Drug development and evaluation for helminths and other neglected tropical diseases

TDR BUSINESS LINE **6**

World Health Organization

TDR For research on diseases of poverty

Design: Lisa Schwarb • Layout: Simon Fenwick
Photo caption: (on left) Community begins construction in March 2008 of a clinical trial centre in Bolahun Liberia funded by TDR, the African Programme for Onchocerciasis Control (APOC) and a $6 million donation from Wyeth Pharmaceuticals.
(on right) By November 2008, the modern centre, built from sun-dried mud bricks, stands ready for opening ceremonies in advance of initiation of the Phase III trial of moxidectin, a drug candidate for eradication of onchocerciasis. The trial in Liberia, Democratic Republic of Congo and Ghana is being co-sponsored by TDR and Wyeth, owner of moxidectin. Pictures: WHO/TDR/Kuesel
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List of abbreviations

ABC ATP-binding casette
ADL Acute episodes of adenolymphangitis
AEs Adverse events
AIDS Acquired immune deficiency syndrome
ANDI African Network for Drugs and Diagnostics Innovation
APOC African Onchocerciasis Control Programme
BENEFIT BENznidaqzole Evaluation For Interrupting Trypanosomiasis Trial
BLs Business Lines
BL6 Business Line 6
CD Chagas disease
CDI Community-directed intervention
CDTI Community-directed treatment interventions
CIHR Canadian Institute of Health Research
DECs Disease-endemic countries
DEC Diethylcarbamazine
DENCO Dengue control
DNDi Drugs for Neglected Diseases initiative
DRC Democratic Republic of Congo
EMEA European Medicines Evaluation Agency
FIOCRUZ Oswaldo Cruz Foundation
GABA Gamma-AminoButyric Acid
GAELF Global Alliance for the Elimination of Lymphatic Filariasis
GCP Good Clinical Practice
GCLP Good Clinical Laboratory Practice
GSK GlaxoSmithKline
HAT Human African trypanosomiasis
HDI Helminth Drug Initiative
INGEVI-CONICET Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular
INRSP Institut National de Recherches en Santé Publique
IV Intravenous therapy
LabMECh Laboratorio de Biologia Molecular de la Enfermedad de Chagas
LF Lymphatic filariasis
Loa loa Loiasis
LTS Lohmann Therapie-Systeme AG
MSF Médecins Sans Frontières
NTD Neglected Tropical Diseases
OCP Onchocerciasis Control Programme in West Africa
OCRC Onchocerciasis Chemotherapy Research Center
Oncho Onchocerciasis
PCR Polymerase chain reaction
PI Principal investigator
PK Pharmacokinetics
PPPs Public-Private Partnerships
PZQ Praziquantel
R&D Research and development
SAC Scientific Advisory Committee
SAE Serious Adverse Events
SOP Standards of Practice
STAC Scientific and Technical Advisory Committee
TDR UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TPP Target Product Profile
VL Visceral leishmaniasis
WHO World Health Organization
WHO/AFRO WHO Africa Region

Overview and highlights

Neglected tropical diseases (NTDs) have been highlighted as a key priority by WHO. A specific WHO strategy to manage populations at risk has been developed. Preventive Chemotherapy and Transmission Control aims to use available anthelminthic drugs either alone or in combination as a public health tool for preventing morbidity due to more than one form of helminthiasis at once. Innovative and Intensified Disease Management focuses on diseases for which cost-effective control tools do not exist and where large-scale use of existing tools is limited. Drugs to address these strategies are available but they are few, and sometimes their mechanisms of action are poorly understood and their dosage and regimens are not based on detailed pharmacokinetic and pharmacodynamic information, which in most cases is lacking. Furthermore, their extended use carries the risk of drug resistance development. Therefore, new or improved tools are required. These considerations have defined the strategic objectives of BL6: development, registration and field evaluation of new drugs and generation of evidence for improved use of currently available drugs for NTDs.

This work builds on the TDR track record and expertise in product development and evaluation, and is set up to respond to NTD control needs.

The current portfolio consists, for the major part, of clinical research activities that were initiated before 2008 and for which commitments to 6860 patients, 39 investigators and institutions in 40 countries have been made. Some of these activities will continue according to pre-established work plans and are an integral part of the conceptual framework of BL6. Some will reach conclusion within 2009, and others will be initiated after discussion at the Strategic Advisory Committee (SAC).

BL6 has also played an active role as secretariat in the 61st World Health Assembly resolution on the *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, as well as in discussions regarding the WHO Strategy on Research for Health.

Key activities are summarized according to the diseases they address.

Onchocerciasis. BL6 projects to support the onchocerciasis control programme objectives demonstrate TDR's capacity to work with pharmaceutical partners, to build research infrastructure and capacity that will support research in and by the countries beyond the TDR-conducted projects, and to conduct clinical trials in extremely remote, difficult conditions.

TDR/BL6 is evaluating moxidectin as a potential macrofilaricidal drug for onchocerciasis in collaboration with Wyeth Pharmaceuticals. During 2008, the Onchocerciasis Chemotherapy Research Center in Hohoe, Ghana, completed the recruitment (172 subjects) for Phase 2. TDR has built the physical infrastructure and clinical trial capacity for three new clinical research centres in Liberia and Democratic Republic of Congo (DRC) in preparation for the upcoming Phase 3 study. The Phase 3 study, involving 1500 subjects in Ghana, Liberia and DRC, is expected to begin in the first or second quarter of 2009. In late 2009/early 2010, a study addressing pharmacokinetics and safety of moxidectin in a paediatric population is planned to be initiated in Ghana. If proven effective and safe, moxidectin could provide the basis for a disease elimination programme.

TDR also supported the clinical (57 subjects) and field evaluation (2283 subjects) of a skin patch test developed by LTS Lohmann Therapie-Systeme AG to detect onchocerciasis infection. Preparation is ongoing for submission for approval by onchocerciasis-endemic countries as a tool to be used for surveillance purposes in areas that have undergone extensive rounds of ivermectin treatment.

TDR has been actively engaged in developing a joint strategy with the African Programme for Onchocerciasis Control (APOC) on studies addressing methods to detect ivermectin resistance in the context of the onchocerciasis control programmes.

Lymphatic filariasis (LF). TDR has set up the first-ever study in children who become infected with LF (*Brugia malayi*). Early treatment may prevent the elephantiasis (enlargement of the limbs and scrotum) that develops after years of untreated LF. The local investigator in Alleppey, India, screened almost 8000 children to identify 200 who could be recruited into this study, which is determining whether the treatment of albendazole + diethylcarbamazine can reverse early lymphatic lesions. The research is being done in close interaction with the national LF control programme.

Schistosomiasis. This multi-country study (800 subjects in Philippines, Brazil, Mauritania and United Republic of Tanzania) compared the safety and efficacy of 40 mg versus 60 mg of praziquantel. The results provided information for countries to decide on treatment policies. Dosage recommendations had never been based on solid evidence.

***Loa loa*.** A clinical study in Cameroon is determining the effect of albendazole on *Loa loa* microfilarial loads. If found effective and safe, the treatment regimen will allow standard ivermectin mass treatment in areas of co-endemic for loiasis and onchocerciasis, and a introduction of ivermectin mass treatment in areas of co-endemicity of loiasis and lymphatic filariasis.

