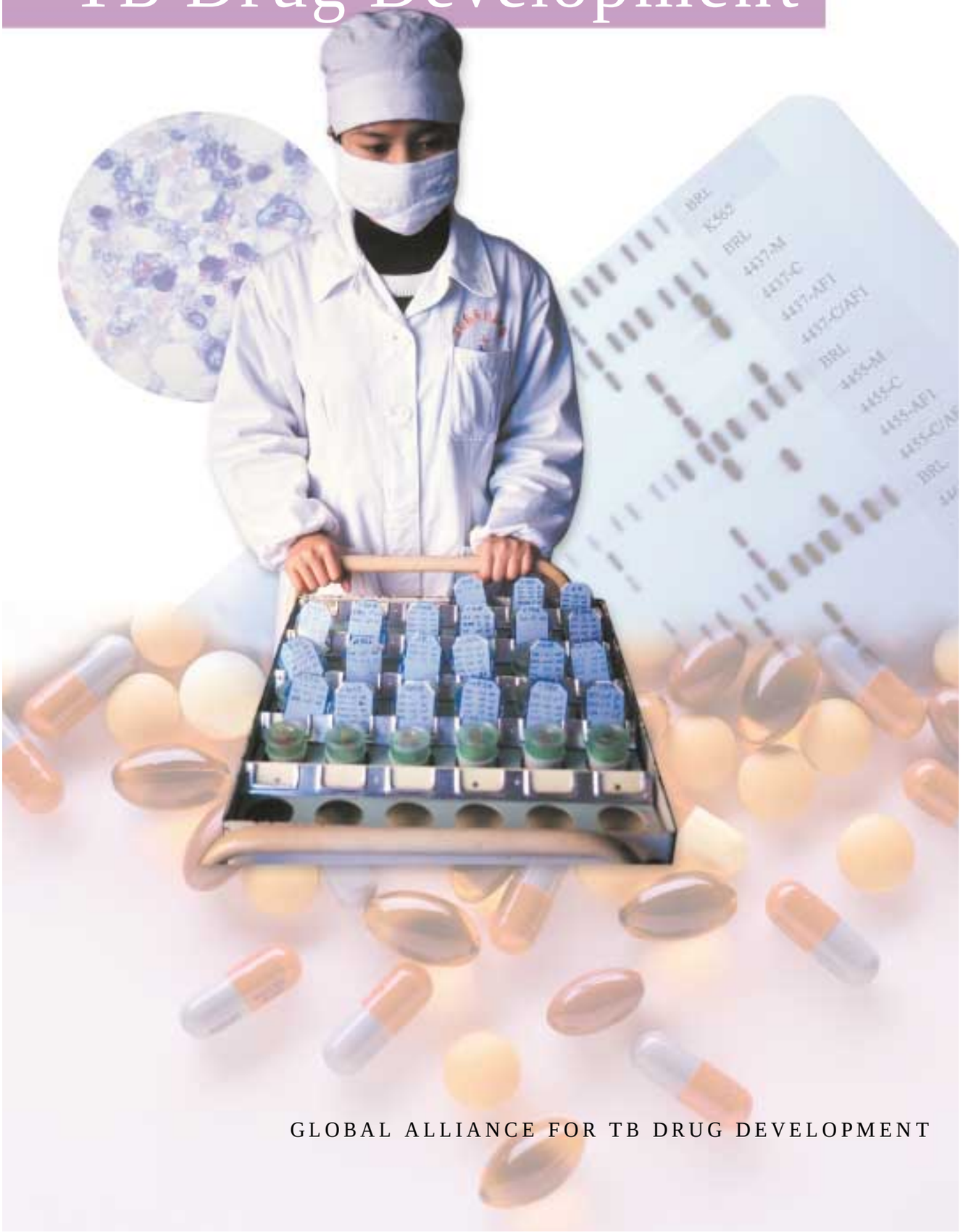
Executive Summary of the

Scientific Blueprint *for* TB Drug Development



GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

This document summarizes *The Scientific Blueprint for TB Drug Development*, to be issued by the Global Alliance for TB Drug Development and published as a supplement to *Tubercule and Lung Disease* in late 2000.

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Introduction

After several decades of neglect, tuberculosis (TB) is receiving the increased attention that this global public health problem deserves. Governments, nongovernmental organizations (NGOs), and philanthropic organizations are beginning to invest the major sums of money required to control and eventually eliminate this scourge. Although most of these new resources are being appropriately invested in TB control programs in countries where the TB epidemic is most severe, a significant commitment also is being made to basic research and the development of new diagnostic, treatment, and prevention tools, including new TB drugs.

