TB Alliance, Wellesly College)	D	D	D/PC	PC	PC/I	I	I/II	II	II/III	III	III
InhA Inhibitors (GlaxoSmithKline, TB Alliance)	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III	III
Novel Antibiotic Class (GlaxoSmithKline, TB Alliance)	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III	III
Proprietary Compounds (AstraZeneca)	D	D	D	PC	PC	I	I/II	II	III	III	III
Ethambutol Analogs (Sequella Inc.)	D	D	D	D	D	PC	PC	I	I/II	II	II
Translocase I Inhibitors (Sequella Inc., Sankyo)	D	D	D	D	D	PC	PC	I	I/II	II	II

d. Summary text on resource needs

One of the most significant expenses in drug development involves the financing of large-scale clinical trials. These are costly both because of the large numbers of persons required (due to the very low rates of failure and relapse achievable with current short-course regimens) and because of the long duration of follow-up (currently 2 years) required to ascertain rates of relapse. If we are to move a large number of promising compounds and regimens rapidly through phase 2 and 3 trials, then a significant expansion of global capacity in TB clinical trials will be needed. Examples include:

Clinical trial planning and execution will involve multiple partners and the resources for meetings and clinical protocol development. Establishment of central data centers and the standardization of reporting system, definitions of adverse events, toxicity monitoring, standardized clinical laboratory values, microbiology standardization, disease and endpoint definitions, data and safety monitoring boards are critical factors that require resources and extensive time. Monitoring for resistance and obtaining resistance profiles on isolates requires the ability to culture and perform advanced testing of isolates. Although this is best performed at the clinical site, few laboratories in high burden countries are adequately equipped for this task either in facilities or trained personnel.

Regulatory approval and registration requirements in multiple countries can be complex and must be harmonized broadly for large clinical trials. The necessity to include persons with HIV infection may add significantly to patient stratifications for stage of disease and outcome measures may be different

Manufacturing, production, and distribution of clinical product must be considered in light of the cold supply chain, pharmacy inventory controls, and patient acceptability. Fixed dose combinations of new drugs will require formulations development, stability and dissolution and bioavailability assessments prior to introduction.

The WGDD will need to facilitate these types of factors by strategic planning and providing resources in advance of clinical trial execution. Substantial capital investment is likely for successful new drugs to become available to the world.

e. Monitoring and evaluation

An important function of the WGDD will be to annually map progress among the partners and other entities that may enter drug development for TB. A small database of projects, compounds, and clinical trials will be established to survey the current status worldwide.

The careful monitoring and evaluation of a large number of clinical trials is expensive. Modest initiatives to expand this capacity are underway at WHO/TDR, but are unlikely to satisfy the demand created by the initiation of multiple regulatory-quality TB clinical trials. The development of international monitoring standards and increased global monitoring ability are needed to assure that promising agents are not impeded in their progress towards registration and utilization to curtail the global TB epidemic.

f. Key risk factors

New TB drug development is founded on efficacy, safety, and affordability. Within the industry, only 1 in 10 new, first-in-human drug candidates progress to large clinical trials. Thus, the WGDD recognizes that the portfolio must be robust with a continual pipeline of candidates entering clinical evaluation.

With the highest burden countries experiencing infectious disease emergencies in HIV/AIDS and TB concomitantly, the paradigm of new drug clinical evaluation is becoming more and more complex. All novel compounds are screened for toxicity, adverse metabolic effects, drug-drug interactions with anti-retroviral therapies, etc. during preclinical development. Careful selection of new drug candidates is imperative given the extensive co-morbidities reported between the HIV and TB epidemics. In particular, expanded capacity for human pharmacokinetic and drug-drug interaction studies will be needed. Such capacity is typically available only in specialized centers with substantial infrastructure. Expansion of this capacity will be necessary to assure that an adequate human clinical database is available for each compound in a timely manner appropriate to these latter phases of development.

Clinical sites for testing of the new drugs in the pipeline exist; however, these centers will be under severe pressure based on the projected activity.

Sustainability

Industry undoubtedly commands the majority of drug discovery and development capacity in the world, and in some specialized areas (e.g., medicinal chemistry), possesses virtually the entirety of existing expertise. The financial realities of TB drug development require that the philanthropic and public sectors participate financially with industry to assume some of the risks involved in candidate drug development. One logical domain in which the public and philanthropic sectors can contribute is in the area of clinical trials capacity. Thus, the global plan proposes quite substantial contributions from these sectors towards the development of expanded clinical trials capacity. It is envisioned that this expansion will take place primarily in the developing world, where this effort will de facto contribute to the development of individual technical skills and the strengthening of program expertise in planning and evaluation.

WORKING GROUP: TB Drug Development 2006 - 2010			
Activities	Financial needs		
	Budget	Funding	Financial gap
Objective 1. Facilitation of Drug Discovery and Development R&D <ul style="list-style-type: none"> ▪ Sustain the pipeline of new drug candidates ▪ Define drug profiles for active disease and for latent infection ▪ Compile resource guides to available tools and data banks for drug development ▪ Facilitate assess to validated bioassays and screening ▪ Identify novel drug targets and specific inhibitors ▪ Elucidate modes of action of drug candidates ▪ Develop a standard animal model that reliably predicts efficacy in humans ▪ Identify resources to validate combinations preclinically ▪ Develop rational combinations to reduce treatment to 1-2 months ▪ Develop surrogate markers for sterilization ▪ Introduce a new drug or combination by 2010 			
Objective 2. Facilitation/Implementation of Global Clinical Trials <ul style="list-style-type: none"> ▪ Establish a network of trial sites capable of an annual enrolment capacity of 5,00 cases ▪ Evaluate enrolment, laboratory and GCP ▪ Conduct a 6-month RCT with existing drugs ▪ Develop clinical trial capacity to evaluate 3 promising and complementary candidate drugs for treatment of active TB up to Phase 3 within 5 years ▪ Develop clinical trials capacity to evaluate 2 promising candidate drugs for treatment of latent TB infection up to Phase 3 within 5 years ▪ Develop standards for monitoring and evaluation of clinical sites and laboratories ▪ Identify and standardize data centers and reporting systems ▪ Conduct a pivotal Phase III RCT to test a 4-month regimen ▪ Commence Phase 3 clinical trials 			
Objective 3. Communications and Advocacy <ul style="list-style-type: none"> ▪ Increase research funding opportunities by major research funders ▪ Develop white papers for publication ▪ Develop web-based projects for mapping activities 			
Objective 4. Working Group Coordinating Activities <ul style="list-style-type: none"> ▪ Mapping of drugs in development ▪ Annual meeting of partners in drug development ▪ Interactions and meetings with other STOP-TB working groups ▪ Information and publications 			
Total research needs (Objectives 1-3)			
Total Working Group running costs (Objective 4)			
TOTAL 2006 - 2010			