Human African trypanosomiasis (HAT). The current treatment for second-stage HAT of IV infusion of eflornithine four times a day (each infusion taking two hours) is burdensome and difficult in remote areas. This Uganda study is identifying whether adding nifurtimox tablets to this regimen can reduce to two the number of daily infusions needed and the total length of treatment from 14 days to 10 days (studying safety and efficacy).

Another ongoing study in early-stage HAT is comparing the safety and efficacy of a three-day pentamidine treatment against the standard seven-day treatment. This is an attempt to reduce the dosage and consequent side-effects of the only drug available.

Chagas disease. This is the largest-ever study (3000 individuals) conducted to determine whether benznidazole can eliminate the parasite and reduce the evolution of cardiac disease in chronic *T. cruzi*-infected individuals. It should generate clinical evidence that could change the current treatment policy.

Additionally, a multi-country activity is under way that aims to standardize and validate the clinical use of polyermase chain reaction (PCR) for analysis of samples in *T. cruzi*-infected individuals. TDR also participated in consultations on the development of posaconazol as a treatment for Chagas disease (one consultation involving DNDi and one involving the drug owner Schering-Plough).

Dengue. A four-year multi-centre clinical study (DENCO) provided the data for an evidence-based classification of dengue disease into three levels of severity: severe dengue, dengue with warning signs and dengue without warning signs. TDR also led consultations with key stakeholders on the definition of a target product profile and the development of antiviral dengue drugs and dengue disease modifying drugs.

The BL6 Strategic Advisory Committee (SAC) will assess at its March 2009 meeting several recently initiated and potential new activities, including:

- Development of tools for ivermectin resistance detection in onchocerciasis;
- Evaluation of praziquantel combination with oxamniquine for schistosomiasis;
- L-praziquantel for schistosomiasis;
- Nifurtimox and eflornithine for the treatment for *T. b. rhodesiense* second-stage HAT.

Commitments from ongoing projects are limiting this business line's ability to initiate already approved projects and to take on new work, and several options are proposed to continue the product development pipeline.

BL6 has strong ties with five other business lines, plus Stewardship and Empowerment. Through its support, it has attracted pharmaceutical funding and free supplies of study drugs and equipment, national control programme support and infrastructure for clinical trials, and support of WHO country and regional office staff.

1. Context, strategic objectives and framework

1.1. Context

The current WHO approach to control NTDs is based on two different strategies. For diseases for which tools are not available or difficult to use (such as Buruli ulcer, Chagas disease, human African trypanosomiasis and leishmaniasis), the emphasis is on increasing awareness and early detection of the disease and ensuring the availability, affordability and cost-effective use of the current tools. For diseases where there are safe and effective drugs (such as cysticercosis, dracunculiasis, foodborne trematode infections, lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis), the strategy is to use these in a context of preventive chemotherapy as tools to control transmission, ideally co-administered when multiple diseases coexist in the same patient or the same area.

For the first group of diseases, there is an urgent need to develop safe and affordable new drugs. For the second group the need is to optimize drug doses and regimens, which requires additional data such as pharmacokinetics, pharmacodynamics, drug interactions and new formulations. Control of these diseases currently depends on a single drug, and expanded use carries the risk of drug resistance. Therefore, new drugs are also needed for the second group of diseases.

TDR is well-positioned to undertake the work required, based on its track record in drug development and evaluation and its networks of investigators and institutions.

1.2. Strategic objectives

The overall objective is to develop new or improved therapeutic tools for neglected tropical diseases and generate new pharmacological information to enhance the impact of the currently available tools.

The research activities will take into consideration the needs of special populations, gender-specific issues and the social, economic and health systems of the countries where the target diseases are prevalent. Researchers and institutions of disease-endemic countries will play a pivotal role in the key decisions and implementation of activities. The specific objectives are:

1.2.1. Development, registration and field evaluation of new drugs for

a) onchocerciasis, lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, foodborne trematodes and dengue, which do not have dedicated public-private partnerships (PPPs) to promote/support drug development like other NTDs; and b) other neglected tropical diseases when the need arises.

Activities include identification of drug candidates, progression into development, and registration and validation for use in the field. This work is conducted in partnership with institutions from developed and developing countries (private and public). The research activities adhere to the highest standards of ethics and good practices. Special attention is given to the specific needs of neglected populations (women and children). The field studies will determine the safety and effectiveness of the drugs in real-life settings. Close collaboration with bio/pharma companies in developed and developing countries is important. Capacity-building with close interaction with disease control programs, health systems and regulatory authorities in developing countries is a prerequisite.

1.2.2. Generation of evidence for improved use of currently available drugs for NTDs to support disease control, elimination or eradication strategies for NTDs, with emphasis on integrated disease management or prophylactic chemotherapy (helminths) or enhanced disease case management (leishmaniasis, African and American trypanosomiasis, dengue).

This objective supports research on:

I) Drug pharmacology, efficacy and safety of currently used drugs. The doses or regimens used for the treatment of many NTDs are not always based on solid pharmacological, efficacy and safety information, and in many instances do not address gender (pregnancy is an especially high priority), ethnicity or age-specific issues. Availability of such information is essential to optimize the use of currently available drugs or to scale up their use.

II) The potential for the development of drug resistance and prevention of emergence of resistance. Priority is given where single drugs are used in mass treatment programs and no therapeutic alternatives are available.

III) The pharmacological basis for the effective and safe use of drug combinations to improve efficacy or compliance for a particular drug or to validate the concomitant use of drugs to address several co-endemic diseases at once (integrated disease control approaches).

1.3. Strategic framework

The decisions on the portfolio content and prioritization are based on the demands of control programmes in disease-endemic countries (DECs) and on evidence-based assessments of research needed to improve NTD control strategies. The current portfolio is to a large extent determined by commitments to product development and clinical studies initiated before 2008. As these studies are completed, new product development opportunities and the availability of collaborators and resources will play increasing roles in determining the portfolio.

The end-products for each objective are summarized as follows:

Objective 1: Development, registration and field evaluation of new products for NTDs

End-product 1 (ongoing): Moxidectin for onchocerciasis (and lymphatic filariasis), product registration (2013) and field validation for onchocerciasis transmission interruption (2015).

Outcome: Change of onchocerciasis control objective from elimination of onchocerciasis as a public health problem to eradication of infection.

End-product 2 (approved, not started): Combination of praziquantel and oxamniquine for schistosomiasis. Registration (2015) or recommendation for use (2011) of drug combination for schistosomiasis treatment.

Outcome: Adoption by schistosomiasis control programme as a means to prevent emergence of drug resistance.

End-product 3 (approved, not started): L-praziquantel registration for schistosomiasis (2015).

Outcome: Adoption by schistosomiasis control programme as a means to decrease side-effects associated with use of racemic mixture.

End-product 4 (concluded): Validation and standardization of polymerase chain reaction (PCR) use in clinic to detect *T. cruzi*.

Outcome: Adoption as the standard for use in patient management, blood screening, drug development and as reference methodology for the development of new PCR kits.

End-product 5 (ongoing): Transdermal delivery of diethylcarbamazine citrate (DEC patch) as a diagnostic tool for onchocerciasis. Clinically and field validated skin patch approved by national authorities for surveillance for residual or resurging onchocerciasis (2009).