Until now, progress in TB drug development has been impeded by two major factors: (1) the belief that there was little need for new agents and (2) the high cost of development coupled with the perception that the potential global market was insufficient to guarantee return on investment.

To address these problems, a number of interested parties, with initial support from the Rockefeller Foundation, have created the Global Alliance for TB Drug Development, a not-for-profit venture that will accelerate the discovery and development of new drugs to fight TB. It is one of a new breed of public-private partnership that pursues a social mission by employing the best practices of the private sector and by drawing upon resources from the public and private realms.

The vision of the Global Alliance is the provision of new medicines with equitable access for the improved treatment of TB. Its mission is to accelerate discovery and/or development of cost-effective new TB drugs that will shorten the duration of TB treatment or otherwise simplify its completion, provide for more effective treatment for drug-resistant tuberculosis, and/or improve the treatment of latent TB infection.

The Global Alliance will function as a lean, virtual research and development (R&D) organization that outsources R&D projects to public or private partners. Based on a survey of TB drug development activities in the public and private sectors, it will selectively intervene when its actions will help move a drug candidate towards registration and use in therapy. The Global Alliance therefore will build a portfolio of projects with varying levels of funding, management, and ownership.

The Global Alliance is issuing *The Scientific Blueprint for TB Drug Development* to provide a detailed, well-referenced document to guide scientists and investigators in academia, industry, and the public sector in all aspects of TB drug discovery and development. *The Scientific Blueprint* contains an analysis of the current TB drug discovery and development environment and identifies research gaps to inform the work of the Global Alliance. It also includes this *Executive Summary*, which serves as a stand-alone synopsis of the document.

1 The Need for New TB Drug Treatments

Tuberculosis is one of the most common infectious diseases known to man. About 32% of the world's population—or 1.86 billion people—are infected with TB. Every year, approximately 8 million of these infected people develop active TB, and almost 2 million of these will die from the disease.[1] In India alone, one person dies of TB every minute.

TB case notifications are soaring in the newly independent states of the former Soviet Union,[2] and HIV-associated TB is out of control in the sub-Saharan African countries hardest hit by AIDS.[3] Moreover, there has been a recent and disturbing increase in the number of TB cases that are caused by organisms that are resistant to the two most important drugs, isoniazid and rifampicin. A survey in 72 countries suggested that the multidrug-resistant (MDR) TB problem is more widespread than previously thought and likely is worsening.[4] MDR TB appears to be especially serious in the Russian Federation, where it has spread in prisons and throughout the general population.[5] **If not prevented and controlled, MDR TB likely will become more widespread in other areas of the world**, including developed countries such as the United States, in Western Europe, Canada, and Australia.

Widespread use of the Bacillus of Calmette and Guérin (BCG) vaccine, which is the only available TB vaccine, has had limited impact on the global burden of TB. Although BCG vaccination does prevent the development of severe and fatal forms of TB in young children, it has not been effective in reducing the greater numbers of infectious pulmonary cases in adults.[6] Recently there has been increased attention given to the development of a new effective TB vaccine, which is thought to be essential to the eventual elimination of TB.[7] However, this effort might take 25 years or more, and in the interval 50 million lives will be lost to TB.

Current Status of TB Control: DOTS 2

In response to the global TB epidemic, the World Health Organization (WHO) has developed an effective control strategy largely based on the pioneering work of the British Medical Research Council (BMRC) and the International Union Against Tuberculosis and Lung Disease (IUATLD). This strategy is known as DOTS (directly observed treatment, short-course).[8]

The essential elements of DOTS are as follows:

- Strong government commitment to TB control
- Diagnosis by smear microscopy (or by culture where resources permit)
- Standardized short-course chemotherapy with directly observed treatment for at least the first 2 months
- Secure supply of safe, high-quality drugs
- Individual reporting of treatment outcome and monitoring of program performance

Although DOTS is highly effective—82% of patients managed under DOTS in 1997 in the 22 countries with the highest TB burden were successfully treated[9]—its implementation has been slow and overall coverage is low, estimated at only 28% worldwide in 1998. Moreover, DOTS is cumbersome and labor intensive, particularly because currently available anti-TB drugs require a minimum treatment duration of 6 months.

