



TB Drugs

EDCTP Stakeholder meeting

Dublin – Ireland

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1. Introduction

The EDCTP stakeholder meeting on tuberculosis (TB) drugs is the fifth stakeholder meeting organised by EDCTP in the light of the amended strategy for funding new projects.

The aim of this meeting, which was hosted by Ireland, was to make recommendations to EDCTP in terms of products in the pipeline, potential sites to do the trials and needs in terms of capacity building in Africa. In addition EDCTP requested a recommendation on the funding procedure that should be implemented.

The meeting was chaired by Professor Peter Small. He is a professor at Institute of Systems Biology (http://www.systemsbiology.org/Scientists_and_Research/Faculty_Groups/Small_Group) and working as the Senior Program Officer for Tuberculosis at the Bill and Melinda Gates Foundation in Seattle. His research interests include multiple aspects of tuberculosis, but are focused on exploiting a strain specific perspective to gain an enhanced understanding of the disease's epidemiology, control and pathogenesis.

2. Science and products

Current tuberculosis (TB) treatment is characterised by the following aspects:

- Active TB has a 6 months of therapy – 4 drugs for 2 months, 2 drugs for 4 months
- Multi-drug resistant TB (MDR-TB) or extreme drug resistant TB (XDR-TB) has individualized, prolonged therapy with few available drugs that are poorly tolerated and difficult to administer
- TB/HIV co-infection treatment as in active TB, but drug interactions with anti-retroviral (ARVs) regimens make simultaneous therapy extremely difficult
- Latent TB has a 9 months of INH therapy

One third of world population is infected with TB. Globally there are 18 million prevalent cases every year of which 8.8 million are new cases. Every year 1.6 million deaths occur due to TB. There is also an estimated 424,000 MDR cases in the world. People living with HIV/AIDS have an increased risk of developing TB.

The three major challenges to testing new or improved drugs against TB are:

- Insufficient knowledge about agents with optimum anti-microbial activity against TB
- Few new compounds
- Inadequate trial capacity

When is the right time to start conducting TB trials? Several factors that have to be considered include:

- Epidemiological impact
 - Different indications
 - Given time frames
 - Realities of uptake
- What is worth taking in to humans?
 - Scientific excellence
 - Acceptability
 - Economically
- Pharmacokinetics / pharmaco-dynamics (PK/PD)
 - What is currently working
 - What is desired / acceptable

Important considerations in conducting TB drug trials include:

- Trial Methodology
 - Can new drugs be tested simultaneously?
 - Can drug resistance TB trials expedite approval?
 - How to include high risk subgroups and stratification?
 - How to optimize best therapy?
 - How to address paediatric TB
- Biomarkers
 - What is a valid endpoint? Is it early bactericidal activity (EBA), 2 months sputum conversion, quantitative culture or relapse?
 - What is regulatory endpoint?
 - Equivalence or non-inferiority: which is better design?
- Risks
 - Delayed uptake
 - Accelerated acceptance as standard therapy

3. Overview participating organisations

3.1 Public organisations

3.1.1 Medical Research Council (MRC) – United Kingdom

The Medical Research Council (MRC) is a publicly-funded organisation dedicated to improving human health. It supports research across the entire spectrum of medical sciences, in universities and hospitals, in its own units and institutes in the UK, and its units in Africa.

Each year the MRC supports researchers working in universities and hospitals through research grants, and funded research training for fellows and postgraduate students through MRC career awards. It also funded 32 of its own research establishments in the UK and Africa, which employ more than 3,500 scientists.

MRC-UK is the main co-funding agency into EDCTP from the United Kingdom.

Dr Diana Dunstan, who is also Chair of the EEIG-EDCTP Assembly, represented MRC in the meeting.

More information can be found at <http://www.mrc.ac.uk/>

3.1.2 Irish Aid

Irish Aid is the Government of Ireland's programme of assistance to developing countries. Ireland has had an official development assistance programme since 1974.

Ireland's development cooperation policy is an integral part of Ireland's wider foreign policy. Their aid philosophy is rooted in our foreign policy, in particular its objectives of peace and justice. Their development cooperation policy and programme reflect a longstanding commitment to human rights and fairness in international relations and are inseparable from Irish foreign policy as a whole.

Irish Aid works in cooperation with governments in other countries, other donors, NGOs and international organisations as part of the global effort to achieve the Millennium Development Goals. Thus Irish Aid supports the aims and goals of EDCTP.

Dr Diarmuid McClean represented Irish Aid in the meeting.

More information can be found at <http://www.irisaid.gov.ie/>

3.1.3 Irish Health Research Board

The Health Research Board (HRB) is the lead agency in Ireland supporting and funding health research. They provide funding, maintain health information systems and conduct research linked to national health priorities. Their aim is to improve people's health, build health research capacity and make a significant contribution to Ireland's knowledge economy.

The HRB will achieve its mission by delivering on the following strategic objectives: (i) Shape the national agenda for research in health and personal social services (ii) Support research and health information systems linked to national health priorities, in order to improve people's health and the effectiveness of the health system (iii) Build capacity for world-class health research in Ireland (iv) Advance the contribution that health research makes to a sustainable knowledge economy (v) Increase awareness and understanding of both the impact and the value of health research and information (vi) Establish Ireland as a significant contributor to international policy on health research.

Teresa Maguire represented the Irish Health Research Board in the meeting.

More information can be found at <http://www.hrb.ie/>

3.1.3 Agence Nationale de Recherches sur le SIDA et les Hepatites Virales (ARNS)

The ANRS is a French research agency fighting against HIV/AIDS and viral hepatitis. Its headquarters is in Paris. It funds research in sub-Saharan Africa, South-east Asia and Latin America. The research, mainly on access to prevention and to treatment, is run in ANRS sites in Cote d'Ivoire, Senegal, Burkina Faso, Cameroon, Vietnam, Cambodia, Brazil and some part of South Africa.

ANRS was represented by Dr Francois Xavier Blanc in the meeting.

More information can be found at <http://www.anrs.fr/>

3.1.4 The Institute of Tropical Medicine in Antwerp, Belgium (ITM)

The Institute of Tropical Medicine in Antwerp, Belgium (ITM) is one of the world's leading institutes for training, research and services delivery in tropical medicine and health care in developing countries. It is strongly committed to academic excellence and genuine partnership for the promotion of "Health Care for All". The European supra national reference laboratory of the Union for drug resistant TB is situated at the ITM. This unit is headed by Dr Leen Rigouts who represented ITM in the meeting

More information can be found at: <http://www.itg.be/>

3.2 Public Private Partnerships

3.2.1 International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis, TB (INTERTB)

The International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis, TB (INTERTB), is a new network that has been established at St. George's, University of London in United Kingdom. The escalating tuberculosis (TB) cases, including multi-drug resistant TB, fuelled by the human immunodeficiency virus epidemic as a major global health problem coupled with limited drug research and development in the last forty years led to a few scientists forming this network. It aims at improving networking of TB drug trialists that operate in sub-Saharan Africa. EDCTP funded a networking meeting of INTERTB in 2007. The coordinator of the network is Dr Amina Jindani and she represented it in the stakeholders' meeting.