Outcome: Adoption by onchocerciasis control programmes as epidemiological tool in data collection to assist in the decision on when and where to stop ivermectin treatment in areas with long-term onchocerciasis control and surveillance post-treatment discontinuation.

Objective 2: Generation of evidence for improved use of currently available drugs

End-product 1 (ongoing): Reduction of *Loa loa* microfilaremia by albendazole and potentially reducing the risk of ivermectin-induced serious adverse events (SAE) in *Loa loa*-infected individuals. Proof of concept of efficacy of albendazole against *Loa loa* (2009).

Outcome: Accelerated expansion of the use of ivermectin against onchocerciasis and implementation of ivermectin + albendazole treatment in lymphatic filariasis loiasis co-endemic zones.

End-product 2 (ongoing): Therapeutic effect of albendazole + DEC in children with lymphatic filariasis. Demonstration of safety and efficacy in curing and reversing lymphatic lesions in children infected with *Brugia malayi* (2009).

Outcome: Lymphatic filariasis control programmes include cure of infection and regression of early lymphatic lesions in children (currently aiming only at interruption of transmission).

End-product 3 (ongoing): Nifurtimox and eflornithine regimen for the treatment of second-stage human African trypanosomiasis (HAT). Data validating a 10-day regimen as providing efficacy equivalent to that of the standard 14-day eflornithine treatment (2010).

Outcome: Adoption by HAT control programmes, inclusion in the WHO list of essential medicines, reduced workload for health care systems and a more acceptable treatment for patients.

End-product 4 (ongoing): Three-day pentamidine treatment regimen for 1st-stage human African trypanosomiasis (HAT). Data validating the efficacy and safety of a three-day regimen over the currently recommended seven-day regimen (2011).

Outcome: Adoption of a shorter treatment course of pentamidine by HAT control programmes, resulting in improved compliance, fewer treatment-related complications and reduced workload for health care systems.

End-product 5 (ongoing): Benznidazole for the treatment of patients in the late indeterminate or early chronic phase of *T. cruzi* infection. Safety and efficacy (clearance of parasites as measured by PCR) in the chronic phase of *T. cruzi* infection in BENEFIT pilot (2010).

Outcome: Contribute to a large multi-centre study, BENEFIT, to demonstrate reduction of the risk of cardiac disease onset and progression in *T. cruzi*-infected individuals after treatment with benznidazole. If results are positive, this will result in changed treatment guidelines.

End-product 6 (ongoing): Effective and safe dose of praziquantel for the treatment of schistosomiasis. Demonstration of safety and efficacy equivalence of 40 mg and 60 mg doses (2009).

Outcome: Adoption by national schistosomiasis control programmes.

End-product 7 (ongoing): Revised dengue classification and updated case management guide. Validation through clinical evidence (2010).

Outcome: Adoption of a new dengue classification for better patient identification and case management.

2. Key stakeholders, roles and responsibilities

The main stakeholders are the African Onchocerciasis Control Programme (APOC), the lymphatic filariasis elimination programmes, schistosomiasis control programmes and national dengue, Chagas disease and African trypanosomiasis control initiatives. Their roles are to highlight the needs and gaps on tools, to link TDR with key national institutions like national drug regulatory agencies, and to advocate for increased funding in these research areas.

TDR depends very much on partnerships with the pharmaceutical industry to accomplish product development and regulatory approval. These partners contribute with expertise, hands-on activities and financial contributions.

Research centres and experts from developing and developed countries are key partners as advisers and disease experts and in implementing research activities.

In addition to the donors who provide undesignated funding to TDR as a whole, the African Onchocerciasis Control Programme, Bayer, GSK, LTS Lohmann Therapie-Systeme, AG Sanofi-aventis, the World Bank and Wyeth contributed cash or in-kind support.

3. Implementation plan 2008–2013 and progress

3.1. Plan, progress and key milestones

OBJECTIVE 1: Development, registration and field evaluation of new drugs

End-product 1: Development of moxidectin for onchocerciasis and lymphatic filariasis

Principal investigator: Dr Kwablah Awadzi, Onchocerciasis Chemotherapy Research Center (OCRC), Hohoe Hospital, Hohoe, Ghana

TDR project manager: Dr Annette Kuesel

Moxidectin, a macrocyclic lactone drug derived from the actinomycete *Streptomyces cyanogriseus*, was developed by Fort Dodge Animal Health as a veterinary product. It is registered worldwide (including the United States) for prevention of canine heartworm and for treatment of parasites in cattle, sheep and horses. It is now being developed in collaboration with Wyeth as a macrofilaricidal/macrofilaria-sterilizing treatment for humans with onchocerciasis to provide a treatment that can be administered through community-based mechanisms to cure patients and permanently interrupt disease transmission. This study is supported by the African Programme for Onchocerciasis Control. Nonclinical study results support clinical trials for the oral administration of moxidectin. Up-to-date, complete animal safety data have been compiled, a suitable dosage form (tablets) has been manufactured, and a (Phase I) clinical trial of safety and PK in 95 healthy volunteers has been conducted. Phases 2 and 3 are being conducted in endemic countries with national ethics and regulatory approval. The development is conducted under article 58 of the European Medicines Evaluation Agency (EMEA) regulatory frame. The registration of the product is targeted for 2013 and deployment as a validated control tool could occur by 2015. If results for onchocerciasis are encouraging, development for lymphatic filariasis will be considered. The detailed work plan is presented in Annex 6.1.

Progress and key achievements

- Phase 2 study (three dose levels for three intensities of infections) completed enrolment of 172 subjects and sufficient follow-up to allow conclusion (based on blinded data) that microfilaricidal efficacy and safety of moxidectin is comparable to that of ivermectin.
- Infrastructure for Phase 3 study completed at site in Liberia and two sites in DRC and available in Ghana.
- Regulatory advice (EMEA) on preclinical and clinical development strategy and plan obtained, EMEA submission for advice on pediatric plan.
- Go decision for initiation of Phase 3 with 8 mg dose.
- Phase 3 (1500 subjects) to be initiated during 1-2Q09.

Project implementation status vs. plan

- Completion of recruitment into Phase 2 was delayed by three months due primarily to longer than anticipated time for subject recruitment and Go decision for initiation of the 4 mg and 8 mg dose levels.
- Initiation of Phase 3 is being delayed by at least 8 months (current estimate) due primarily to delays in site capacity-building caused by delays in finalization of the legal agreement, WHO's implementation of its new administrative system, delivery of WHO-ordered equipment to sites (transport, customs clearance), finalization of

documentation for the ethics committee and regulatory authority submissions, and longer than anticipated time for obtaining authorization for study conduct.

Leverage

- Wyeth investment in manufacturing site preparation and qualification (including regulatory inspection), study drug manufacture and qualification, pre-clinical toxicology and pharmacology studies, assembly of regulatory submissions, operational support for Phase 2 study data management, preparation of operational support of Phase 3 data management, consultation with European regulatory authorities (EMEA), regulatory reporting of drug-related SAEs, preparation of three clinical pharmacology studies required for the submission of an application for a scientific opinion from the EMEA and drug registration in onchocerciasis-endemic countries.
- Wyeth grant of US$ 6 million to TDR.