Although great strides have been made in the treatment of TB during the past half century, the most significant progress occurred more than 30 years ago. The current treatment is a 6-month, four-drug combination of isoniazid, rifampicin, pyrazinamide, and ethambutol. All four drugs are given during the initial 2-month "intensive phase," and then isoniazid and rifampicin are continued during the 4-month "continuation phase." When followed as recommended, this regimen is highly effective, and rates of severe adverse reaction are low. However, many patients experience unpleasant side effects, and adherence with the relatively long course of treatment often is poor. Such nonadherence commonly leads to treatment failure and the development of drug resistance. The second-line drugs used for MDR TB are more expensive, less effective, and more toxic than the four-drug standard treatment.

Objectives for TB Drug Development 3

photo credit: WHO/TDR/Crump

A new TB treatment should offer at least one of three improvements over the existing regimens:

- Shorten the total duration of effective treatment and/or significantly reduce the total number of doses needed to be taken under DOTS supervision;
- Improve the treatment of MDR TB, which cannot be treated with isoniazid and rifampicin; and/or
- Provide a more effective treatment of latent TB infection (LTBI), which is essential for eliminating TB.

It is likely that a new, highly effective drug will achieve all three goals.

Although few truly novel compounds to treat TB have been introduced into clinical practice in the past 30 years, some promising work has been done on the following classes of drugs:

- Long-acting rifamycins (e.g., rifapentine, rifabutin, rifalazil)[10–12]
- Fluoroquinolone compounds (e.g., levofloxacin, moxifloxacin, gatifloxacin)[13-15]
- Oxazolidinone compounds[16]
- Nitroimidazopyrans[17]

These drug classes might provide the best means for rapidly improving TB treatment.

Genomics—the systematic identification of all of the genes in a cell through DNA sequencing and bioinformatic analysis—also offers great potential in terms of drug target discovery and development of new antibacterial agents, and the recently sequenced genome of *Mycobacterium tuberculosis* should provide a number of new targets for novel drugs.[18]

Needed Improvements for TB Treatment

- Shorten treatment and/or reduce supervised doses
- Improve treatment of MDR TB
- More effectively treat latent TB infection

Overcoming the Barriers to TB Drug Development 4

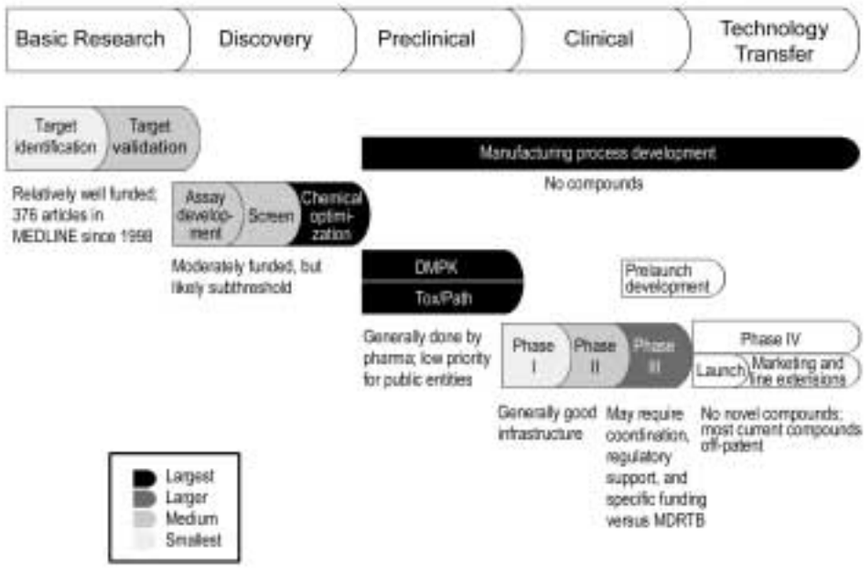


Exhibit 1: Gaps in the R&D Pipeline

Several gaps in the R&D pipeline are impeding the discovery, development, and introduction of new drugs to treat TB:

