Strategic Plan

Stop TB Partnership Working Group on New TB Drugs

Prepared for the
Global Plan to Stop TB:
2006–2015

Working Group
on new TB drugs

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ACHIEVEMENTS: 2000–2005

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 New TB Drugs 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 coordinated portfolio of promising new compounds, some of which have the potential to become the cornerstone drugs of TB control and even to contribute to the elimination of TB in the future (see Table 1). This remarkable achievement is the result of critical collaborations between public and private partners, which 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 governments, foundations, and industry.

Table 1 shows research and development (R&D) activity in virtually all stages of TB drug discovery development—from early discovery projects through to clinical phase 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 is used to help optimize compounds. Examples of the first category include molecules like the nitroimidazole PA-824, the diarylquinoline TMC207, and the pyrrole LL-3858. Included in category (2) are molecules in the macrolide family, compounds derived from various first-line drugs (e.g. ethambutol and isoniazid) and newer fluoroquinolone antibiotics (e.g. moxifloxacin and gatifloxacin), all of which show potent activity *in vitro* against M. *tuberculosis*. These compounds and the projected timetable of activities are shown in Table 2 later in this document. There are also other, still-unexploited opportunities, such as the expected products of rational drug design based on mycobacterial genetics and pharmacogenomics, as well as natural products exploration. These products should further enrich this promising group of candidate drugs.

Table 1—Global TB Drug Pipeline (September 2005)

DISCOVERY		PRECLINICAL	CLINICAL TESTING
Carboxylates TB Alliance, Wellesley College	**Nitrofuranylamides** NIAID, University of Tennessee	**Diamine SQ-109** Sequella Inc.	**Diarylquinoline TMC207** Johnson & Johnson
Cell Wall Inhibitors Colorado State University, NIAID	**Nitroimidazole Analogs** NIAID, Novartis Institute for Tropical Diseases, TB Alliance	**Dipiperidines (SQ-609)** Sequella Inc.	**Gatifloxacin EC** OFLOTUB—Consortium, Lupin Ltd., NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Dihydrolipoamide Acyltransferase Inhibitors Cornell University, NIAID	**Novel Antibiotic Class** GlaxoSmithKline, TB Alliance	**Non-Fluorinated Quinolone** TaiGen.	**Moxifloxacin** Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance
InhA Inhibitors GlaxoSmithKline, TB Alliance	**Picolinamide Imidazoles** NIAID, TAACF	**Synthase Inhibitor FAS20013** FASgen Inc.	**Nitroimidazole PA-824** Chiron Corporation, TB Alliance
Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, TB Alliance	**Pleuromutilins** GlaxoSmithKline, TB Alliance	**Translocase I Inhibitors** Sequella Inc., Sankyo	**Proprietary Compound** Otsuka
Macrolides TB Alliance, University of Illinois at Chicago	**Quinolones** KRICT/ Yonsei University, NIAID, TAACF, TB Alliance		**Pyrrole LL-3858** Lupin Limited
Methyltransferase Inhibitors Anacor Pharmaceuticals	**Screening and Target Identification** AstraZeneca		
Natural Products Exploration BIOTEC, California State Univ., ITR, NIAID, TAACF, University of Auckland	**Thiolactomycin Analogs** NIAID, NIH		

STRATEGIC VISION: 2006–2015

The Working Group on New TB Drugs (WGND) 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. One of the lessons learned since the introduction of the existing anti-TB drugs is that continued worldwide commitment, research and vigilance to ensure a consistent pipeline of new antimicrobials will be required to eradicate tuberculosis in the 21st century.

Specifically, the WGND's vision is to have new TB regimens that will achieve cure in 1-2 months or less, be effective against MDR-TB, compatible with antiretroviral drugs used for treating HIV/AIDS and effective against latent TB infection. In addition, new regimens must be affordable and easily managed in the field. It is recognized that this goal is ambitious, but it is imperative that we succeed if we are to change the face of future TB therapy. It is conceivable, should progress continue to be made in the basic understanding of *Mycobacterium tuberculosis* (*M.tb*) biology, that the course of therapy could be reduced even further, to 10-12 days before 2050, or that other advances in therapeutic or prophylactic options not available today may also greatly reduce TB incidence.