Implications of progress/delays and changes in the global context for 2008–2013 plans

If project is delayed further, the availability of ivermectin-naive patients for the Phase 3 will be jeopardized due to plans for expanding ivermectin distribution in key study areas in 2009.

Ivermectin resistance has not been demonstrated. Should it appear, moxidectin development would need to be reassessed.

Specific activities for 2009

Continue Phase 2, initiate Phase 3, prepare and perhaps initiate paediatric study, initiate selection of sites for community studies.

End-product 4: Validation and standardization of clinical use of polymerase chain reaction (PCR) for detection of *T. cruzi*

Principal investigator: Dr Alejandro G Schijman, LabMECh, INGEBI-CONICET, Buenos Aires, Argentina

TDR project manager: Dr Janis K Lazdins-Helds

PCR technology has been used extensively to address basic research questions pertinent to *T. cruzi*. However, application and utility of this technology to clinical research has been limited, mainly due to the differences in methodology which make comparisons of results among centres difficult or impossible. Following a request from key investigators from Argentina, Colombia and Brazil, TDR sponsored an initiative aimed at standardizing the use of PCR for analysis of clinical samples. This leveraged additional funding from Consejo Nacional de Investigaciones Cientificas y Tecnicas (Argentina), United Nations University, and Fundacion Bunge y Born (Argentina). This initiative was based at INGEBI-CONICET, Buenos Aires. Twenty-nine centres located all over the world were provided blinded samples to conduct PCR analysis according to their own protocols. Results were submitted to the coordinating centre and those that fulfilled the minimum ranking of concordance with the results of the reference protocol participated in a "hands-on" workshop of four days at INGEBI, Buenos Aires, Argentina. The workshop defined best PCR practices for clinical sample analysis and established the limitations of this technology. The consensus protocol is seen as an important step to study patients across geographical areas, to address special clinical situations (such as post-transplantation, AIDS, congenital infection)

and to quantify treatment outcome, in particular the evaluation of drug candidates in clinical studies. This protocol was also proposed as the standard reference for evaluating new (commercial) PCR kits. The outcomes of the discussions and technical aspects describing the consensus PCR protocol will be submitted for publication in a relevant peer-reviewed journal. The representatives of the 29 laboratories also committed themselves to use and further validate the process through application of the consensus protocol in their routine activities within their respective institutions. This activity concluded within pre-established timelines.

End-product 5: Transdermal delivery of diethylcarbamazine citrate (DEC) in a patch as diagnostic tool for onchocerciasis

Principal investigators: Dr Kwablah Awadzi, Onchocerciasis Chemotherapy Research Center (OCRC), Hohoe Hospital, Hohoe, Ghana; Dr L Diawara, Senegal; Dr MO Traore, Mali.

TDR project manager: Dr Janis K Lazdins-Helds

Following the success of the Onchocerciasis Control Programme in West Africa (OCP) in eliminating onchocerciasis as a blinding disease, a system of surveillance to detect outbreaks of new infections that could jeopardize the gains made in the onchocerciasis-freed zones became a necessity. The diagnostic procedure required should be simple, safe, cheap, non-invasive, sensitive to low-intensity infections, specific, stable, suitable for use in the field and well accepted by the populations. OCP developed a test based on the application of DEC in a suitable carrier (Nivea cream) on the skin, allowing the drug to penetrate the skin and kill the parasites. This results in local inflammation which is indicative of an infection (Boatin et al., 1998, 2002; Toe et al., 2000). TDR motivated Lohmann Therapie-Systeme AG, Germany, to apply its transdermal delivery technologies to develop prototypes for ready-to-use DEC skin patches (at no cost). These have been tested in a clinical setting (30 subjects/OCRC) showing good efficacy allowing identification of infections. No safety issues have been noted.

In 2008, this tool was further examined in a longitudinal study in Senegal and Mali. This study determined the impact of 17–18 years of ivermectin treatment on onchocerciasis prevalence — a first step to testing the hypothesis that the level of onchocerciasis infection and transmission has been reduced to such a low level that ivermectin treatment can be safely stopped. Presence of infection was examined in 2283 persons from 28 villages via skin snips and the transdermal delivery DEC patch some two years after the last ivermectin treatment. All skin snips and DEC patch tests were negative for *Onchocerca volvulus*. Furthermore, the DEC patch test proved easy to use, and was accepted by the study populations (who are becoming increasingly reluctant to submit to skin snipping). These results suggest that the DEC patch test is an appropriate and practical epidemiological screening tool. The main limitation of the findings in the present study is that there were no skin snip positive individuals. Further operational experience with the DEC patch test, run in parallel with the skin snip, is still needed to calibrate the relationship between skin snip and DEC patch test results at the community level.

Activities are on track, with a dossier being prepared for approval of the DEC patch for surveillance purposes by the national regulatory authorities and onchocerciasis control programs (March 2009).

OBJECTIVE 2: Generation of evidence for improved use of currently available drugs

End-product 1: Reduction of *Loa loa* microfilaremia by albendazole and potentially reducing the risk of ivermectin induced SAE in *Loa loa* infected individuals

Principal investigator: Dr Joseph Kamgno, Filariasis Research Center, Yaoundé, Cameroon

TDR project manager: Dr Annette Kuesel

Loiasis is a parasitic infection endemic in the rain forest areas in sub-Saharan Africa caused by the filarial nematode *Loa loa*. Clinical manifestations include 'Calabar swelling', a hypersensitivity response to the antigenic material released by the macrofilaria, which lasts a few hours or days with itching, swelling of lids and pain. Hydrocele caused by adult worms in the scrotum can also be seen. In most cases loiasis is a relatively benign disease with a good prognosis, and many patients do not have defined signs or symptoms for years before the infection is diagnosed. There is currently no safe treatment to reduce or eliminate *Loa loa* infection. The main problem occurred when large numbers of *Loa loa* infected subjects were treated with ivermectin (Mectizan) within the framework of onchocerciasis control programmes. People heavily infected with *Loa loa* who take ivermectin can have severe and/or serious adverse events (SAEs), including encephalopathy and death. Ivermectin treatment in onchocerciasis/*Loa loa* co-endemic areas has changed to ensure that appropriate medical care is available in case of such AEs. The fear of serious and/or severe adverse events leads to a reduced participation of the population in community-directed treatment interventions (CDTI). Following an analysis of SAEs during onchocerciasis control and a risk-benefit assessment, it was decided not to move albendazole-ivermectin mass treatment into areas co-endemic for lymphatic filariasis and loiasis.

Previous studies suggested that multiple exposures of the *Loa loa* macrofilaria with albendazole at two-month intervals may have the desired effect on the reproductive capacity of the macrofilaria. Therefore, a randomized, double-blind, placebo-controlled field-based small study of 60 subjects infected heavily with *L. loa* was conducted in Cameroon to provide a proof-of-concept for the effect of an albendazole dose of 800 mg, administered every two months two or six times. Data analysis is ongoing; preliminary results have been discussed with stakeholders from the onchocerciasis and LF control initiatives and it has been decided to amend the protocol to continue follow up for an additional 6 months (3Q09) to see if the microfilaremia-lowering effects observed persist or become apparent in additional study subjects.