- **Basic Research**: Targets and compounds identified through recent basic research are not being fully exploited.
- **Discovery**: Private companies are not willing to dedicate the screening resources or medicinal chemists to optimizing new compounds with TB activity (lead compounds).
- **Preclinical Development**: Private companies do not have an interest in preclinical TB studies, and the public sector has limited resources for the coordinated development of preclinical studies.
- **Process Development/Chemistry**: Activities to develop appropriate manufacturing processes are inhibited by the lack of compounds available for scale up, as well as the unwillingness of pharmaceutical companies to dedicate process chemistry resources to TB chemotherapeutics.
- **Clinical Trials**: Although the infrastructure for Phase I and II clinical trials is well established, Phase III trials require additional coordination, regulatory support, and funding. However, these limitations are irrelevant without promising novel compounds emerging from preclinical studies.
- **Technology Transfer**: Little commercialization activity is taking place because of the lack of novel compounds in development, pharmaceutical companies' pessimistic view of the TB market, and concerns about toxicity associated with long-term use.

As the list on page 9 illustrates, the R&D gaps are due to two facts: (1) very few new drugs are in the pipeline and (2) drug companies have not been interested in TB because the disease appears not to be a major problem in industrialized nations. However, TB does pose a major threat to all nations. The time has come to ensure that new anti-TB drugs make it through the R&D pipeline.

In the face of the significant obstacles to new TB drug development, the Global Alliance for TB Drug Development is working with several partners, including private pharmaceutical companies, to close the gaps in TB drug discovery and development. The Global Alliance's efforts will encourage creative engagement of the public and private sectors in improving the drug development process at every stage in the R&D pipeline, giving priority to the major bottlenecks that occur relatively early in the process (i.e., late discovery and preclinical research):

- **Basic Research**
  - Encourage researchers to focus on translational research
  - Encourage researchers to move beyond target identification and validation to assay development
  - Provide funding for target-directed screening activities
- **Discovery**
  - Provide funding for medicinal chemists, particularly those in developing countries, to pursue TB lead optimization
- **Preclinical Development**
  - Coordinate and support integrated toxicological and pharmacological resources during lead development
  - Encourage early evaluation of lead compounds in animal models of TB
- **Chemical/Process Development**
  - Increase the number of compounds available for scale-up
  - Leverage the process chemistry resources available in developing countries
- **Clinical Trials**
  - Encourage efforts to move promising novel compounds out of preclinical activities and into clinical trials
  - Support the development of a network of sites for conducting cost-effective trials in high-burden countries
  - Identify surrogate markers to streamline trials
- **Technology Transfer**
  - Encourage cooperative partnerships among companies with the ability to commercialize new treatments, particularly firms with existing franchises in infectious or tropical diseases
  - Leverage the expertise of public organizations that are positioned to commercialize drugs that benefit the public

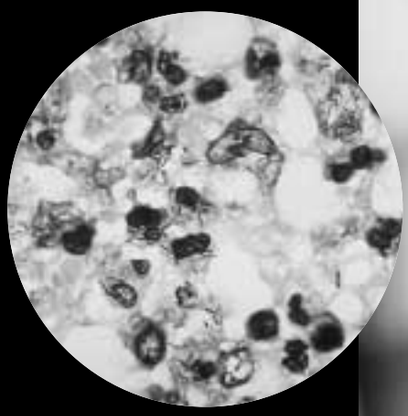


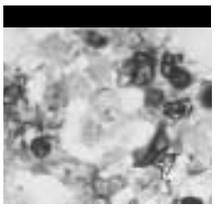
Exhibit 2: Sample of Organizations Working in TB Drug R&D

As stated previously, closing the gaps along the tuberculosis R&D pipeline requires the involvement of the public and private sectors. Exhibit 2 lists some of the organizations currently working in TB drug discovery and development. It should be noted that the participants presented above do not represent every organization conducting tuberculosis R&D. The Global Alliance developed this preliminary list based on an informal survey of some 50 leading scientists, business people, and program administrators in the TB field.

The probability that a single candidate will progress from discovery through registration is less than 0.5%. Therefore, the Global Alliance will distribute its support across multiple targets and mechanisms of action, among multiple partner organizations, and along multiple phases of the R&D pipeline. The focus will be on developing a broad portfolio of promising candidates with a special emphasis on developing fast-track compounds that might exhibit success early in the development phase (e.g., quinolones, oxazolidinones). The Global Alliance calls on funding agencies and research organizations to devote the resources needed to support these efforts.

A Successful Drug
Discovery and Development Process 5

As efforts to develop a new treatment for tuberculosis improve, researchers and their sponsoring organizations should consider following the process outlined in this section as they proceed through drug discovery and development. The Global Alliance believes that this process will help ensure that new compounds to treat TB will move successfully through development, receive rapid regulatory approval, and be transferred into clinical use.