3.2.2 The Global Alliance for TB Drug Development (TB Alliance)

The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit, product development partnership accelerating the discovery and development of new tuberculosis (TB). Its mission is to develop new, better treatment for TB; coordinate and act as catalyst for global TB drug development activities and ensure the three A's (affordability, availability, adoption) of such drugs. It concentrates on drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB patients currently on such therapies, and improve treatment of latent infection. The organisation was founded in 2000, and has offices in New York, Pretoria and Brussels.

TB Alliance was represented by Dr Anne Ginsberg in the meeting

More information can be found at <http://www.tballiance.org/>

3.2.3 International Union against TB and Lung Disease (IUATLD) / the Union

The International Union against TB (IUAT) was formed in 1920 in Paris. After adopting control of other lung diseases the union changed its name to International Union against TB and Lung Disease (IUATLD), commonly referred to as the Union. The main activities of the Union include 1) education directed at health-care providers, decision makers and the public at large; 2) dissemination of information; 3) training of health-care professionals; 4) public education and 5) technical assistance to Union's Constituent Members (countries and organizations).

A Clinical Trials Programme was established by the Union in 1998 to evaluate two 8-month regimens of chemotherapy in the treatment of newly diagnosed pulmonary tuberculosis, one of which consists of an intermittent intensive phase of chemotherapy.

The Union was represented in the meeting by Dr Christian Lienhardt.

More information can be found at: <http://www.iuatld.org/>

3.2.4 International Network for the study of HIV associated IRIS” (INSHI)

The International Network for the study of HIV associated IRIS (INSHI) is a recently formed network. The network has been formed to study the poorly understood Tuberculosis Immune Reactivation Inflammatory Syndrome (TB IRIS). With the high number of TB/HIV co-infected patients in Africa and the increased access to Highly Active Antiretroviral Treatment (HAART), an increasing number of patients will develop the syndrome. The exact incidence, however, of this phenomenon is unknown. Moreover it remains unclear how to diagnose this condition and how to prevent and treat it. One of the problems in carrying out research in this field is that at the moment we do not have a universally accepted case definition of TB IRIS. The partners of the network include Makerere Medical School, the Infectious Diseases Institute in Uganda, the Institute of Tropical Medicine Antwerp, WHO, Médecins sans Frontières, MRC Uganda, University of Minnesota, University of Colorado, John Hopkins/NIH, Centre of Poverty Related Communicable Diseases at the AMC, St Stephen's Centre, Chelsea and Westminster Healthcare NHS Trust in UK, ART-LINK and the TREAT ASIA. EDCTP funded a networking meeting for INSHI in 2007.

Dr Robert Colebunders represented the network in the meeting.

3.2.5 African Poverty Related Infection Oriented Research Initiative – APRIORI

APRIORI - African Poverty Related Infection Oriented Research Initiative (2006-2010) aims at establishing a state-of-the art clinical research centre, and by involving

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African centres of excellence, strengthening south-south collaboration. The programme consists of the following 5 projects:

- Capacity building
- Phase I and II testing of malaria vaccines
- Capacity building and establishment of clinical trial centre for testing new TB-vaccines (phase-I/IIa) and TB-drug interactions in the context of HIV in Africa
- Concurrent treatment in TB and HIV co-infection
- Development of drug regimens to shorten treatment for tuberculosis

Dr Martin Boeree and Dr Robert Aarnoutse represented the network in the meeting.

More information can be found at: www.priornetwork.org

3.3 Private Sector

3.3.1 Médecins Sans Frontières (MSF) - Switzerland

Médecins Sans Frontières (MSF) is an international humanitarian aid organisation that provides emergency medical assistance to populations in danger in more than 70 countries. In countries where health structures are insufficient or even non-existent, MSF collaborates with authorities such as the Ministry of Health to provide assistance. MSF works in rehabilitation of hospitals and dispensaries, vaccination programmes and water and sanitation projects. MSF also works in remote health care centres, slum areas and provides training of local personnel. All this is done with the objective of rebuilding health structures to acceptable levels. In carrying out humanitarian assistance, MSF seeks also to raise awareness of crisis situations; MSF acts as a witness and will speak out, either in private or in public about the plight of populations in danger for whom MSF works.

On 11-12 January 2007 MSF, supported by Weill Cornell Medical College, convened a symposium entitled 'No *Time to Wait*' in New York aimed at stimulating efforts to accelerate the development of effective new treatments for TB. MSF were invited to the stakeholders meeting present the recommendations of the mentioned symposium.

Dr Unni Karunakara represented the network in the meeting.

More information can be found at <http://www.msf.org>

3.3.2 Roche Pharmaceuticals - London

Roche are a pharmaceutical company involved in development of drugs and diagnostic. In terms of TB drugs they are interested in Phase I trials of promising anti-mycobacterium agents.

Dr Jane Belinda Marshal represented Roche in the meeting.

More information can be found at <http://www.roche.com/>

3.4 Other

3.4.1 Scientists / experts

The following experts also attended the meeting: Professor Stephen Gillespie (University College of London and also EDCTP grantee on moxifloxacin trials), Dr Ase Bengard Andersen (University of Copenhagen) and Dr Samuel J McConkey (Royal College of Surgeons Medical School of Trinity College in Dublin).

3.4.2 European and Developing Countries Clinical Trial Partnership (EDCTP)

EDCTP was represented by the Chair of the assembly, two European Network Officers (ENO) from Ireland and Spain, two members of the Partnership Board (PB), one member of the Developing Countries Coordinating Committee (DCCC) and five members of the Secretariat.

More information can be found at <http://www.edctp.org>

4. Overview of presented products

Participants acknowledged the scientific fact that mono-therapy has no place in TB treatment. Products under discussion can only be used to improve or optimise a multi-drug regimen that combines registered drugs already available on markets.

4.1 Moxifloxacin

- It is a fluoroquinolone antibiotic with significant potency against *M. tuberculosis*
- Preclinical data show that when combined with rifampicin and pyrazinamide (MRZ) based regimen could potentially shorten therapy to 4 months or less
- Chennai data showed that a fluoroquinolones (ofloxacin) could potentially shorten therapy to 3 months or less
- It offers a novel mechanism of action for TB
- It has an excellent safety record in humans (>60 million uses)

TB Alliance and Bayer signed contract August 2005:

- Agreement to conduct joint program for the clinical development and registration of moxifloxacin in TB
- Other parties TB Trials Consortium (TBTC) / Centres for Disease Control (CDC), Johns Hopkins University (JHU), University College of London (UCL), British Medical Research Council (BMRC) agreed to coordinated effort under TB Alliance/Bayer umbrella
- Issue of affordability is addressed

EDCTP agreed to provide partial funding for Phase III clinical trials and is currently funding a study taking place in Tanzania, South Africa and Zambia whose PI is Prof Stephen Gillespie.

