

### 10.3.2 Working Group on New TB Drugs: summary strategic plan, 2006–2015

The Working Group on New TB Drugs was established in 2000. Its goal is the development of new, affordable TB drugs. In 2005, 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 contribute to future elimination of TB.

#### Strategic vision: 2006–2015

The Working Group on New TB Drugs (WGND) envisages 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. Continued worldwide commitment, research and vigilance to ensure a consistent pipeline of new antimicrobials is required to eliminate tuberculosis within the twenty-first century.

TB control has long been hindered by the lengthy (6–8 months) and complex treatment required by current drugs, and is further complicated by the disease's deadly interaction with HIV/AIDS and the rise of multidrug resistance. The WGND's vision is to have new TB regimens that will achieve cure in 1–2 months or less, will be effective against MDR-TB, will be compatible with antiretroviral treatments, and will be effective against latent TB infection. In addition, new regimens must be affordable and easily managed in the field. It is conceivable, should continued progress be made in the basic understanding of the biology of *M. tuberculosis*, that the course of therapy could be reduced even further, to 10–12 days before 2050, or that additional advances in therapeutic or prophylactic options not currently available may greatly reduce TB incidence.

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

- (a) basic discovery biology to identify and validate new targets and identify candidate compounds using effective screens and creative medicinal chemistry;
- (b) active and sustained drug development efforts;
- (c) planning and execution of more effective clinical trials, including identification of improved biomarkers and methods of assessing latent disease; and
- (d) clear and efficient regulatory guidance.

#### Objectives

##### Discovery biology and chemistry

Objective 1: Identify and validate drug targets for persistent bacilli and latent disease.

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

The objective of the WGND is to identify and validate drug targets for both persistent bacilli and latent disease by 2015 or earlier. This will require 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 and rapidly eliminate these organism phenotypes.

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, with maximum bactericidal and sterilizing activity. The WGND further recognizes that there is a unique opportunity produce a new generation of TB drugs with maximum therapeutic impact, through rational combinations of these compounds. *M. tuberculosis* is an unusual pathogen in that there is no horizontal exchange of drug resistance (e.g. through plasmids). Therefore, the introduction of multiple novel drugs in fixed combinations would not only treat existing drug-resistant strains but, if properly managed, could eliminate the potential for future resistance. Specifically, the target by 2015 is to ascertain the mechanisms of action of the drugs in the global portfolio in order to generate complementary or even synergistic combinations effective against mycobacteria.

Recognizing the promise of multiple approaches to drug discovery, the WGND pursues a balanced approach to drug development, encompassing identification and screening of new targets, medicinal chemistry, combinatorial chemistry, and exploration of natural products.

##### Drug development

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

Objective 4: Develop animal models that can be used to predict the activity and side-effects of compounds, and validated surrogate markers that are broadly adopted by TB drug developers.

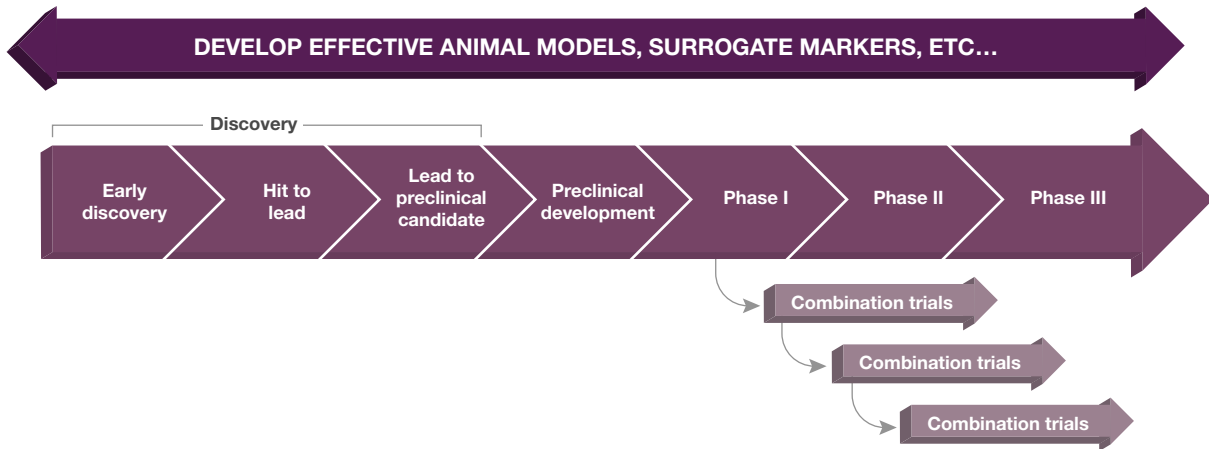
The objective by 2015 is to have a sustainable portfolio of new drug candidates under development that meet the drug profile criteria required for a duration of therapy of 1–2 months. There are 11 compounds with novel modes of action for TB that are currently in or approaching clinical development. Some of these compounds, e.g. 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.