To achieve this vision, the WGND has identified the following areas of strategic importance:

- basic discovery biology to identify and validate new targets and identify candidate compounds using effective screens and creative medicinal chemistry;
- drug development;
- more effective clinical trial planning and execution, including identification of improved biomarkers and methods of assessing latent disease; and
- clear and efficient regulatory guidance.

This document outlines the goals and objectives set forth for the next 10 years.

The WGND recognizes that affordability, adoption and access to new drugs and the implementation of new regimens are intimately linked to the manufacture and production of medicines, alone or in combination, and to the adoption of such therapies as international standards. The WGND will therefore 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, successful introduction and adoption of the new regimens in the field.

In areas of high HIV/AIDS prevalence, such as sub-Saharan Africa, new therapies are urgently needed so that TB and HIV treatment can be administered

concurrently, avoiding dangerous drug-drug interactions that occur with the medicines available today. The WGND recognizes the urgency of developing new therapeutic interventions if we are to achieve the Millennium Development Goals and the Partnership's targets in this region, and is striving to make these innovative therapies available as soon as possible.

Drug R&D is an expensive enterprise. The momentum achieved in the past five years has been possible because of the financial commitment made by public and private entities. To implement the vision set forth by the WGND, substantial additional resources and political commitment will be needed over the next 10 years.

OBJECTIVES, TARGETS AND INDICATORS

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. Current treatment for latent TB infection is a 9-month course of isoniazid. By 2015, if not earlier, the objective of the WGND is to identify and validate drug targets for both persistent bacilli and latent disease. Meeting this goal will require concerted international efforts to develop a comprehensive understanding of the basic biology of persistence and latency so that new agents in development can effectively and rapidly eliminate organism with these phenotypes.

A second objective is to understand fully the mode of action of all compounds under development. This knowledge is important in devising novel, enhanced molecules for specific drug targets, thereby maximizing their bactericidal and sterilizing activities. The WGND further recognizes that there is a unique opportunity to proactively select and combine a new generation of TB drugs, with the goal of obtaining maximum therapeutic impact, by putting together rational combinations of these compounds. *M.tb* is an unusual pathogen in that it shows no horizontal exchange of drug resistance (e.g. through plasmids); therefore, the introduction of multiple novel drugs in fixed combination should not only treat existing drug-resistant strains but, if properly managed, can eliminate the potential for future resistance. Specifically, the goal by 2015 is to determine the mechanisms of action of drugs in the global portfolio and then to use this information to generate complementary or even synergistic combinations effective against the mycobacteria.

Recognizing the promise of multiple drug discovery approaches, the WGND pursues a balanced approach to drug development, which involves maximizing new target identification and screening, medicinal chemistry, combinatorial chemistry, and natural products exploration methods.

Drug Development

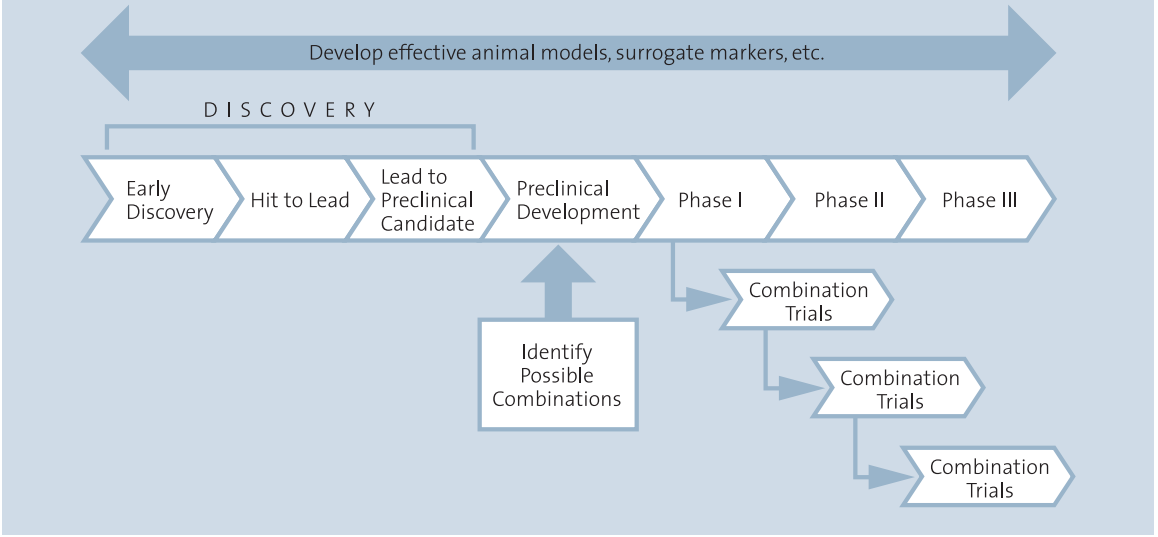
The objective by 2015 is to have in development a sustainable portfolio of new drug candidates under development that meet the drug profile criteria required for the 1–2 month therapy outlined in the new strategic vision of the WGND outlined above.