Future plans with moxifloxacin:

- Pre-Phase III meetings with regulatory authorities. Discussion of non-inferiority design may result in increasing sample size and required number of trial sites
- Complete Phase II and III clinical evaluation of M for E and M for H – based regimens
- Consider evaluation of other drug combinations – e.g., high dose rifamycins and moxifloxacin combos
- If data are supportive registration of Moxifloxacin for Ethambutol and/or Moxifloxacin for Isoniazid is envisage in 2011

4.2 Gatifloxacin

Gatifloxacin is related Ofloxacin which:

- Has proven bactericidal activity against *M. tuberculosis* (Garcia–Rodrigues 1993, Gillespie 1998)
- Is rapidly absorbed
- Has high concentrations in respiratory cells, secretions and macrophages
- Is of low cost, included in the WHO essential drug list
- Has had several clinical trials (Tsukamura 1986, Hong Kong) conducted

Gatifloxacin is:

- an 8-methoxy-fluoroquinolone active against Gram + and Gram – organisms
- more active than ofloxacin against susceptible and resistant *Mycobacterium tuberculosis* isolates *in vitro* and *in vivo*
- anti-TB activity similar to moxifloxacin
- free of many of the class effects of quinolone antibiotics (e.g. photo toxicity)
- reported to have early effect on glucose homeostasis with potentially severe hypo- or hyperglycaemia
- a generic production with low cost of synthesis and intermediates

Gatifloxacin has already undergone Phase I/II studies and is now in Phase III trial. This trial is done by a consortium called OFLOTUB and is funded by the European Commission. The trial is pivotal "Proof of Concept" Phase III Trial with the following elements:

- First *Proof of Concept* trial on shortening treatment of pulmonary TB to 4 months with the inclusion of a fluoroquinolone
- Phase III multi-centre open-label randomised controlled trial. Study sites are in Guinea, Benin, Senegal, Kenya and South Africa with Dr Christian Lienhardt as Principal Investigator.
- The study arms have 4-month Gatifloxacin-containing short-course regimen *versus* standard 6-month regimen
- Gatifloxacin substituted for Ethambutol

4.3 Rifamycins

The rifamycin group includes the "classic" rifamycin drugs as well as the rifamycin derivatives rifampicin, rifabutin and rifapentine. Rifampicin the commonly used rifamycin for treatment of tuberculosis was first introduced in 1966. It is currently the backbone of the WHO recommended short course treatment of TB comprising 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol followed by 4 months of daily rifampicin and isoniazid (2RHZE/4RH).

Three key areas of improving current TB treatment are in:

- The effect of increasing the dose size of the rifamycins on the reduction of treatment duration
- The effect of substituting a fluoroquinolone (either moxifloxacin or Gatifloxacin) for isoniazid and/or ethambutol during the initial intensive phase or throughout treatment
- Non-rifamycin based regimens or rifamycin-based regimens with modified doses for treatment of patients co-infected with HIV

The use of rifamycins that are already registered has more advantages as clinical trials are taking longer and costing more. Time to develop a new drug has increased from 8.1 years in 1960 to 15.3 years in 1990. Phase III trials cost in the ranges of 4 million to 20 million US\$.

4.4 PA-824

It is a lead nitroimidazole. The rationale for developing PA-824 includes its:

- Potent bactericidal activity against replicating and static *Mycobacterium tuberculosis* – potential for shortening therapy
- Novel mechanism of action
- Active against drug sensitive and multi-drug resistant (MDR) strains of *Mycobacterium tuberculosis*
- Narrow spectrum of activity

However the product is still in Phase I trials. A Food Interaction Study is ongoing and its extended EBA Study is due in August 2007. Still to follow are a Drug Interaction

Study, a QT Study and a Phase IIb efficacy trials. It clarified that this product is not ready for EDCTP funded Phase II/III trials.

4.5 Summary discussion on products and science

Name of Product	Name of producer	Where in pipeline	Availability	Licensing Status	Tiered price
Moxifloxacin	Bayer	Phase II / III	TB Alliance / Bayer	Registered / pre-FDA approval	–
Gatifloxacin		Phase III	EC / OFLOTUB	–	–
Rifampicin	Merrell / Ciba	Registered	WHO pre-qualified	generic	–
PA-824		Phase I	TB Alliance	–	–

5. Sites in Africa

5.1 Overview of participating organisations and sites

The overview of African sites was given through a preliminary report of TB Alliance who in 2006 assessed 21 clinical trial sites in Africa as part of a global capacity assessment. Comprehensive and detailed assessments were conducted using six separate evaluation questionnaires eighty pages long. Sites were assessed in terms of their readiness to conduct trials for clinical product development and how long it would take to bring them to stage of readiness if found to have weak capacity. Two days was spent on clinical site assessment and another two days on laboratory assessment per site. The sites sampled do not include all sites where clinical trials are conducted in Africa but the data provides a snap shot of the general expectation in sub-Saharan Africa.

The results whose details can be obtained from TB Alliance are summarised in table below:

Name of site	Country	Availability (time to readiness)
UCT Lung Institute, Cape Town	South Africa	6 to 12 months (lab: less than 6 months)
Division of Clinical Pharmacology, Cape Town	South Africa	6 to 12 months (lab: less than 6 months)
Tiervlei Trial Centre, Belville	South Africa	6 to 12 months
Medical Research Council (MRC), Durban	South Africa	6 to 12 months
TBTC, site, Durban	South Africa	6 to 12 months
Perinatal Unit, Johannesburg	South Africa	Less than 6 months (lab: 12 to 24 months)

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Aurum Institute, Klerksdorp	South Africa	6 to 12 months (lab: 12 to 24 months)
U.S. CDC TBTC/TBRU/NIAID site, Kampala	Uganda	Less than 6 months
Infectious Disease Institute, Kampala	Uganda	Less than 6 months
Rakai Health Sciences Program, Rakia	Uganda	Less than 6 months (lab: 6 to 12 months)
Kibong'oto , Kilimanjaro	Tanzania	Less than 6 months (lab: 12 to 24 months)
Kilimanjaro Christian Medical Centre, Moshi	Tanzania	Less than 6 months (lab: 12 to 24 months)
Bagamoyo and Rufiji centres Ifakara	Tanzania	Less than 6 months (lab: to be decided)
EDCTP/UCL/MRC UT Hospital, Lusaka	Zambia	Less than 6 months (lab: 6 to 12 months)
Tropical Disease Centre, Ndola Central Hospital	Zambia	Less than 6 months (lab: 12 to 24 months)
KEMRI), Nairobi	Kenya	Less than 6 months
FWACP (Paed); BMRC site	Gambia	6 to 12 months (lab: 12 to 24 months)
A H R I, Addis Ababa	Ethiopia	Less than 6 months (lab: 12 to 24 months)
Centre Hospitalier, Cotanou	Benin	12 to 24 months (lab: more than 24 months)
CHU Ignace Deen, Conakry	Guinea	6 to 12 months (lab: to be decided)
Manhica	Mozambique	Less than 6 months (lab: 12 to 24 months)

6. EDCTP procedures

6.1 Overview of EDCTP procedures

6.1.1 Call / Brokering

Both the procedures were explained to the audience as outlined in the EDCTP presentation which is available from the EDCTP website

6.1.2 Timelines for initiating funding procedure

These are summarised under recommendations to EDCTP under section 6 below.

7. Summary discussion

The meeting was opened by Dr Ruth Barington, CEO of the Irish Health Research Board, who welcomed participants and wished them good discussions.