New in vitro data suggest that compounds currently under development could reduce treatment duration even further. 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.

Figure 35 outlines the drug development process from discovery to registration, including the proposed concurrent testing of multiple rational drug combinations.

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. Animal models that can predict

**FIGURE 35:** TB DRUG DEVELOPMENT PIPELINE



compound activity and side-effects as well as validated surrogate markers that are broadly adopted by TB drug developers are urgently required.

**Planning and execution of clinical trials**

Objective 5: Build clinical trial sites and initiate and conduct clinical trials that meet regulatory requirements and the highest ethical standards. Develop biomarkers, surrogate end-points, and testing programmes to speed future clinical development programmes.

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 that meet the standards of Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). Trained personnel, sound infrastructure and appropriate procedures for patient recruitment, adherence and retention are also needed.

Proof of cure in TB requires lengthy clinical trials. Thus, biomarkers and surrogate end-points must be developed as part of a translational research strategy to speed future clinical development programmes. Testing programmes that allow more rapid and precise dose selection and optimization of complementary drug combinations are also needed.

**Regulatory approval and registration**

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

There has been a hiatus in TB drug development of over 40 years, and there are no TB-specific regulatory guidelines for drug development. Therefore, as compounds enter into 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.

**Activities**

**Discovery biology and chemistry**

Many promising discovery activities are in progress in 2005, coordinated by Working Group partners, and are likely to produce several new lead candidates by 2015. The Novartis Institute for Tropical Diseases, TB Alliance, and National Institute of Allergy and Infectious Disease (NIAID) are collaborating on work on nitroimidazole analogues. GlaxoSmithKline and the TB Alliance are assessing candidates in the classes of pleuromutins, 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 US National Institutes of Health are exploring the nature of the M. tuberculosis proteosome in persistence, and 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.tuberculosis proteins to obtain a better understanding of potential targets and hence design inhibitors. The Institute for Tuberculosis Research, University of Illinois, and the TB Alliance are exploring the biology and chemistry of newer macrolide antibiotics.

Several discovery programmes are testing natural products from plants and ocean sources, performing combinatorial and focused chemistry around known antitubercular agents, synthesizing analogues to attack novel targets (such as methyl transferase and 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 assess and compare candidates in animal model efficacy tests.

Key milestones in discovery include factors 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 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 by several sponsors. The key milestones for discovery-stage compounds will be achieved when lead compounds meet sponsor criteria set for advancement of leads into advanced preclinical development. Most of the decisions about proceeding or not are driven by the development plan, and are based on how the new drug will be used clinically. Thus, criteria for a drug to be added to existing regimens with daily dosing for many months may be different from those for a drug that is intended for prophylaxis with intermittent dosing. Animal safety tests, pharmacokinetic and pharmacodynamic characterizations, spectrum of microbial activity including against resistant TB strains, chemical synthesis routes, and cost factor into the decision to enter a candidate compound into animal safety studies under good laboratory practice (GLP). These tests are lengthy, expensive and require large amounts of purified compound. The formal reports are included in submissions to regulatory agencies for investigational new drug applications (IND). An IND submission is a critical milestone, as it indicates that objective data generated by a GLP-certified laboratory have supported the sponsor's decision to proceed. 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, 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 registered and launched.

The failure of drug candidates to complete the research and development process is a significant risk for sponsors, both in terms of time and funds. Only roughly 10% of candidates that enter the clinical pipeline advance to registration, mostly because of safety concerns. Thus, a robust and sustained pipeline of new candidates and back-up discovery programmes is essential to success. As new drug entities arise as candidates, the WGND will assist in fostering early communication among partners to allow modelling to begin of drug compatibility and complementarities in efficacy. The Working Group will serve as a platform for interaction among partners to increase efficiency and decrease risk for the process as a whole.

#### ***Planning and execution of clinical trials***

Clinical trials of 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 successful trials of existing drugs in a variety of combinations.

However, the need for clinical trial sites that meet registration-standard regulatory criteria is increasing dramatically, as the new compounds under development in the global TB pipeline reach preclinical milestones.

Because no centralized roster of qualified sites exists, clinical trial sites are being assessed individually and independently by individual sponsors of compounds in the pipeline. Bilateral agreements, as is customary and appropriate, are being established between the sponsors and principal investigators at each site. It is expected that trials will commence as each site, or group of sites, is prepared for the proposed trial and is not withdrawn by regulatory agencies.

This process is time-consuming and leads to redundancies. Therefore, the WGND will seek to streamline the clinical trial process by carrying out a mapping exercise to identify registration-standard qualified sites worldwide. It is expected that this mapping will be based on information provided by members of the Working Group and will be finished by late 2006.