As Table 1 shows, there are 11 compounds with novel modes of anti-TB action currently in or approaching clinical development. Some of these compounds, such as moxifloxacin, have already been shown to reduce treatment time in animal models. The interim goal, by 2010, is therefore the introduction of a new drug or combination of drugs that can reduce time of treatment to 3-4 months.

New *in vitro* data suggest that compounds under development can reduce treatment duration even further. Genomic and microbiological research on novel targets in persistent organisms provides reason for optimism that a one-month TB treatment may be attainable and could be in clinical trials by the 2015 timeframe of this report. New regimens that combine agents which attack different targets should maximize therapeutic effectiveness. Therefore, the goal for 2015 is to bring into clinical testing a rational combination drug therapy that can reduce the required treatment time to 1-2 months or less.

Figure 1 outlines the drug development process from discovery to registration, including the proposed concurrent testing of multiple rational drug combination therapies.

Figure 1—TB Drug Development Pipeline



Successful drug development is predicated on preclinical 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. To aid in the early identification of promising versus unpromising candidates, animal models that can predict compound activity and side effects, and validated surrogate markers that are broadly adopted by TB drug developers, are urgently required.

Clinical Trial Planning and Execution

The objective is the timely initiation and conduct of clinical trials according to appropriate regulatory requirements and the highest ethical standards. This demands clinical trial sites meeting Good Clinical Practice (GCP) and Good

Manufacturing Practice (GMP) standards, the international regulatory standards with which trials must comply to achieve registration of a drug. This, in turn, requires trained personnel, sound infrastructure and appropriate procedures for patient recruitment, compliance and retention.

Proof of cure in TB requires 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.

Regulatory Approval and Registration

TB drug development has essentially been at a standstill for over 40 years, and there are no TB-specific regulatory guidelines for drug development. Therefore, as portfolio compounds enter clinical development, it is imperative that harmonized regulatory guidelines, including fast-track approval, become available for TB drug developers worldwide. This will require open and active dialogue during the next decade among drug development groups, regulatory agencies and external experts to define and agree on novel trial approaches and registration criteria for TB drugs.

Objectives, Targets and Indicators

OBJECTIVE 1: Identify validated drug targets for persistent bacilli and latent disease.

TARGETS	INDICATORS
● Inclusion of related goals on TB drugs in the funding programs announced by major research funders (e.g., NIH, MRC, INSERM, European Commission, Wellcome Trust, etc.)	● Number of candidate targets validated by molecular biology and animal experiments
● Identification of novel drug targets and specific inhibitors	● Number of research funders who have announced funding opportunities
● Clarification among academics and industry on the criteria by which drug targets can be considered validated	● Number of relevant announcements offering at least $5 million in total awards
● Publication of 10 validated drug targets	● Number of relevant, validated bioassays available
● Broad access for TB drug developers to validated bioassays, including high throughput screening, to identify new drug candidates in a timely fashion	

Objectives, Targets and Indicators (continued)

OBJECTIVE 2: Ascertain mechanisms of action of drugs in the global portfolio to generate complementary or even synergistic combinations effective against *M.tb*.

TARGETS	INDICATORS
● Elucidate modes of action ● Validate combinations	● 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 preclinical testing

OBJECTIVE 3: Develop a sustainable portfolio of new drug candidates that meet the drug profile criteria.