The presentations addressed the leading products in the pipeline that might move into human trials in the next 2 years, some of the sites with suitable expertise for conducting such trials (see section 2 above) and many of the allied issues. High points of the presentations were:

- that the new strategy was to use large trials as the driver for infrastructure development and network building with a focus on Ph II and III trials in Africa.
- that brokering was appropriate if there were few products and limited number of sites
- that there were limited regimens that have comprehensive preclinical animal studies supporting human trials, but that these now include two licensed drugs (Moxifloxacin and Rifampicin), and in subsequent discussion the options of Gatifloxacin and Rifapentine
- that trials take time to set up, but can be done and that Gatifloxacin was potentially still licensable with increased toxicity surveillance
- that we need to get away from preparing trials for individual product trials to infrastructure based preparations for a series of products
- that there is potential benefit in the much nearer future from existing drugs than from new drugs
- that Immune Reactivation Inflammatory Syndrome (IRIS) will occur in TB trials and that a coordinated group has been brought together by EDCTP that is asking this on in a rational way and that should be included in the planning for any new drug trials IRIS is a big clinical conundrum (diagnosis, prevention, treatment) but did not justify separate trials, but should be nested in any trials that are done
- that paediatric TB is a problem area, with little or no data upon which to base care and an immediate opportunity for improved diagnostics and for an urgent need for PK studies. Paediatric TB might be a good topic around which to raise additional matching funds. However, diagnostics is a huge impediment and thus, might be best linked with the TB vaccine trials who are making huge efforts to diagnose paediatric TB since it is an endpoint in their trials
- that drug resistance was a problem, but should not be the focus or driver of clinical trials. Specifically, given the methodological uncertainties and the time frame of the EDCTP, optimized best therapy was felt not to be an appropriate design
- that infection control is underappreciated and should be specifically mentioned in any call or brokering to ensure patient safety and raise awareness of TB transmission in health care settings
- that TB/HIV, whether a local priority in some parts of Africa or a pressing global issue, can not be ignored for clinical, humanitarian and political

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reasons. These trials could include the issues of when to start therapy, how to adjust ART and TB drugs.

- that in any clinical treatment trial there will need to be attention paid to diagnostics, and even though not a specific EDCTP priority, some attention must be paid to diagnostics if EDCTP is to accomplish the therapy goals

Conclusion and recommendations:

In Africa many aspects of TB are problematic, including Paediatric, HIV and drug resistant TB. However, given 14 to 30 million Euros and the networking capacity of the converged group it was felt that success would only come from focus. Recently generated animal and accumulating human data suggest that a combination of a quinolone and higher doses of rifamycins could shorten therapy. Furthermore, since these drugs are already approved and available these trials could be conducted relatively quickly and, if found effective, the regimens could be rolled out rapidly. To accomplish this will require a coordinated clinical development program that brings together a number of groups who are each currently addressing parts of the problem. Thus, the group recommended that the major focus (and vast majority of funds) be a clinical development program to optimize the use of moxifloxacin and high dose rifampicin to shorten the duration of therapy to less than 4 months. This would be a consortium of consortia to conduct the necessary Phase II trials (in the order of 5 to 8 trials at 1 to 3 million Euros) and culminate in pivotal Phase III trials (at about 10M Euros each). Fortunately there are some African sites virtually ready for such trials and others which could be ready within a few years with appropriate technical and financial support (see table in section 3). The specific scope of this clinical trial program (e.g. extent of specific HIV/TB focus, linkage to biomarker and basic research, etc) is best dictated by the scientists involved. Because of the restricted scope of activities and the clearly identifiable list of experts in this area, it was further suggested that this be issued as a brokered call. Such an activity would focus on north-north, north-south and south-south networking around an extremely relevant clinical trial that is likely to be otherwise unfunded while providing a unique opportunity for capacity building for future clinical trials for TB and other diseases.

Recommended procedure: Brokering

Recommended time to initiate funding procedure (s): August 2007

Possible funding partners:

Pledged and potential contributions to topic			
Organisation	Country	Amount	Certainty
ANRS	France	TBD	If HIV/TB is part
APRIORI	Netherlands	TBD	TBD
MRC-UK	UK	€5,000,000	Highly
Irish AID	Ireland	TBD	Highly
Instituto de Salud Carlos III	Spain	TBD	Highly
Antwerp School of Trop Med / TBTech	Belgium	TBD	Probable
DANIDA (Peter Abbey in Guinea Bissau site)	Denmark	TBD	Probable

8. Recommendations to EDCTP

It was recommended that such a brokering process should be presented to the EDCTP-EEIG assembly by the secretariat in June 2007, if approved to be

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announced in July 2007, and a meeting of consortia and funders convened to work through details in August 2007.

9. Annexes

Annex 1: Member state and third party contribution to the stakeholder meeting

Estimate of all costs covered by hosting country	
Item	Amount
Travel	0
Hotel	0
Catering	0
Administration support	0
Venue	€2,516 (including catering and Audiovisual)
Other	0
Sum	€2,516

Signed by organising Member State: IRELAND

Name TERESA MAGUIRE (Health Research Board)

Date 11 July 2007

Annex 2: EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 - The development of cooperative projects and coordination of efforts
 - Priorities for EDCTP:
 - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

The stakeholder meeting on Nodes of Excellence has similar priorities:

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- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials
- Experts in the field. Each European Member State may bring one expert of their own choosing

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- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting

Topic
location, date 2007
Address
Contact

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties
- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

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The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

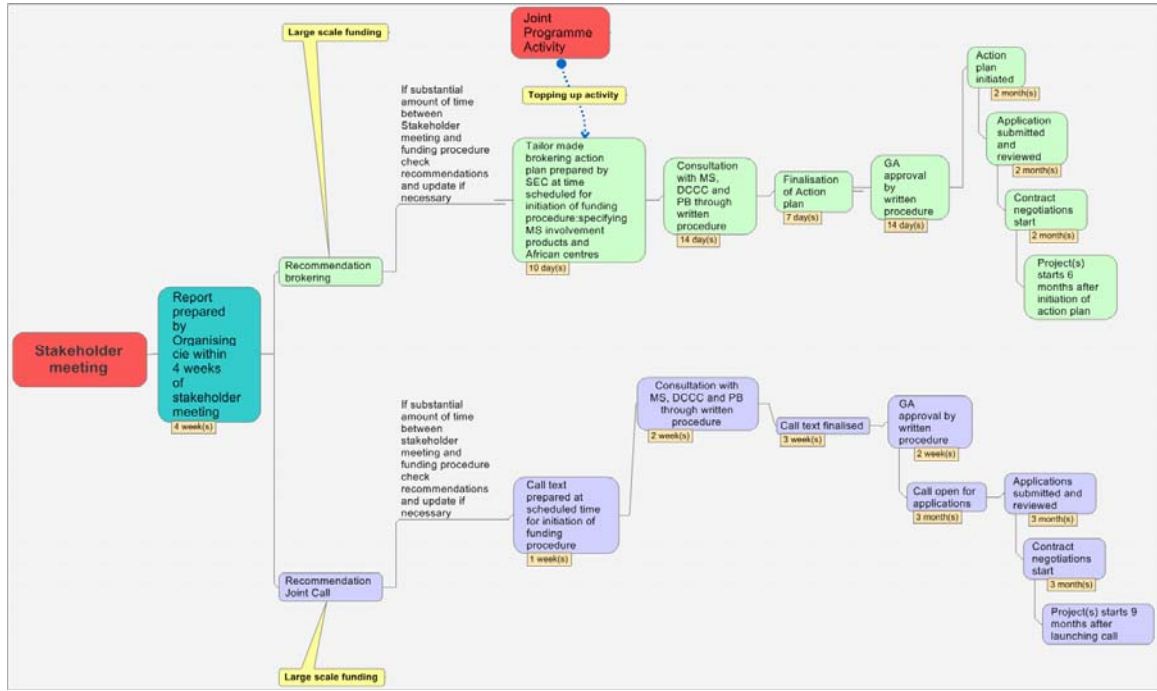
Outcome/follow up

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB make the final recommendation for funding to the General Assembly who approve the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