5.1 Target Selection

In general, drug discovery programs are aimed at proteins whose function is known to be essential to the bacterial cell. Several important criteria are used to evaluate the suitability of a candidate enzyme or protein as a drug target:

- The level of existing validation of the target
- The deduced tractability of the target
- Availability of three-dimensional structure data
- An approachable assay system that can be readily adapted to high-throughput screening technology
- Lack of mammalian homologs

Because one-third of the global human population is asymptomatically infected with TB (i.e., has latent TB infection) and at continued risk for activation of the disease, much basic research has focused on understanding the physiology and metabolism of the latent bacilli within such patients. Candidate proteins and processes have emerged that might be critical for the continued persistence of bacteria within such patients.[19] These processes might offer a viable treatment target for patients with LTBI, but such targets have several problems. For example, these targets might not be essential for normal growth of the bacilli, and thus conventional microbiological laboratory procedures for determining resistance might not be applicable. However, these targets are approachable through conventional assay development, inhibitor design, lead optimization, and preclinical development processes, and they are an important component of future TB drug development considerations.

5.2 Identification of Lead Compounds

In most cases, lead compounds are identified through successfully implemented high-throughput assays and surveys of chemical diversity for compounds that inhibit the target selected. **The process of lead compound identification has been greatly enhanced by the advent of combinatorial chemical approaches to generating compound diversity.**[20] This technology has allowed the creation of literally millions of discrete substances that can be individually assessed for their potential to inhibit the target. Each of the resulting inhibitors then represents a starting point (i.e., lead compound) whose structure is further manipulated to improve binding and other important characteristics.

Lead compounds also can be identified based on known inhibitors, chemical intuition, or even known drugs. If the target enzyme has a solved three-dimensional structure, lead compounds also can be identified *in silico* through the application of molecular docking algorithms. All of these processes together can produce a series of lead compounds that might be suitable for further medicinal chemical manipulation to produce candidates for preclinical evaluation.

5.3 Optimization of Lead Compounds

Lead compounds are optimized through synthesis of related substances while maintaining the essential features of the original compound that conferred the inhibitory property. Such processes are facilitated by the knowledge of a crystal structure of the target, especially if a cocrystal of the lead compound can be obtained. Both computer simulation and trial-and-error testing are used when attempting to maximize the "fit" of the compound into the active site of the protein.

Selection of a lead compound and analog generation generally occurs in parallel with an initial evaluation of a compound's drug-likeness and an investigation of preliminary characteristics known to be associated with successful development programs. In general, these processes should happen simultaneously—that is, an assessment of binding affinity for a potential analog should be coupled with an evaluation of the likelihood that such an analog represents a viable development candidate. Such evaluations typically involve the following:

- Assessment of toxicity (on a eukaryotic cell-line initially)
- *In vitro* determination of the minimum inhibitory concentration (MIC) of the lead compound against *M. tuberculosis*
- *In silico* prediction of the likelihood that the compound will enter the bloodstream following oral administration
- Evaluation of bioavailibility and efficacy in animal models
- Initial measurement of the compound's serum stability using hepatic microsomal stability assays

All of these data must be integrated with analog generation to select a lead series that has the greatest hope of advancement to preclinical status.

5.4 Late Discovery

"Assessing the robustness" of a short list of compounds is essential in defining and balancing a set of preferred characteristics and in eliminating compounds that might not successfully complete development. The process of validating lead compounds according to predefined criteria generally incorporates standard tests (that have been developed to assess key characteristics of any compound) and specific tests (that incorporate disease-specific characteristics desired in a new drug candidate):

- **Formulation feasibility:** A pharmaceutical chemist should be able to formulate an orally bioavailable, stable finished drug product that meets all of the characteristics required of a new anti-TB compound.
- **Pharmacokinetics; absorption, distribution, metabolism, and excretion (ADME); and pharmacodynamics**: The key parameters to assess are (1) the relationship between the blood and tissue levels of the compound in comparison to its MIC/MBC (minimum bactericidal concentration) against TB and (2) the plasma or serumcidal activity of a compound against *ex vivo M. tuberculosis*.
- **Toxicology**: Commonly performed studies include mutagenicity studies, acute single dose toxicity studies, subacute (5- to 7-day) toxicity studies, and preliminary dose-ranging studies.
- **Safety (secondary) pharmacology**: These tests discover whether a compound has pharmacological activity against other human receptors that control biologic functions.
- **Intellectual property (patent) situation**: The strongest intellectual property protection an organization can seek is for a new previously undescribed chemical class.