TARGETS	INDICATORS
● A sustained pipeline of new drug candidates ● Introduction of a new drug or combination by 2010 ● Development of rational combinations to reduce treatment to 1-2 months by 2015	● Number of clinical trials evaluating shortened TB treatment regimens ● 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

OBJECTIVE 4: Develop animal models that can predict compound activity and side effects, and validated surrogate markers that are broadly adopted by TB drug developers.

TARGETS	INDICATORS
● 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 2 months	● Animal models developed that reliably predict tolerability and efficacy and require shorter observation periods ● At least one surrogate marker shown to reliably predict outcome at 2 years ● Percent reduction in length of required follow-up period

Objectives, Targets and Indicators (continued)

OBJECTIVE 5: Build clinical trial sites and initiate and conduct clinical trials that meet regulatory requirements and highest ethical standards. Develop biomarkers, surrogate endpoints and testing programs to speed future clinical development programs.

TARGETS	INDICATORS
● Within 5 years, develop sufficient clinical trial capacity to evaluate –evaluate 3 promising and complementary candidate drugs for treatment of active TB up to Phase III within 5 years –evaluate 2 promising candidate drugs for treatment of latent TB infection up to Phase III within 8 years –enroll up to 2,000 patients for each Phase III trial ● Establish an effective 1-2 month regimen for the treatment of tuberculosis by 2015 ● Establish a network of trial sites able to enrol at least 5,000 cases annually ● Ensure the timely registration of compounds	● 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 preclinical and early (Phase I and II) clinical trials for each drug tested ● Number of sites with an annual incidence of new cases of greater than 200 ● Sites with laboratories capable of carrying out microscopy, culture and susceptibility tests and surrogates as they are developed ● Sites with GCP and GLP international standards

OBJECTIVE 6: Establish harmonized regulatory guidelines, including fast-track approval for TB drug developers.

TARGETS	INDICATORS
● Approval of surrogate markers for conditional registration of TB therapies ● Expansion of global expertise in monitoring clinical trials ● Registration of new drugs, singly and in combination	● Surrogate marker(s) of cure or efficacy 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

ACTIVITIES, TIMELINES AND MILESTONES

Discovery Biology and Chemistry

Many promising discovery activities by Working Group partners are ongoing in 2005 and are likely to identify several new lead candidates by 2015 (see Tables 1 and 2). The Novartis Institute for Tropical Diseases, the TB Alliance and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) have an active collaboration on the nitroimidazole analog class. GlaxoSmithKline and the TB Alliance are 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* proteosome in persistence, as well as developing assays and strategies to attack slowly replicating mycobacteria.

The Tuberculosis Structural Biology Consortium and individual investigators continue to decipher the large M. *tuberculosis* genomic sequence and crystallize M.*tb* proteins to better understand potential targets and design inhibitors. The Institute for Tuberculosis Research, University of Illinois and the TB Alliance are studying 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 steps such as identification of compounds with drug-like qualities (solubility, medicinal chemistry, metabolic stability), development of structure-activity relationships for a specific target, achievement of selectivity for the target, completion of cell-based toxicity assessments, identification of molecular mode of action and demonstration of efficacy in an appropriate animal model of disease. The WGND will support meetings and other information-sharing activities to inform partners about global activities and progress towards increasing the number of preclinical candidates entering development.

Drug Development

Eleven compounds are currently in clinical or advanced preclinical development (Table 1) by several sponsors. The key milestones for discovery-stage compounds will be achieved when lead compounds meet sponsor criteria for the advancement of leads into advanced preclinical development. Most of the go/no-go decisions are driven by the development plan and are predicated on how the new drug will be used clinically. Thus, criteria for these milestones may differ between a drug that would be added to existing regimens, with daily dosing for many months, versus a drug that would 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 all affect the decision to move a candidate into Good Laboratory Practice (GLP) animal safety studies, which require lengthy, expensive tests and large amounts of purified compound.

These data are included in the package developers submit to regulatory agencies for Investigational New Drug Applications (IND)—a step that represents a critical milestone for experimental drugs since 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. This is followed by initiation of Phase II and III trials, which lead 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 registered and launched.