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Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local malaria situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

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Annex 3: Agenda

EDCTP Stakeholder Meeting
Tuberculosis treatment
 Dublin, May 2007
 Burlington Hotel - O' Connell Suite
 Upper Leeson Street, Dublin 4, Ireland
 9:00hs - 16:00hs

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
Coffee/Tea	All	9:00 – 9:15
1.0 Welcome	Charles Mgone, Mairin Ryan and the Chair Peter Small	9:15 – 9:30
2.0 Approval of the Agenda	All	9:30-9:40
3.0 EDCTP procedures	Cynthia Naus	9:40-9:50
4.0 Science and products		
4.1 Scientific overview of the field	Peter Small	9:50-10:05
4.2 Products in the pipeline: Global TB Alliance	Ann Ginsberg	10:05-10:20
4.3 Products in the pipeline: International Union	Christian Lienhardt	10:20-10:35
4.4 Global funding needs of TB drug trials	Dr Unni Karunakara	10:35–10:50
Coffee break	All	10:50-11:00
5.0 Discussion on products and science	All	11:00-11:30
6.0 Sites in Africa		
6.1 Needs in field of TB treatment	Joseph Odhiambo	11:30-11:45
6.2 Inter TB network	Amina Jindani	11:45-12:00
6.3 TB Iris network	Robert Colebunders	12:00-12:15
Lunch	All	12:15-13:15
7.0 Discussion on sites	all	13:15-13:45
8.0 Member States commitment	Member State representatives	13:45-14:30
9.0 Concluding remarks	Chair	14:30-14:45
10.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	14:45-15:15
11.0 Summary of recommendation	Chair	15:15-15:30
Tea	all	15:30-16:00

Annex 4: List of participants

Number	Name	Address	Organisation	E-mail
1	Amina Jindani	UK	Inter TB network - St. George's, University of London	ajindani@sgul.ac.uk
2	Ann Ginsberg	USA	Global TB Alliance	ann.ginsberg@tballiance.org
3	Ase Bengard Andersen	Denmark	Rigshospitalet, University of Copenhagen	bengaard@rh.dk
4	Charles Mgone	Netherlands	EDCTP	mgone@edctp.org
5	Christian Lienhardt	France	International Union against TB and Lung Disease	clienhardt@iatld.org
6	Cynthia Naus	Netherlands	EDCTP	naus@edctp.org
7	David Coles	Netherlands	EDCTP	coles@edctp.org
8	Diana Dunstan	UK	MRC	diana.dunstan@headoffice.mrc.ac.uk
9	Diarmiud McClean	Ireland	Irish Aid	Diarmuid.mcclean@dfa.ie
10	François Xavier Blanc	France	ANRS	xavier.blanc@bct.aphp.fr
11	Jane Belina Marshal	UK	Global Head Business Development - Roche	jane.marshall@roche.com
12	Joseph Odhiambo	Kenya	PB member - Centers for Disease Control	jodhiambo@ke.cdc.gov
13	Leen Rigouts	Belgium	Institute of Tropical Medicine	lrigouts@itg.be
14	Mairin Ryan	Ireland	National Centre for Pharmacoeconomics – St. James's Hospital	mairin.ryan@ireland.com
15	Maria Carmen Audera	Spain	Instituto de Salud Carlos III	caudera@isciii.es
16	Marjolein Robijn	Netherlands	EDCTP	robijn@edctp.org
17	Martin Boeree	Netherlands	Apriori network	m.boeree@ulc.umcn.nl
18	Peter Small	USA	Bill & Melinda Gates Foundation	peter.small@gatesfoundation.org
19	Richard Adegbola	Gambia	PB member - Medical Research Council	radegbola@mrc.gm
20	Robert Aarnoutse	Netherlands	Radboud University Nijmegen	r.aarnoutse@akf.umcn.nl
21	Robert Colebunders	Belgium	Institute of Tropical Medicine	bcoleb@itg.be
22	Stephen Gillespie	United Kingdom	University College London	s.gillespie@medsch.ucl.ac.uk
23	Teresa Maguire	Ireland	Health Research Board	tmaguire@hrb.ie
24	Thomas Nyirenda	South Africa	EDCTP	nyirenda@edctp.org
25	Tumani Corrah	Gambia	DCCC member - Medical Research Council	tcorrah@mrc.gm
26	Unni Karunakara	Switzerland	MSF	unni.karunakara@msf.org

Annex 5: Discussion paper

Challenges in tuberculosis drug research and development

Ann M Ginsberg & Melvin Spigelman

The present decade has seen a reawakening of tuberculosis (TB) drug research and development (R&D), spurred on by an urgent need to stem the tide of the disease globally and develop new, more effective treatments against drug-sensitive and resistant strains. As a result, there are now seven products in clinical development and the largest pipeline of early-stage projects and compounds in history. The primary goals of this resurgent activity are to shorten and simplify the treatment of active TB, provide safer and more efficacious treatments for drug-resistant TB, simplify treatment of TB-HIV coinfections by eliminating troublesome drug-drug interactions, and shorten treatment for latent TB infection. Successful development of new, safe and effective TB therapies faces a number of challenges, some unique to TB drug R&D, many with implications for other therapeutic indications.

In February 2000, TB and global health stakeholders gathered in Cape Town, South Africa and declared an urgent need for development of improved TB treatments¹. The reasons were obvious. Two billion people worldwide are estimated to be infected with *Mycobacterium tuberculosis*, the bacterium that causes TB, although less than one percent of these have active tuberculosis at any given time. The rest are referred to as having latent TB infection (LTBI). Of the approximately nine million new cases of active TB each year, all but approximately 425,000 are estimated to be sensitive to current therapy, a regimen that routinely demonstrates greater than 95% efficacy in clinical trials. However, despite the potential effectiveness of standard therapy for drug-sensitive disease, there are close to two

million deaths attributable to this disease each year. The urgency for improved treatments is driven by the fact that globally TB is not being controlled effectively with presently available treatment, particularly in parts of the world with limited public health infrastructure, high HIV incidence, or both^{2,3}. The limited effectiveness of current therapy stems largely from the lengthy and complicated nature of first-line treatment for active TB: a six- to nine-month course of four drugs in combination (two months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by four to seven months of isoniazid and rifampin). *M. tuberculosis* shows a still poorly understood ability to persist in very low numbers for long periods in human and animal hosts despite treatment with drugs to which it is genetically sensitive. This phenomenon, called phenotypic resistance or tolerance, is also commonly referred to as 'persistence', and the bacilli that remain in the host for relatively long periods despite appropriate drug treatment are referred to as 'persistors'. Investigators have demonstrated that isoniazid alone at the standard dose kills over 90% of the infecting mycobacteria in the first two days of treatment⁴. Yet, it takes months of isoniazid-containing combination drug therapy to eradicate the relatively few remaining persistors and ensure that patients won't relapse once therapy is stopped.