5.5 Preclinical Development

Researchers must use animal models to assess *in vivo* the antimicrobial activity of a lead compound in comparison with that of existing drugs. In addition, the models test the compound's antagonistic, additive, or synergistic effects when given in combination with other drugs and its ability to sterilize the lesions of the experimentally infected animal. **Because of its ease of handling in terms of size, supply, maintenance, robustness, and reproducibility, the mouse is the model of choice for TB**.[21,22] When used with care, the mouse model is able to reproduce bacteriologic conditions close to those present in the natural human disease and provide information on drug activity that can be extrapolated to human beings.

Animal studies should assess bacterial burden, mortality, and organomegaly in lung tissue at baseline; during therapy; at the end of therapy; and post-therapy

to assess relapse, postantibiotic effect, and development of resistance. They should include combination drug evaluations to better identify the place for a new TB drug within the established therapeutic regimens.

Finally, properly planned toxicology studies must be conducted. Some of these studies might have been conducted during the late discovery phase; however, it is essential that researchers conduct preclinical toxicology studies in compliance with good laboratory practice—an absolute requirement for regulatory purposes. These studies are highly controlled and documented safety tests to demonstrate possible toxic effects of the compound in order to define a window of safety for subsequent human clinical trials.

Early discussions and interactions with representatives of regulatory agencies are encouraged and can provide critical guidance on the types and design of studies (both preclinical and clinical) likely to facilitate TB drug development.

5.6 Process Development/Chemistry

Before clinical trials begin, the chemical and pharmaceutical development team continues its task of scaling up the previously determined method of drug substance production, dosage form development, and development of analytical methods to ensure that good manufacturing practices can be maintained for each batch produced.

A series of steps related to process development and chemistry also must be taken. The chemical and pharmaceutical development team produces a description of the lab-scale route of synthesis (i.e., extraction or other process that yields the candidate compound). The team also performs a feasibility assessment to ensure that the compound, based on the proposed method of production, can be produced in large-scale quantities. In addition, the team produces an early estimate of the candidate compound's stability, a description of its physical-chemical properties, and an assessment of its chiral or diastereomeric purity.

photo credit: WHO/TDR/Crump

5.7 Clinical Trials

All clinical trials must conform with internationally accepted standards of good clinical practice. Researchers should ensure that institutional review boards and/or independent ethics committees are properly established in the countries where the research is to be conducted and that these committees have the resources and independence to review the proposed studies. Whenever possible, the control and comparison treatments should be masked and placebos used to avoid the introduction of bias for or against the new treatment. The assessment of adverse events always must be

included. Documenting, monitoring, and auditing the study process is essential to ensure the quality of the data. Exceptions to the protocol and protocol errors must be documented. Adequate safety information will need to be included in the submission for regulatory approval. The safety database should include representation from racial and ethnic groups likely to receive the product, patients of both genders, and patients infected with HIV. Researchers should generate sufficient pharmacokinetic information to assess the likelihood of interactions with the most common concomitant therapies, including both TB and non-TB drugs.

5.7.1 Phase I and II Trials

Phase I trials are conducted in healthy normal volunteers (HNV) of either gender and are designed to give the investigator an idea of the pharmacokinetic profile and limited safety data (clinical and laboratory) on a new drug. In addition to Phase I HNV trials, researchers might also incorporate the pharmacokinetic and safety instruments into a larger Phase II study that enrolls patients with active TB and uses additional data instruments, such as efficacy and multiple treatment groups.

A critical function of Phase I/II trials is determining the optimal drug dose for the Phase III trials. One well-documented method to rapidly demonstrate drug activity in man and to assist in selection of the optimal drug dosage is the early bactericidal activity (EBA) study.[23] For the EBA study, newly diagnosed TB patients are treated for 2 to 5 days with various dosages of a new drug, while carefully measuring the colony-forming units (CFU) in expectorated sputum.