*Table 2—Selected Drugs in Development: Timetable Towards Launch**

Compound/ Project	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Gatifloxacin	II	II	II/III	III	III	III/NDA					
Moxifloxacin	II	II	II/III	III	III	III/NDA					
Diarylquinoline TMC207	I	I/II	II	II/III	III	III	III	NDA			
Otsuka Compound	I	I/II	II	II/III	III	III	III	NDA			
Pyrrole LL3858	I	I/II	II	II/III	III	III	III	NDA			
Nitroimidazole PA-824	I	I	I/II	II	II/III	III	III	III	NDA		
Diamine SQ-109	I	I	I/II	II	II/III	III	III	III	NDA		
Quinolones	D	D	PC	PC	I	I/II	II	II/III	III	III	III
Nitroimidazole Analogs	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
Macrolides	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
Pleuromutilins	D	D	PC	PC	PC/I	I	I/II	II	II/III	III	III
AstraZeneca Screening and Target Identification	D	D	D	PC	PC	I	I/II	II	III	III	III
Isocitrate Lyase Inhibitors	D	D	D	D	PC	PC	I	I/II	II	II/III	III
InhA Inhibitors	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III	III
Novel Antibiotic Class (GSK/TB Alliance)	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III	III
Methyltransferase Inhibitors	D	D	D	D	D/PC	PC	PC/I	I	I/II	II	II/III

**Timetable based on information provided as of September 2005.*

It must be acknowledged that drug candidate attrition throughout drug R&D is a significant risk for sponsors in terms of both time and funds: Only about 10% of candidates that enter the clinical pipeline advance to registration, mostly due to safety concerns. Thus, a robust and sustained pipeline of new candidates and back-up discovery programs is absolutely essential to success. As new drug entities are identified as potential candidates, the WGND will assist in early communication among partners to begin modeling for drug compatibility and complementarities in efficacy. The Working Group on New TB Drugs serves as a venue for interaction among partners to increase efficiencies and decrease risk for the process as a whole.

Clinical Trial Planning and Execution

Clinical trials using tuberculosis drugs are being conducted around the world in sites sponsored by organizations such as the National Institute of Pharmaceutical Education and Research (NIPER), CDC's Tuberculosis Trials Consortium (TBTC), the European and Developing Countries Clinical Trials Partnership (EDCTP), the South African Medical Research Council (MRC), the International Union against Tuberculosis and Lung Disease (IUATLD), the National Institute of Allergy and Infectious Diseases (NIAID), and the NIAID/Case Western Reserve University-funded Tuberculosis Research Unit (TBRU), among others. These sites have previously carried out trials successfully using existing drugs in a variety of combinations.

However, the need for clinical trials that meet registration-standard regulatory criteria is increasing dramatically as the new compounds under development reach preclinical milestones and go into humans. Because no centralized roster of qualified sites exists, clinical trial sites are being assessed individually and independently by the sponsors of each compound. Bilateral agreements are being established between principal investigators at each site and the sponsors, as is customary and appropriate. It is therefore expected that trials will commence as each site, or group of sites, is readied for the proposed trial and is not withdrawn from regulatory agencies. Table 2 illustrates the expected start for the trials, should the preclinical work be satisfactory and regulatory agencies allow the trials to proceed.

This process is time-consuming and leads to redundancies. Therefore, streamlining the clinical trial process by conducting a mapping exercise to identify registration-standard qualified sites worldwide is the first activity by the WGND in this category. It is expected that such mapping will be based on the information provided by members of the WG and finalized by late 2006. The WGND is committed to supporting these activities for the next generation of compounds by establishing a Clinical Trial Site Roster, which will outline the capabilities of each site, including all the regulatory assurances. The WGND Secretariat will compile and place this Roster in a database that will be made public via the internet at a readily available website, such as the Stop TB Partnership site.

Information gathered for the Clinical Trial Roster will also help assess the capacity for each site and identify the existing worldwide gaps, whether in human resources, ability to recruit patients, infrastructure needs or other areas. This assessment will inform the WG of the requirements to ensure viable, ethical and competent sites. This activity will be ongoing.