The difficulty in killing low infecting numbers of *M. tuberculosis* organisms is also highlighted in the treatment of LTBI. The present standard of care requires nine months of therapy with isoniazid to eradicate an extremely small population of cells, which are thought to exist in a 'latent' form. The relationship, if any, between persistors and latent organisms is not understood, although they share the common distinction of requiring lengthy periods of therapy despite genotypic sensitivity to the treating agents.

The most problematic issue with the current first-line TB regimen is that inadequate adherence to the treatment course, attributable to its length, complexity and associated adverse effects, is driving selection of much more difficult- and expensive-to-treat multi-drug-resistant tuberculosis (MDR-TB) strains. Inadequate adherence to treatment occurs despite extensive global efforts by the World Health Organization (WHO), ministries of health, and others to implement the highly labor-intensive TB treatment program known as DOTS, which includes direct observation of treatment by public health workers. The WHO has estimated that in 2004 there were 424,203 cases of MDR-TB globally; 181,408 occurred in patients who had already been treated with standard (first-line) therapy³. Treatment for MDR-TB typically requires 18–24 months of combination therapy with second-line drugs that are less efficacious, more toxic and much more expensive than the four first-line drugs. Recently, a subset of MDR-TB strains has been identified as 'extensively (or extremely) drug-resistant' (XDR-TB). These are now defined⁵ as being resistant not only to isoniazid and rifampin, but also to fluoroquinolones and to at least one of three injectable drugs usually employed in second-line therapy of MDR-TB: capreomycin, kanamycin and amikacin. A recent survey conducted by the WHO and the US Centers for Disease Control and Prevention (CDC) on 2000–2004 data found evidence of XDR-TB strains in all regions of the world. XDR-TB was found most frequently in areas of the former Soviet Union and Asia, but even in the United States 4% of MDR-TB cases met the criteria for XDR-TB. In Latvia, a country with one of the highest rates of MDR-TB, 19% of MDR-TB cases met the XDR-TB criteria⁶. In some cases, XDR-TB has been shown to represent a particularly aggressive form of TB, causing very high mortality and, at least in one

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setting, killing HIV-positive patients within an average of 25 days from diagnosis^{7,8}.

TB treatment in HIV-positive patients is further complicated by drug-drug interactions between some of the antiretroviral agents (ARVs) and key antituberculous drugs, especially rifampin. It is very difficult, especially in resource-constrained settings, to accurately adjust dosages of the drugs in order to safely and effectively treat individuals affected by both TB and HIV⁹.

Goals of improved TB therapy

Improving TB therapy can be conceived as having four primary goals: shortening and simplifying the treatment of active, drug-sensitive TB; improving therapy of drug-resistant disease; being able to simultaneously treat TB and HIV-AIDS; and shortening therapy of LTBI (see **Box 1**). The limitations of current TB treatment drive the need for shorter, simpler, yet still-affordable regimens to treat active, drug-sensitive TB. A markedly shorter treatment regimen for active TB would have an extraordinary impact on TB patients and public health systems, rendering treatment adherence much easier, potentially obviating the need for DOTS, and drastically reducing the selection drive leading to development of new drug-resistant strains of *M. tuberculosis*. Achieving this goal will, however, require overcoming the still perplexing phenomenon of persistence.

To effectively treat and control current MDR- and XDR-TB cases, physicians and national TB treatment programs require regimens based on safer, more tolerable and more efficacious drugs that also have new mechanisms of action. To eradicate the two billion-person reservoir of future cases comprising those who at present are latently infected with *M. tuberculosis*, there must be a treatment that is shorter than, and at least as safe and efficacious as, the presently recommended prolonged course of isoniazid. Whether new types of drugs that overcome the persistence phenomenon in active disease will also be effective against latent infections remains to be seen, but may be a key factor in markedly improving LTBI treatment in the foreseeable future.

The current TB drug pipeline

In February 2000, at the time of the Cape Town Declaration, there was a dearth of TB drug development activity. Largely owing to a lack of market incentives, no major pharmaceutical company was expending significant resources to develop new types of TB drugs, and only a handful of smaller, biotechnology companies had active programs¹⁰. Rifamycins, first introduced for TB treatment in 1966 and approved

Box 1 Goals and challenges of TB therapy

Goals

1. Shorten and simplify the treatment of active, drug-sensitive TB.
2. Improve efficacy and safety and shorten duration of therapy for drug-resistant disease.
3. Develop drugs for those with TB who are coinfecting with HIV that can be readily coadministered with ARVs.
4. Shorten therapy of latent TB infection.

Challenges in reaching these goals

1. Elucidate the biological mechanisms of mycobacterial persistence and latency.
2. Discover and develop new drugs that have novel mechanisms of action and are effective against persistent bacilli.
3. Develop and validate animal models that reliably predict human treatment duration.
4. Develop and validate biomarkers and surrogate endpoints that predict efficacy and thereby shorten clinical trial duration.
5. Develop new preclinical approaches to identifying optimized drug combinations and new clinical and regulatory approaches to testing drug combinations in phase 2 and 3 clinical trials.
6. Enhance capacity to conduct clinical trials in high-burden countries.

by the US Food and Drug Administration (FDA) in 1971, were the last new drug class added to the TB armamentarium. Despite the relatively short time since the Cape Town Declaration, there are now seven drugs in clinical trials being specifically developed for TB (**Table 1**). There are also a significant number of discovery and preclinical projects, with diverse sponsors contributing to these efforts. This represents the most active pipeline for TB drug development in known history.

The two furthest advanced of the seven clinical candidates are the 8-methoxy-fluoroquinolones gatifloxacin and moxifloxacin (see **Table 1**). Gatifloxacin, being developed by a consortium of public- and private-sector partners for an active, drug-sensitive, pulmonary TB indication, is now being evaluated in combination with isoniazid, rifampin and pyrazinamide in a four-month regimen (two months of daily gatifloxacin, isoniazid, rifampin and pyrazinamide followed by two months of thrice-weekly gatifloxacin, isoniazid and rifampin) versus standard six-month, first-line therapy, in an open-label, noninferiority, multicenter, phase 3, randomized, controlled trial in Africa. Patients are being followed for relapse during the two years following treatment completion for the primary efficacy endpoint. A particular issue for this program's ultimate success is the reported increased risk of dysglycemia with this compound compared to other fluoroquinolones, primarily but not exclusively in the elderly or diabetic¹¹. In the United States and Canada, these data resulted in a change in label, contraindicating prescription of gatifloxacin for diabetic patients (February 2006).