5.7.2 Phase III Trials

Phase III trials are usually large-scale, randomized clinical trials designed to show improved or equivalent efficacy of a new treatment compared to the standard treatment among diseased patients. For TB, up to 1,000 patients are commonly enrolled in a two-arm study, treated, and then followed for TB relapse for up to 2 years, the commonly accepted primary end point for demonstrating efficacy.[24]

The Phase III trial design should outline the parameters that will be used to define primary and secondary end points, including the sample sizes, confidence intervals, and statistical methods that will be used to assess the data. It is imperative that microbiologic evaluations take place at the appropriate times during the Phase III clinical trials in order to assess the true activity of the investigational agent.

To ensure that a sufficient study population can be obtained for the Phase III trials, **researchers might need to site trials in countries with high TB incidence rates**. One desired characteristic for establishing a clinical trial site in a particular country is that the national tuberculosis program should be strong and steadily expanding to serve the entire country (if it does not already do so). Only a program of this type can provide essential information, such as the annual incidence of cases by type (e.g., site of disease, smear status, drug resistance) and the prevalence of complicating comorbidity. These data allow for accurate estimates of patient enrollment in the study and whether a particular treatment is appropriate for that site.

The reporting system and collection of results must be carefully designed to avoid errors. A reference laboratory also is required for most trials, but the extent to which it duplicates the procedures carried out in the local laboratory depends on the local laboratory's standards and its capacity to do the necessary work.

Finally, validated surrogate markers of relapse could provide evidence on the sterilizing activity of a drug/regimen with great savings in development time and cost. The most useful method for studying a drug's sterilizing activity is to determine the proportion of patients who have a negative culture of a single sputum specimen at 2 months (8 weeks) after the start of treatment with an experimental regimen compared with the proportion on a standard regimen.[25] Newer molecular methods might provide better surrogate markers of response but require further study and validation.[26]

5.8 Regulatory Approval

Given the lengthy development process, any delay in receiving regulatory approval will be seen by industry as an additional tax on an already limited profit potential. Regulatory uniformity among national agencies would help remove some of the current disincentives to TB drug development. *The Scientific Blueprint* provides information, particularly in the area of clinical studies, that can be used in developing harmonized international guidelines for regulatory approval of new TB drugs. It is hoped that such guidelines will enhance the efficiency in registering new anti-TB agents while continuing to follow current national requirements that are designed to protect individuals and public health.

5.9 Technology Transfer

Product development efforts, including patenting, describing biological activity, assessing toxicity, developing a safety profile in humans, and demonstrating clinical efficacy at the proposed dosage and mode of administration, are well-established steps of the preclinical development and clinical testing processes. Performing these studies under codes of good manufacturing, laboratory, and clinical practice enhances the technology transfer effort. **The commercialization strategy must be developed before clinical testing** to ensure that the needs of the target market are clearly understood and taken into consideration in developing the drug product.

Two types of postmarketing (Phase IV) studies are required: (1) evaluations under program conditions of new treatment regimens in comparison to locally mandated regimens and (2) surveillance for less common adverse effects related to the new drug, including the development of drug resistance. Patient acceptance of the new drug must be objectively assessed. Economic and financial benefits of using the new drug also should be assessed.

To generalize the use of a new drug internationally, intergovernmental organizations, NGOs, and drug manufacturers have certain responsibilities:

- WHO establishes technical norms and informs drug manufacturers of them via the International Federation of Pharmaceutical Manufacturers Association (IFPMA) and/or the International Generic Pharmaceutical Alliance (IGPA).
- IFPMA and IGPA disseminate technical and other requirements to their constituent members through the appropriate channels.
- Public health agencies, NGOs, and professional societies issue technical guidelines on the use of new drugs in TB treatment.
- WHO should consider including any new anti-TB drug on its Essential Drugs List (EDL), and international suppliers such as UNICEF and the International Drug Association should consider placing the new drug in their catalogues of available therapeutics.
- Development institutions such as the World Bank, regional development banks, and other international aid agencies and foundations should accommodate the purchase of the new drug in loan or aid agreements.
- Countries establish national drug policies and regulations to suitably control the new drug. Policy and regulation development requires full coordination among the national tuberculosis program, the national drug regulatory authority, and the national procurement office.

New TB drugs will become widely accessible and properly used only if all of these systems are sufficiently integrated and supported by strong national TB programs with appropriate training at all levels of the health system.