Regulatory Approval and Registration

Starting in 2006 and throughout the term of this strategic plan, as appropriate, the WGND will co-sponsor meetings with regulatory agencies in developed and endemic countries. The first such meeting will work towards establishing regulatory guidelines to allow registration of a new compound for the treatment of TB by 2010. Additional meetings and symposia sponsored or co-sponsored by the WGND to discuss, validate and help establish surrogate markers will take place yearly in conjunction with other international fora such as the IUATLD conference in Paris or the Gordon TB Research Conference.

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 study volunteers needed (due to the very low rates of failure and relapse seen with current short-course regimens) and because of the long duration of follow-up (currently up to 2 years) required to ascertain rates of relapse. If we are to move a large number of promising compounds and regimens rapidly through Phase II and III trials, then a significant expansion of global capacity in TB clinical trials will be needed.

Clinical trial planning and execution will involve multiple partners and resources for meetings and clinical protocol development. Resources and extensive time are also required to establish central data centers and standardize reporting systems, define and identify adverse events, monitor toxicity, determine standardized clinical laboratory values, microbiology standardization, disease and endpoint definitions, and establish data and safety monitoring boards. Monitoring for resistance and obtaining resistance profiles on isolates requires the ability to culture and perform advanced testing of isolates. Although this is best carried out at the clinical site, few laboratories in high burden countries are adequately equipped for this task in terms of either facilities or trained personnel.

TB drug development would also benefit greatly from the creation of better TB diagnostics. In already-lengthy clinical testing, long diagnosis times caused by archaic diagnostics hinder progress. Shortening time to the start of treatment translates into more efficiency in drug testing. Improved diagnosis of pediatric TB and sputum smear-negative TB would also greatly facilitate clinical trials in these patient populations.

As described above, regulatory approval and registration requirements in multiple countries can be complex and must be harmonized broadly for large, international clinical trials. The necessity of including volunteers with HIV infection may add significantly to patient stratifications for stage of disease, and outcome measures may also 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 WGND will need to facilitate the activities made necessary by this strategic planning and, therefore, to provide resources in advance of clinical trial launch. Substantial capital investment is necessary for successful new TB regimens to become available to the world.

MONITORING AND EVALUATION

An important function of the WGND will be to annually map progress among the partners and other entities that may enter drug development for TB. A 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.

KEY RISK FACTORS

New TB drug development is founded on the goals of achieving efficacy, safety, and affordability. Within the industry, only 1 in 10 new, first-in-human drug candidates achieve registration. Thus, the WGND 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 new drugs in the pipeline exist; however, these centers could be severely overburdened if projected activity in this area continues to grow.

Finally, while the responsibility of the WGND is to generate new medicines that treat TB faster and more effectively, the WG fully recognizes that these efforts will be for naught if the new regimens are not made readily available to patients. All members of the WG, as noted earlier, are committed to ensure affordability and strive to make their medicines broadly available. However, experience has shown that establishing and implementing standard treatments in the field can take years, particularly for TB. Because of this, and in order to reach the Partnership's targets of halving TB prevalence and death rates by 2015, all working groups and the international community will need to focus on the safe, prompt and effective adoption of new tools.

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 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 much of 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.

BUDGET REQUIREMENTS

APPENDIX 1. WORKING GROUP ON NEW TB DRUGS BUDGET REQUIREMENTS: 2006-2015

Activity	Costs[1]
1. Early-Stage Drug Development and Research	
Basic Research (Including physiology and mechanism of action studies)	$50,000,000
Lead Optimization	$1,950,000,000
Preclinical	$110,000,000
2. Clinical Trials	
Phase I Trials	$70,000,000
Phase II Trials	$500,000,000
Phase III Trials	$1,500,000,000
3. Regulatory Approval and Registration	
Registration	$5,000,000
4. Working Group Operations	
Meetings, Symposia and Consultations	$1,000,000
Publications and Coordination	$750,000
TOTAL COSTS	$4,186,750,000[2]
CURRENT RESOURCES	$620,250,000
GAP	$3,566,500,000

[1] *For detailed information regarding the derivation of these figures, please contact the Working Group on TB Drug Development at StopTBDrugWG@tballiance.org.*

[2] *Accounting for inflation, total costs rise to $4,800,000,000 for the 10-year period of the Strategic Plan.*

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