The WGND will establish a roster of clinical trial site, which will outline the capabilities of each site, including all the regulatory assurances. The roster will be placed in a database that will be made public via the Internet at a readily available website, such as the Stop TB Partnership site.

The information gathered for the clinical trial site roster will also help in assessment of the capacity of each site and identification of existing gaps, whether in human resources, ability to recruit patients, infrastructure needs, or other areas. This assessment will identify what is needed to ensure viable, ethical and competent sites. This activity will be continuous.

#### ***Regulatory approval and registration***

Starting in 2006, and throughout the term of this strategic plan, as appropriate, the WGND will cosponsor meetings with regulatory agencies in developed and endemic countries, with the first objective being the establishment of regulatory guidelines to allow registration of a new compound for the treatment of TB by 2010. Additional meetings and symposia sponsored or cosponsored 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.

### **Monitoring and evaluation**

An important function of the WGND will be to map progress among the partners and other bodies that may start activities in TB drug development. A database of projects, compounds, and clinical trials will be established to reflect the current status worldwide.

Careful monitoring and evaluation of a large number of clinical trials will be expensive. Modest initiatives to expand capacity are under way at WHO/TDR, but are unlikely to satisfy the demand created by the initiation of multiple regulatory-quality TB clinical trials. Development of international monitoring standards and increased global monitoring ability are needed to ensure that promising agents are not impeded in their progress towards registration and utilization.

### **Key risk factors**

Only one in 10 new, first-in-human drug candidates achieve registration. The portfolio must therefore be robust with a continual pipeline of candidates entering clinical evaluation.

With the highest-burden countries experiencing emergencies in relation to HIV/AIDS and TB concomitantly, the paradigm of clinical evaluation of new drugs is becoming more and more complex. Expanded capacity for human pharmacokinetic and drug interaction studies will be necessary to ensure 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 exist, but the projected level of activity suggests that they will be under severe pressure.

New regimens may not be made available to the patients (e.g. because of delay in the establishment of standard treatments and their subsequent implementation in the field). All working groups and the international community will need to focus on the safe, prompt and effective adoption of new tools.

### **Budget requirements for the Working Group on New TB Drugs: 2006–2015**

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. The momentum achieved in the past five years has been possible only because of the financial commitment of public and private entities. To implement the WGND's vision, substantial additional resources and political commitment will be needed over the next 10 years.

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 people necessary and because of the long duration of follow-up (currently up to 2 years) required to determine rates of relapse. A significant expansion of global capacity in TB clinical trials will be needed to move a large number of promising compounds and regimens rapidly through phase II and III trials. 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 programme expertise in planning and evaluation. This is a domain in which the public and philanthropic sectors can make substantial contributions. The WGND will facilitate the activities needed for strategic planning and providing resources in advance of clinical trials. Substantial capital investment is necessary for successful new TB regimens to become available to the world. The total funding necessary is US\$4800 million; the funding available amounts to US\$620 million, leaving a total funding gap of US\$ 4180 million.

*See Table 26: Budget requirements for the Working Group on New TB drugs, 2006–2015*

TABLE 26: BUDGET REQUIREMENTS FOR THE WORKING GROUP ON NEW TB DRUGS, 2006-2015 (US\$ MILLIONS)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	All years	% total
<b>Early-Stage Drug Development and Research</b>	<b>211</b>	<b>217</b>	<b>224</b>	<b>231</b>	<b>237</b>	<b>245</b>	<b>252</b>	<b>260</b>	<b>267</b>	<b>275</b>	<b>2,419</b>	<b>50%</b>
Basic Research	5.0	5.2	5.3	5.5	5.6	5.8	6.0	6.1	6.3	6.5	57	1%
Lead Optimization	195	201	207	213	219	226	233	240	247	254	2,235	47%
Preclinical	11	11	12	12	12	13	13	14	14	14	126	3%
<b>Clinical Trials</b>	<b>207</b>	<b>213</b>	<b>220</b>	<b>226</b>	<b>233</b>	<b>240</b>	<b>247</b>	<b>255</b>	<b>262</b>	<b>270</b>	<b>2,373</b>	<b>49%</b>
Phase I	7.0	7.2	7.4	7.6	7.9	8.1	8.4	8.6	8.9	9.1	80	2%
Phase II	50	52	53	55	56	58	60	61	63	65	573	12%
Phase III	150	155	159	164	169	174	179	184	190	196	1,720	36%
<b>Regulatory Approval and Registration</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>6</b>	<b>0.1%</b>
Registration	0.0	1.0	0.0	1.1	0.0	1.2	0.0	1.2	0.0	1.3	6	0.1%
<b>WG Operations</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>0.2</b>	<b>2</b>	<b>0.04%</b>
<b>TOTAL</b>	<b>418</b>	<b>432</b>	<b>444</b>	<b>458</b>	<b>471</b>	<b>486</b>	<b>499</b>	<b>516</b>	<b>530</b>	<b>547</b>	<b>4,800</b>	