Progress and key achievements

Clinical study of two different albendazole dosing regimens vs placebo completed and unblinded. Data analysis ongoing.

Leverage

- GSK, World Bank, APOC provided designated funds to TDR for the study.
- Study drug was donated by GSK.
- Should the data show that albendazole has the effect desired, subsequent studies to validate the results obtained will likely be conducted by other organizations (Mectizan donation program, GAELF).

Project implementation status vs. plan

On track

Main changes in the global context

- APOC is developing a plan to move towards elimination of transmission of onchocerciasis in as many regions as possible. The slow implementation of CDTI in *Loa loa* co-endemic areas impacts these efforts negatively.

Implications of progress and changes in the global context for the 2008-2013 plans

- If therapy is proven positive, TDR could promote research on how to integrate *Loa loa* treatment into the community-directed interventions programmes in *Loa loa*/LF/onchocerciasis co-endemic areas.

Specific activities for 2009

There are no plans to continue involvement in further evaluation of albendazole for *Loa loa*.

End-product 2: Therapeutic effect of albendazole + DEC in children with lymphatic filariasis

Principal investigator: Dr RK Shenoy, Dept. of Medicine, T.D. Medical College Hospital, Alleppey, Kerala, India

TDR project manager: Dr Janis K Lazdins-Helds

In many tropical countries, the vector-borne disease lymphatic filariasis (LF) is a major cause of considerable chronic and acute disability. Until recently, LF was considered to be a disease of adults. The late manifestations like lymphoedema involving the limbs or genitalia, hydrocele of the scrotum and chyluria are usually seen in this age group. Acute episodes of adenolymphangitis (ADL) are also more common in the adult population, since these episodes occur more frequently in the later stages of the disease. Thus, the disease in children was very often overlooked.

There are few observational and descriptive studies of the prevalence and character of the signs of LF in infected children. Though some information is available regarding microfilaraemia and antigenaemia status of children, information on the clinical manifestations, particularly in *Brugia malayi* infection, is low. Globally, 22 million children under the age of 15 are estimated to have LF infection. The present study, *A cross sectional study of children to define the clinical and pathological changes caused by Brugia malayi infection in an endemic area*, was initiated in 4Q04. Following the screening of 7934 children (3 to 15 years of age), 200 were recruited. All the children enrolled in the study are followed up every six months over 36 months for occurence of any entry lesions, acute adenolymphangitis or swelling of the limbs via routine blood and urine examintion, night blood examination for microfilaria count by Nuclepore membrane filtration, Doppler sonography and lymphoscintigraphy. They were treated with single doses of diethyl carbamazine 6 mg/kg and albendazole 400 mg on discharge from the inpatient wards after the first visit and every six months during the follow-up. The last child enrolled on 25 January 2006 is expected to complete the final follow-up by the end of January 2009. The final report is expected to be available in summer of 2009.

Progress and key achievements

- Following a 6-month treatment, declines in microfilaremia and Bm14 antibody were observed, along with improvement of the subclinical pathology. All of these results, and especially the apparent reversibility of early lymphatic lesions, are extremely important to the global programme. The results have been presented at the 17th International Congress for Tropical Medicine and Malaria, Jeju Island, Republic of Korea.

Project implementation status vs. plan

- On track.

Leverage

- A new (non-TDR) study on the effect of albendazole dose and interval, sponsored by the LF Global Programme, will be started under a Bill and Melinda Gates Foundation research grant.

Main changes in the global context

- Increased attention to disease in children and the need for early detection and treatment.

Implications of progress and changes in the global context for the 2008-2013 plans

- These results highlight the reversibility of early lymphatic lesions and the need for early treatment. These observations have been recognized as extremely important to the Global Programme for Lymphatic Filariasis. No further action by TDR is envisioned.

Specific activities for 2009

Finalization and publication of results.

End-product 3: New nifurtimox and eflornithine regimen for the treatment of second-stage HAT

Principal investigators: Drs Freddie Kansiime, Omugo Health Centre, Omugo, Uganda, and Seraphine Adibaku, Moyo District Hospital, Moyo, Uganda

TDR project manager: Dr Deborah W Kioy

A clinical study comparing the efficacy and safety of a ten-day nifurtimox-eflornithine combination treatment regimen with the standard 14-day eflornithine regimen for the treatment of *T.b. gambiense* human African trypanosomiasis in the meningo-encephalitic phase was initiated in two TDR-sponsored clinical trial sites in Uganda in 2005. A total of 109 patients were recruited at these two sites and the follow-up of these patients will continue until June 2009.

If the data shows therapeutic equivalence, an alternative treatment for late-stage *T.b. gambiense* could become available. The combination treatment will advance the approach to disease control and management by:

- reducing the hospital admission period for patients;
- reducing the intensity of the nursing care required;
- improving acceptability of the treatment;
- reducing costs associated with long administration of infusion and prolonged admission of patients;
- may reduce the probability of emergence of resistance against individual drugs.

Progress and key achievements

- Completion of recruitment: 109 patients recruited.
- Follow-up to be completed in June 2009.
- Clinical trials facilities and equipment in Omugo were handed over to the health centre at the end of recruitment.
- Empowerment of two teams (in Omugo and Moyo) through participatory training to attain skills of international quality for the conduct of GCP clinical trials. Translation of the principles and knowledge learned during the conduct of the study to general patient care activities, especially nursing care.
- Preparation of an interim in-hospital safety data report.
- The study provides patient treatment because at the time there were no disease control activities. The study is increasing community awareness of the disease.

Project implementation status vs. plan

- On track.

Leverage

- Funding for the study provided by Sanofi-aventis.
- Donation of the two drugs for clinical trial by Bayer Healthcare AG and Sanofi-aventis through the WHO NTD Department.
- Logistical support within the country from WHO country representative in Uganda and national control programme.
- Collaboration with multi-site sponsorship of the study by TDR (Uganda), DNDi (DRC) and MSF (Congo, Brazzaville).

Main changes in the global context

- The relapse rate of patients treated with eflornithine alone has increased, making the continued use of monotherapy very questionable.

Implications of progress and changes in the global context for the 2008-2013 plans

- The study has raised awareness for the need to assess the size of the burden to family and local communities due to persisting physical, neurological, intellectual and/or mental disabilities as a result of late treatment (even after the parasitological cure of the late stage for HAT has been successful) and to increase awareness of the disease in communities.
- During the recruitment of patients, a high rate of relapse in patients who had previously been treated with eflornithine monotherapy was observed in Omugo. Evaluation of the possible emergence of resistance to eflornithine needs to be discussed with the control programmes.

- TDR could play a role in implementation research for the new treatment.

Specific activities for 2009

- Follow-up, data management and report preparation.
- Submit the report to WHO essential medicines list to supplement the data presented by DNDi.
- Present the report to Ugandan Ministry of Health as evidence for policy decision-making process.
- Address research needs highlighted above.

End-product 4: Three-day pentamidine treatment regimen for first-stage HAT

Principal investigators: Dr Jimmy Opigo, Moyo District Local Government, Moyo, Uganda; Dr Benard Opar, Adjumani Hospital, Adjumani, Uganda.