Moxifloxacin, being evaluated under the umbrella of a Bayer Healthcare–Global Alliance for TB Drug Development (TB Alliance) partnership (see **Table 1**), is being tested in two different combination regimens. The first regimen, whose evaluation began as an academic exercise by investigators before animal model data were available, substitutes moxifloxacin for ethambutol in the standard first-line regimen. In the phase 2 Tuberculosis Trials Consortium (TBTC) Study 27 (ref. 12), this regimen was demonstrated to be just as efficacious as the standard control regimen in converting patient sputum to culture-negative after two months' treatment and showed a favorable safety and tolerability profile. A *post hoc* analysis further demonstrated that moxifloxacin substituted for ethambutol resulted in a greater rate of sputum culture conversion at early time points (four and six weeks) than the control treatment. A second, similar phase 2 trial of this regimen is now underway and has almost completed enrollment in Brazil (R. Chaisson, Johns Hopkins University, personal communication). Data from the mouse model, acquired after these trials were initiated, are entirely consistent with the Study 27 results and indicate that moxifloxacin is likely to be most efficacious when substituted for isoniazid rather than for ethambutol in the standard first-line regimen¹³. This combination treatment is now under evaluation in a double blind, randomized, controlled phase 2, two-month treatment trial (TBTC Study 28). A phase 3 trial, to include both these regimens if Study 28 data are supportive, is being planned for initiation in the second half of 2007 (REMox TB trial). This trial will evaluate the ability of moxi-

floxacin-based regimens to shorten treatment to four months with safety and efficacy not inferior to the current standard six-month therapy for active, drug-sensitive, pulmonary TB in HIV-positive and HIV-negative adults.

TMC207 (Tibotec), the next-most-advanced compound in development, is a diarylquinoline, now in phase 2 clinical development. First identified in a whole-cell screen¹⁴, TMC207 represents a new drug class for TB, is equally potent *in vitro* against drug-sensitive and drug-resistant strains of *M. tuberculosis*, and has been demonstrated to inhibit the bacilli's ATP synthase. As recently reported¹⁵, although the compound is extremely potent with excellent *in vitro* and mouse *in vivo* activity, there are at least three potential obstacles to its successful registration as a first-line TB treatment: first, it demonstrates a two-fold increase in serum concentration when delivered in the fed versus the fasted state, which could complicate its appropriate delivery to TB patients in a variety of settings globally; second, it is metabolized by the cytochrome P450 3A4 enzyme, and its serum concentration is therefore reduced by rifampin, one of the cornerstone drugs for first-line TB treatment (by 50% percent in a recent trial); and third, TMC207's early bactericidal activity (EBA, a measure typically used as a proof of concept in TB drug development for lack of other biomarkers—see discussion below) in adult patients with active, drug-sensitive, pulmonary TB, is minimal for at least the first four days compared to either isoniazid's or rifampin's. However, in data from Days 5 to 7 of this study, TMC207 at 400 mg per day demonstrated an EBA similar to that of either isoniazid or rifampin during this same time period. Promisingly, TMC207 has demonstrated a good safety and tolerability profile so far, with linear pharmacokinetics in humans. Tibotec is planning to further evaluate the activity of TMC207 in a phase 2 trial in MDR-TB patients. This setting is expected to provide an optimized opportunity to demonstrate potential efficacy, owing to both the absence of rifampin in MDR-TB treatment regimens and the relatively low efficacy of the control, standardized MDR-TB regimen.

Another exciting class of compounds that contributes two candidates to the list of products now in development is the nitroimidazoles. Although they are known to act through a new mechanism of action for TB treatment, the exact intermediaries of activity have not yet been fully elucidated. These two compounds have been demonstrated to be prodrugs whose nitroreductive activation is likely to lead to formation of a number of radicals^{16,17}, in turn leading to bactericidal activity, presumably through negative effects on a range of critical bacillary functions.

Otsuka Corporation is at present evaluating its nitroimidazo-oxazole, OPC-67683, and the TB Alliance is evaluating the nitroimidazo-oxazine PA-824, originally discovered at Pathogenesis and subsequently outlicensed from Chiron Corporation (now Novartis). OPC-67683 is reported¹⁸ to have completed phase 1 safety, tolerability and pharmacokinetic testing and a 7-day, EBA, proof of concept study at a dose of 400 mg. A new formulation, intended to minimize a fed-versus-fasting effect on drug pharmacokinetics, is being tested in an extended (14-day), multiple-dose, multicenter, EBA study now in progress in South Africa with a standard four-drug control regimen. PA-824 has been tested for safety, tolerability and pharmacokinetic parameters under an investigational new drug application in the United States and at present is being planned for evaluation in a 14-day, EBA study, to be conducted in South Africa. If either or both compounds demonstrate significant EBA with an acceptable therapeutic window between efficacious dose and maximum tolerated dose, the next step will be longer-term efficacy trials—most likely two-month, combination-regimen phase

2 studies to assess superior ability to convert patient sputum to culture-negative, as well as to further assess longer-term safety.

Lupin Ltd. is developing a new pyrrole, known as sudoterb or LL-3858. In a mouse model, this compound, when administered in combination with first-line drugs, is reported to have sterilized lungs and spleens in less time than the standard first-line regimen¹⁹. It is now in multidose phase 1 clinical development.

The seventh compound known to be in clinical development is Sequella Inc.'s SQ-109 (ref. 20). This compound, an ethylenediamine, is believed to have synergistic interactions with both isoniazid and rifampicin²¹. It has recently entered phase 1 evaluation, and results of the first-in-human study are expected in the first quarter of 2007 (ref. 22).

The current discovery and preclinical pipeline feeding the clinical development portfolio must be robust, even more so than it is today, if it is to adequately support the goals for improved TB therapy described above. To that end, the Bill & Melinda Gates Foundation has recently initiated a TB drug development 'accelerator' program to stimulate research

Box 2 Factors contributing to the long duration of TB drug clinical development

- 1. Limited biomarkers of drug efficacy for use in early clinical development.** Well validated efficacy predictors that could be used in phase 1 and 2 to decide whether to advance a compound to late-stage trials would help streamline clinical development. At present, the best substantiated and most broadly accepted biomarker for assessing efficacy in a phase 2 trial is the two-month sputum culture conversion rate. Serial sputum colony counts (SSCC) with nonlinear mixed-effects modeling may prove to be a better biomarker, in that statistically significant differences appear to be achievable with considerably fewer patients²⁹. There are, however, no data yet that compare SSCC results with the gold-standard efficacy endpoint of treatment failure and relapse rates in the one to two years following treatment completion. The ongoing gatifloxacin phase 3 trial will provide the first such data.
- 2. Long doubling time of *M. tuberculosis*.** The 24-hour doubling time of *M. tuberculosis* means that standard microbiological endpoints based on culture of mycobacteria from sputa require at least six weeks of growth for solid media-based techniques and typically three to four weeks for liquid culture-based techniques.
- 3. Lengthy treatment periods.** Current TB treatment for active, drug-sensitive disease is highly efficacious and therefore must be included in any pivotal trial as a control arm. This necessitates a minimum six-month treatment period in any phase 3 trial.
- 4. Requisite long patient follow-up times.** Presently, the only validated efficacy endpoint for pivotal, phase 3 trials requires following patients for one to two years after completion of the full treatment regimen to measure the combined failure and relapse rate of a TB therapy. Data indicate that six-month post-treatment follow-up rates might be an acceptable surrogate, as the majority of relapses occurring in the first two years occur in the first six months of follow-up after treatment completion^{30,31}. Recently, efforts have begun to identify surrogate endpoints that could be measured at the end of treatment, or even earlier, and would accurately predict long-term relapse rates. Such a surrogate, once validated, would dramatically decrease pivotal trial timelines.
- 5. Relatively large patient numbers.** Current TB treatment's high efficacy means that demonstrating even noninferiority of a new regimen requires a relatively large number of patients per arm, and hence relatively long enrollment periods.