Summary 6

The Scientific Blueprint for TB Drug Development—which this document summarizes—presents the following information in detail:

- The status of the tuberculosis epidemic
- The need for new chemotherapeutic agents
- An analysis of the current TB drug discovery and development environment
- Approaches for bridging gaps in the R&D process that prevent the timely development of new anti-TB drugs
- Guidelines for the development process that might increase the chances of obtaining regulatory approval for an effective new treatment

The Global Alliance for TB Drug Development is dedicated to closing the R&D gaps. However, advances cannot be made without investment by national and international health organizations, private sector pharmaceutical and biotechnology firms, foundations, and others. By combining our resources into R&D efforts to discover and develop a broad portfolio of promising candidates, the Global Alliance and its sponsors can make a vitally important contribution to improved control and the eventual elimination of tuberculosis from every country of the world.

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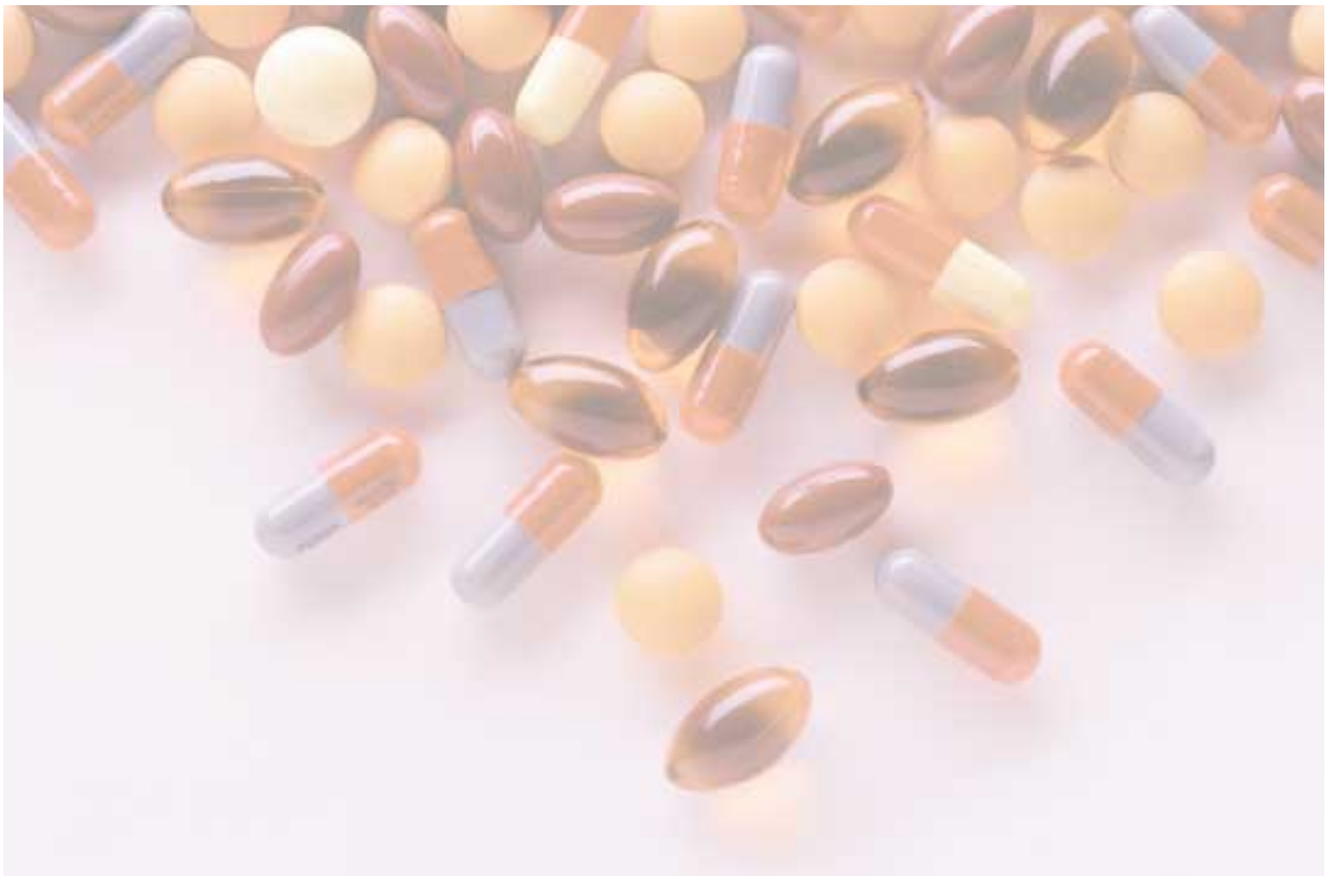

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