TDR project manager: Dr Deborah W. Kioy

The study *Assessing three-day pentamidine for early-stage human African trypanosomiasis* started in February 2008 in Adjuman and Moyo, Uganda. The hypothesis is that a three-day pentamidine regimen can achieve cure rates for early stage *T.b. gambiense* equivalent to those of the current 7–10 day regimen. This hypothesis is based on recent pharmacokinetic information on pentamidine showing a prolonged elimination period, thus keeping the drug at therapeutic levels for over 29 hours after a single IV administration.

Availability of a shorter regimen with pentamidine may not only reduce adverse effects but also reduce treatment costs of the health systems and be more convenient for patients.

Progress and key achievements

- Recruitment started at a low rate, but increased after a lot of effort from the study teams. The study is now on track with 80 patients recruited (target 200).
- The teams have developed very efficient case finding strategies and Standards of Practice (SOP), which is an improvement from the traditional methods. These new SOP will be introduced to the control programmes as a capacity strengthening effort for surveillance.

Project implementation status vs. plan

- On track.

Leverage

- Funding for the study given by Sanofi-aventis.
- Donation of the two drugs for clinical trial by Sanofi-aventis through WHO NTD Department.
- Logistical support within Uganda from the WHO country office and the national control programme.

Main changes in the global context

- No new drug candidate being developed for this stage of disease since the only one that was promising, DB289, has been discontinued.
- Discovery of new compounds is being undertaken by TDR, DNDi and other institutions. This may result in a new candidate for development. Once identified, it would take at least seven years to develop.

Implications of progress and changes in the global context for 2008-2013 plans

- The reduced disease prevalence will result in a slow rate of recruitment and may require additional sites (North Uganda or Democratic Republic of Congo [DRC]).
- Additional support resources could enhance active case finding.

Specific activities for 2009

- Continue recruiting in Uganda and follow-up of enrolled patients (monitoring, data management) as per project work plan.

End-product 5: Benznidazole for the treatment of patients in the late indeterminate or early chronic phase of *T. cruzi* infection

Principal investigator: Dr Carlos A. Morillo, Department of Medicine, Arrhythmia Service, Cardiology Division, McMaster University, Population Health Research Institute, Hamilton, Canada

TDR project manager: Dr Janis K. Lazdins-Helds

Patients with documented Chagas infection determined by a positive *T. cruzi* serology test have a 20-30% chance of progressing to dilated cardiomyopathy. The role of antitrypanozomal therapy to prevent this progression has been suggested in observational studies. However, this hypothesis has not been tested in a double-blinded placebo-controlled intervention trial. Because chronic Chagas disease (CD) may indeed be triggered by persistent parasitic infection, it appears plausible that therapy with an antiparasitic agent may delay or reduce the progression of chronic CD. These recent findings raise the exciting possibility that antitrypanosomal therapy in the chronic stage of Chagas disease can eradicate the parasite and prevent the progression to end-stage cardiomyopathy and death. The study BENznidazole Evaluation For Interrupting Trypanosomiasis Trial (BENEFIT) is the largest clinical trial conducted in Chagas disease, with 37 active centres and plans to recruit further centres from Bolivia, Peru and Venezuela. It is a double-blind placebo-controlled randomized clinical trial that will test the hypothesis that in patients with evidence of chronic Chagas' heart disease, treatment for 60 days with benznidazole will reduce the rate of clinical disease progression (BENEFIT FULL) and reduction of *T. cruzi* in the blood (BENEFIT PILOT) using PCR technology to determine the rate of negativization after active therapy. PCR technique has been standardized and samples are analysed in three core laboratories located in Argentina, Colombia and Brazil. Samples are collected at baseline, after completing therapy at 60 days and at the end of follow-up at three years.

Progress and key achievements

- The study is on track, with 770 patients from Argentina, Brazil and Colombia in 37 centres having been randomized. Further patients from Bolivia, Peru and Venezuela will be included. Safety and tolerability issues have been lower than the expected rates (fewer safety issues than usually mentioned). Samples for quantitative and qualitative PCR analysis for efficacy have been drawn and are being processed by the core labs in Argentina, Brazil and Colombia.
- A manuscript describing the study strategy has been published.

Project implementation status vs. plan

- On track.

Leverage

- TDR funding has leveraged funding from Canadian Institute of Health Research (CIHR).

Main changes in the global context

- With the success of vector control and blood safety-based disease control strategies, more emphasis is being given to the individuals in the indeterminate and chronic phase of the disease.

Implications of progress and changes in the global context for the 2008–2013 plans

- Once the BENEFIT pilot is finished (2010), TDR will have to consider the role it wants to play in the progression of the BENEFIT full study.

Specific activities for 2009

- Continuation of enrolment and patient follow-up as per work plan.

End-product 6: Effective and safe dose (40 versus 60 mg/kg) of praziquantel for treatment of schistosomiasis

Principal investigators: Dr Otávio Pieri, Laboratory of Eco-epidemiology and Control of Schistosomiasis and Soil-transmitted Helminthiasis, Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil; Dr Vicente Belizario, National Institutes of Health, University of the Philippines, Manila, Philippines; Dr Mohamed Ouldabdallahi dit Hamad, Institut National de Recherches en Santé Publique (INRSP), Nouakchott, Mauritania; Dr Lwambo Nicholas Joseph Stephen, National Institute for Medical Research, Mwanza Medical Research Centre, Mwanza, United Republic of Tanzania.

TDR project manager: Dr Piero Luigi Olliaro

The dose-effect relationship is not well established for praziquantel; currently both 40 and 60 mg/kg are recommended and registered for the treatment of schistosomiasis (independently of the type). However, they have never been compared formally in randomized controlled trials. With the expansion of the use of praziquantel (chemo prophylactic treatment of at-risk populations), policy decision-makers are requesting information on which dose should be used in their settings.

To address this question, TDR is supporting a multi-country study (800 patients) comparing these two doses in children with intestinal schistosomiasis in Brazil, Mauritania, and United Republic of Tanzania, where *S. mansoni* is endemic, and in the Philippines, where *S. japonicum* is endemic. The study has been completed and data from the different centers analysed.

The study in the Philippines is published, and Brazil reported its results in a recent schistosomiasis meeting. While the results (efficacy and safety) in both countries were substantially similar, the Philippines has changed country policy to use the 40 mg/kg dose. On the other hand, Brazil will most probably retain the 60 mg/kg dose.

Progress and key achievements

- Four studies completed.
- Two analysed, one published, with no significant differences in efficacy or safety between Brazil and Philippines.

Project implementation status vs. plan

- Six months' delay in data report from Mauritania and Tanzania and final study data analysis.

Leverage

- TDR funding helped initiate the contribution of expertise, time and effort of national professionals, as well as the provision of the infrastructure necessary to conduct these studies. Dr Belizario wrote: "*May I also report that significantly more resources have now been provided for the control program partly as a result of the research work that TDR and other donors have funded.*"

Main changes in the global context

- Availability of praziquantel (donation) and the WHO/NTD recommendation for expanded treatment of schoolchildren populations in endemic zones has prompted national control programmes to reassess their treatment policies.