Table 1 TB drug candidates in clinical development

Compound	Development stage	Sponsor or coordinator
Gatifloxacin	Phase 3	OFLOTUB Consortium; European Commission; WHO TDR; Lupin Ltd.
Moxifloxacin	Phase 2, 3	Bayer; TB Alliance; CDC; University College of London; Johns Hopkins University
TMC207	Phase 2	Tibotec
OPC-67683	EBA	Otsuka Pharmaceutical Co., Ltd.
PA-824	Phase 1	TB Alliance
LL-3858	Phase 1	Lupin Ltd.
SQ-109	Phase 1	Sequella, Inc.

WHO TDR, World Health Organization Tropical Disease Research; CDC, US Centers for Disease Control and Prevention.

that would lead to identification of persistence targets, and to further develop and validate relevant animal models. Positive outcomes from this initiative and related research funded by other sources such as the US National Institutes of Health and the European Commission would be a crucial stimulant to successful TB drug development.

Challenges for drug development

Identification of drugs that will shorten treatment and thereby improve adherence is key to radically improving active TB treatment, decreasing demands on national TB control programs, and preventing further selection of resistant strains. Ideally, finding such drugs would be based on knowledge of the underlying mechanisms of mycobacterial persistence, enabling identification of crucial targets. At present, both a clear understanding of persistence mechanisms and fully validated animal models that reliably predict human treatment duration are lacking, and thus so is an efficient path to developing drugs for shortening treatment. The mouse model²³ appears to reflect human treatment results in most but not all circumstances, but it lacks adequate prospective data to be considered truly validated at this time. In the absence of fundamental biological understanding of persistence, shortening therapy of active disease to days rather than months is likely to remain a distant goal. Realistically, current animal model evidence and clinical data indicate that shortening treatment to three to four months should, however, be achievable even with combinations of current and new drugs already in the pipeline.

A second challenge for TB drug R&D is the long timeline of clinical trials. Phase 2 studies for TB drugs typically require at least two years, and pivotal trials a minimum of three years from beginning patient enrollment to finalized study reports. These relatively long periods result from a number of factors (see **Box 2**).

The requirement for multidrug therapy represents one of the crucial challenges for TB drug R&D, as it has several repercussions that affect the R&D process. First, because as little as a few weeks of monotherapy may lead to the development of drug resistance^{24–27}, it is not ethical to test single drugs beyond the stage of EBA studies (which have maximally involved 14 days of treatment). Furthermore, current therapy, being highly efficacious, should not be withheld for any longer than necessary. This means that any new drug must be evaluated for efficacy in the context of combination therapy. Second, the need for combination therapy necessitates extensive drug-drug interaction studies, not only with potential concomitant medications, such as antiretroviral agents, but also with other drugs in the proposed TB treatment regimen. The fact that people must be treated at present with a combination of four drugs, rather than with a single drug, means that to replace the current regimen with a totally new three- or four-drug regimen by testing the substitution of one drug at a time into the standard regimen will require not a minimum of six years (an estimated one year for phase 1, two years for phase 2, and three years for phase 3 as an aggressive clinical development timeframe), but at least four × six years—over two decades—just for the clinical phase of development. Clinical development for TB drugs would be much more efficient if the unit of drug development were considered to be the combination regimen rather than the single new agent. This strategy can be thought of as analogous to vaccine development approaches, in which a new vaccine may include a number of distinct antigens, all of which are developed together as a single ‘candidate’. Identifying and developing a three- or four-drug regimen as a single unit would cut development time dramatically to within a timeframe commensurate with the urgency of the need for improved TB treatments.

New regimens that take maximal advantage of even the existing TB drug pipeline and

dramatically shorten the treatment duration for active disease will most probably require more than one new drug. In order to develop a new regimen that contains more than one new chemical entity, we propose preclinical and full phase 1 safety, tolerability and pharmacokinetic testing of each individual drug, in parallel with *in vitro* and *in vivo* preclinical evaluation of potential drug combinations to identify optimized candidate regimens. A preclinical approach has been proposed by the FDA in draft guidance for nonclinical testing of new drug combinations²⁸. An optimized candidate combination regimen could then be advanced into phase 2 testing as a development unit, perhaps both in EBA and in two-month treatment trials for proof of concept and dose finding, and then, if the data are supportive, into full, phase 3, safety and efficacy testing. Although it would be intellectually gratifying and regulatorily preferable to understand the contributions to safety and efficacy of each individual drug in a combination regimen based on comparative human data, this is not possible for TB drugs. The current first-line regimen was developed in an era where such regulatory requirements did not exist and the necessary trials were never conducted to acquire most of the relevant data for current first- or second-line TB drugs. As it is now unethical to test these drugs individually in TB patients for safety and efficacy beyond one to two weeks of treatment, it is not possible to document clinically the individual contributions of each component in the context of a combination regimen in TB.

Another challenge in TB drug development is presented by the very high efficacy of the current standard regimen for active, drug-sensitive disease—routinely over 95% under trial conditions. As a result, a new regimen must be tested for noninferiority rather than superiority compared to a standard control arm to avoid impractically large patient numbers and the very small ‘window’ in which a new regimen could possibly be shown to be ‘superior’ to standard treatment. However, superiority of a new TB regimen may be demonstrated by providing convincing data that clinically significant shortening of treatment duration with the new drug combination is ‘noninferior’ to standard therapy.

TB clinical development may be impeded further in coming years by a lack of adequate clinical trial capacity for the conduct of both EBA and late-stage clinical trials to registration and internationally accepted standards of good clinical practice and good laboratory practice. As most TB patients are in low- and middle-income countries, late-stage clinical trials must and should be conducted in these high-burden settings.

The dearth of new TB drug development, particularly of trials to support regulatory registrations, over the past 30 to 40 years means that relatively few sites are experienced in the appropriate conduct of clinical trials. The TB Alliance has recently conducted a baseline assessment of over fifty clinical sites, including their mycobacteriology and safety laboratories, in 25 countries on five continents. Although the data from this study are still being analyzed, it is clear that developing adequate capacity to fully evaluate even the seven compounds now in the clinic will require significant capacity-building over the next few years at a number of sites throughout the world. Although approximately one-third of all TB patients are now in India and China, the WHO-identified 22 high-burden countries for TB are scattered throughout Asia, Africa, Eastern Europe and South America, and the disease has been identified in every country investigated. Global registration of new, improved treatment regimens will therefore require safety and efficacy testing in appropriately diverse populations.

Last, despite the recent, significant contributions of major funders such as the Bill & Melinda Gates Foundation, the Rockefeller Foundation and a number of governments throughout the industrialized world, a key challenge for this field remains increased and sustainable funding to meet the demands of

research to fight TB. Improved therapies for this disease must not only be discovered and developed, but must also be made affordable, accessible and adopted throughout the world to help eliminate TB as a major public health problem and leading infectious killer.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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