Implications of progress and changes in the global context for the 2008–2013 plans

- Evidence generated from this study has informed policy change in the Philippines (use of 40 mg/kg). It is expected that further individual study and meta-analysis will produce local and general evidence. As the study is reaching its conclusion, there are no implications for 2008–2013 TDR plans.

Specific activities for 2009

- Closing studies, data entry and analysis.

End-product 7: Revised dengue classification and updated case management guide

Principal investigators: Dr Lucy Lum, Malaysia; Dr Efren Dimaano, Philippines; Dr N Hung, Viet Nam; Dr J Farrar, Viet Nam/United Kingdom; Dr Siripen Kalayanarooj, Thailand; Dr Khampe Phomgsavath, Lao People's Democratic Republic; Dr Eric Martinez, Cuba; Dr Elci Villegas, Venezuela; Dr Joao Siqueira, Brazil; Dr Ivo Castelobranco; Dr Tomas Jänisch, Germany; Dr Angel Balmaseda, Nicaragua; Dr Eva Harris, USA; Dr E Pleites, El Salvador; Dr Gladys Ramirez, Peru; Dr Carmen Soria; Dr Lyda Osorio, Colombia; Dr Jose G Martinez, Mexico.

TDR project manager: Dr Axel Kroeger

Dengue disease was classified in the early 1970s, based on the experience of Bangkok's Children Hospital, into three categories: dengue fever, dengue hemorrhagic fever and dengue shock syndrome. However, clinicians have had difficulties using this classification, citing its rigidity and focus on hemorrhagic manifestations. TDR organized a meeting of dengue clinicians in 2003 in Cuba, commissioning a systematic literature review about the actual use of the classification and organizing a prospective clinical multi-centre study in seven countries of Asia and Latin America. In this effort, 2261 patients were enrolled over a period of ten months; of these, 1724 patients had a full data set and were confirmed as dengue or highly suggestive. Clinical management by experienced dengue physicians, care level and type of medical interventions were used as criteria for distinguishing between three levels of severity. Laboratory parameters, as well as clinical signs and symptoms, were analysed for their association with different levels of disease severity. The statistical analysis showed that there was a clear distinction between severe and non-severe dengue. Additionally, "warning signs" associated with severe disease were established. An international clinical expert group reviewed all this evidence and suggested a new three-level severity classification which would be more suitable for triage and clinical management: severe dengue, dengue with warning signs and dengue without warning signs. It was recommended that this new classification be validated in a multi-country setting. This is being organized by TDR, and several other donors will help finance the study. The results are expected to be discussed in Cuba in 2009.

Progress and key achievements

- After 4 years of work, the TDR-supported multi-centre clinical study (DENCO) has generated an evidence base for proposing a new classification of dengue disease into three levels of severity: severe dengue, dengue with warning signs and dengue without warning signs.
- Clinical and laboratory criteria have been assessed and their sensitivity/specificity for correctly classifying dengue has been determined.
- TDR conducted an expert meeting of dengue clinicians (Oct. 2008) resulting in a proposal for revised treatment guidelines with a model slide series for training, a flyer for the daily use in the clinical practice and a flow chart for wall posters in reception areas for dengue patients.

Project implementation status vs. plan

- On track.

Leverage

- The DENCO clinical project was financed by the EU with roughly US$ 500 000 and an additional US$ 100 000 by the Wellcome Trust. TDR contributed roughly US$ 200 000.

Main changes in the global context

- Once the revised classification is validated and approved, it will have major implications for triage and case management.
- The new classification will contribute to vaccine and drug trials and for surveillance by providing dengue outcome endpoints.

Implications of progress and changes in the global context for the 2008–2013 plans

- The Geneva expert meeting of dengue clinicians (Oct. 2008) recommended the validation of the revised case classification in a large number of countries (to be completed in 2009) as well as the use of the severity classification in forthcoming drug and vaccine trials. This has to be explored regarding budget and staff implications when preparing for the new biennium.

Specific activities for 2009

- Implementation of a TDR-coordinated validation study of the revised dengue case classification and modified case management guidelines in 17 countries. The studies are financed by TDR and Wellcome Trust and from government sources in Singapore, Saudi Arabia, Puerto Rico, Colombia and Peru. TDR ensures the high quality and comparability of the study through external monitoring, data management and central data analysis, which will be done at the University of Heidelberg, Germany. The results will be discussed at an international expert meeting in Cuba in August 2009.

New activities approved in 2007 but not initiated

The initiation of these activities will be reassessed during the next SAC meeting (March 2009):

Evaluation of praziquantel combination with oxamniquine for schistosomiasis (Objective 1; end-product 2)

Principal investigator: Prof. Mamoun Homeida, Academy of Medical Sciences and Technology, Kartoum, Sudan

TDR project manager: Dr Piero Luigi Olliaro

This is a study designed to evaluate the PK, efficacy and safety of using both drugs in combination with the purpose to enhance not only efficacy but also to protect praziquantel from resistance, especially in view of the dramatic expansion of its use.

The study is to be conducted in Sudan and the protocol and site preparation have been completed. The study has been on hold for more than a year due to difficulties in access to oxamniquine (the only source in Brazil).

L-praziquantel for schistosomiasis (Objective 1; end-product 3)

Principal investigator: Dr Matthew H Todd, University of Sydney, Australia

TDR project manager: Dr Piero Luigi Olliaro

Praziquantel (PZQ) preparations that are available on the market are racemic 50:50 mixtures of two stereoisomers, only one of which possesses anti-schistosomal properties. The manufacturing procedures currently used are not selective for the active enantiomer. It was shown by the original developers of the drug that the anthelmintic activity is concentrated in the laevorotatory (–) isomer which has (*R*) configuration. This notion was repeatedly confirmed by in vitro and in vivo tests. Most importantly, a randomized double-blind study on 139 matched pairs of patients infected with *S. japonicum* showed that a single 20 mg/kg dose of (*R*)-PZQ was as efficacious as 40 mg/kg of racemic praziquantel, but (*R*)-PZQ produced fewer side-effects than racemic PZQ.

There are several valid reasons for developing an enantiomer pure PZQ: a decrease of side-effects, closer conformity to guidelines of drug regulatory agencies and easier administration (currently used 600 mg PZQ tablets often create swallowing problems).

An agreement was signed with the University of Sydney in Australia to demonstrate that synthetic routes are chemically feasible, scalable and economically viable by identifying and testing routes in the laboratory and then sharing this work with the entire community for further refinement/ work via the "open source" approach. Dr Todd is attempting to leverage the TDR contribution into an agreement with the Australian Research Council Linkage Agreement. Some of the terms are not compatible with WHO status and discussions on the legal framework for the collaboration are ongoing. Meanwhile, the funds provided by TDR have not been implemented by the PI.

New activities with available background information (and discussions with experts) to be considered for initiation in 2009. These proposals will be presented to SAC for recommendation in March 2009:

Development of tools for ivermectin resistance detection in onchocercosis.

Until recently, TDR-supported clinical and molecular biology research conducted in Australia and Canada aimed at identifying phenotypic or genetic changes associated with the repeated use of ivermectin. Such changes have been detected at the genetic level on the β-tubulin, ABC transporters, GABA and Glucls genes, as well as some other 35 anonymous markers. None of the genetic changes have been validated as ivermectin resistance markers, mainly because there is no indication that ivermectin is failing as a drug to address the onchocerciasis control programme objectives.

At the clinical-parasitological level, no changes in the response of microfilaria to ivermectin have been detected, but an adult female phenotype where the embryogenesis does not seem to be impaired by ivermectin to the extent expected based on historical data has been described. The onchocerciasis control programmes have recognized these clinical and genetic observations as potential warning signs of developing ivermectin resistance. Several strategic discussions at WHO/NTD and APOC have been conducted on how to link the research necessary to identify genetic markers of (potential) resistance to ivermectin with surveillance activities. A work plan was presented to the Technical Consultative Committee of APOC. The recommendation was to identify suitable research centres in Africa and initiate the technology transfer from the research centres in Australia and Canada to endemic countries. TDR has been requested to play a technical role in moving this forward.

Nifurtimox + eflornithine for treatment of *T.b. rhodesiense* second-stage HAT

Melarsoprol is currently the only drug for treatment of *T.b. rhodesiense* HAT. There is an urgent need to identify an alternative treatment for second-stage disease due to melasoprol toxicity. A "proof of principle study" to investigate the effectiveness and safety of a nifurtimox-eflornithine combination regimen for first-line treatment of patients with second-stage *T.b. rhodesiense* HAT has been proposed to TDR.

New product development proposals.

TDR has recently received proposals from pharmaceutical companies to support drug evaluation for dengue (disease progression modifier) and leishmaniasis (oral lipid amphotericin). Academic institutions have proposed evaluation of molecular and biochemical markers as predictors of Chagas disease progression.

4. BL6 leverage, contribution to empowerment and stewardship and synergy with TDR business lines

4.1. Leverage

This has been addressed in Section 3 for each of the activities.

4.2. Contribution to overall empowerment and stewardship activities

Through the clinical research nature of TDR projects, BL6 has played a major role in empowerment in developing countries. It has helped build capacity to conduct clinical research according to Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) standards. It has also contributed to the improvement of project management practices and ethical review procedures.

Below are some specific empowerment examples:

- GCP and GCLP training of investigators and key study staff for the moxidectin Phase 3 study (Liberia and DRC) and HAT nifurtimox+eflornithine and pentamidine (Uganda), *Loa loa* (Cameroon), Chagas disease (Latin America) and schistosomiasis (Sudan, Phillipines, Brazil, Mauritania).
- Training in essential parasitological techniques for laboratory staff for the moxidectin Phase 3 study (Liberia, DRC) taught by the Onchocerciasis Chemotherapy Research Centre with mediation by TDR.
- Basic training of new clinical monitors from Liberia and DRC.
- Moxidectin protocol discussion with Ghana, Liberia and DRC national drug regulatory authorities and ethics review committees.
- Support of a national research laboratory to lead an international standardization and validation process with immediate clinical use application (INGEVI, Argentina).
- Support of national clinical researchers from endemic countries to generate evidence to reassess treatment guidelines (dengue).

In the areas of stewardship, during 2008 BL6 supported key decisions of and addressed research gaps and priorities identified by national disease control programmes, academic institutions and industry partners, helping to:

- Coordinate APOC and NTD discussions on how to move forward to address the issue of potential development of resistance to drugs used for NTDs. Particularly relevant were the discussions on potential ivermectin resistance detection.
- Set up discussions that brought together clinicians, drug regulators and representatives of the pharmaceutical sector to define the target product profile for dengue drugs.
- Discuss with DNDi and Schering Plough the strategy to pursue for the development of posaconazole for Chagas disease.
- Set up review of evidence (Cochrane review) on the efficacy and safety of drugs for schistosomiasis.
- Provide technical input into the WHO process addressing public health, innovation and intellectual property, as well as the WHO research strategy.

4.3 Synergy with the work of TDR business lines

By the nature of its strategic objectives, BL 6 is well positioned to establish synergies with many other BLs in TDR. Specific examples:

Stewardship. Given the BL6 activities on helminths and kinetoplastids, the interaction with reference groups for these diseases established by the Stewardship Function is essential. Some key decisions for BL6 will be driven by the output of the disease reference groups, such as the identification of key laboratories in Africa to take forward research on markers for potential ivermectin resistance. BL6 expertise in the NTDs has also contributed to structuring some of these disease reference groups and their activities.

Empowerment. Through expertise and hands-on activities in product development and evaluation, BL6 has contributed to the empowerment function on capacity-building for product R&D (Nagasaki-Thammasat University diploma course on research and development of products to meet public health needs). BL6 also will provide a "home" for some leadership fellows (project management). BL6 has benefited perhaps more than any other business line from the empowerment activities in capacity-building for clinical research (GCP, monitoring, ethics).

BL3. The natural partner for BL6 is BL3, which is set up to contribute drug candidates for the BL6 pipeline such as emodepside, a potential macrofilaricidal for onchocerciasis. These two business lines' work together could play a key role in the definition of product target profiles for NTDs.

BL5. Given that there is some overlap in the scope of diseases (HAT and Chagas disease) between BL5 and BL6, their interaction is relevant when providing input to disease control programmes and interacting with experts in these diseases.

BL7. Diagnostics for onchocerciasis and Chagas disease have not been within the disease mandate of BL7, and for historical reasons diagnostic products for these diseases have been addressed within BL6 (such as the DEC patch for onchocerciasis, tools for detection of ivermectin resistance and markers for Chagas disease progression and cure). However, BL6 has benefited from the know-how in BL7, and this could be enhanced. It is important to note that both business lines are active in schistosomiasis and dengue. There are many opportunities to synergize resources, as in the use of patients/patient samples, research facilities, training and possibly study protocols which simultaneously address diagnostics and drug development.

BL10. BL6 is working closely with BL10 in the area of development of tools for pharmacovigilance for VL elimination in the Indian subcontinent. The use of drugs for VL is a key element in the disease elimination strategy. However, given that these drugs are new with very limited field use experience, it is essential to institute systems that allow collection of new information on their safety and efficacy. BL6 is contributing its knowledge and expertise to support BL10 to achieve this objective.

BL11. The currently expected products from BL6 are to be transitioned into control programmes that are based on community directed intervention (CDI) strategies. Therefore, it is important to anticipate what these products will require (e.g. moxidectin post-registration study on the interruption of onchocerciasis transmission or DEC patch validation within the context of surveillance) for BL11 planning. Close interaction of these two BLs is critical.

5. Critical issues and suggested solutions

At present, the portfolio of BL6 is mainly determined by NTD product development or evaluation activities that were initiated several years ago and for which TDR must fulfil commitments with patients, investigators and partners. These commitments will fully occupy BL6 human and financial resources through 2010. This makes engagement in required new activities that have been identified by disease control programmes, experts and advisers very challenging. A possible solution is to share resources and expertise from other relevant business lines, work on patients, and institutions that can serve projects from multiple BLs or engage resources from disease control activities. Transferring some of the activities to other organizations should also be considered.

Communication and exchange of information with disease control programmes has not been optimal. The use of know-how or expertise across units addressing NTDs has not been exploited to the maximum potential. These difficulties could be addressed by physically moving TDR closer to the NTD group and by creating a framework that would integrate research and disease control activities for NTDs.

6. Annexes

6.1. Overview of moxidectin development plan and status

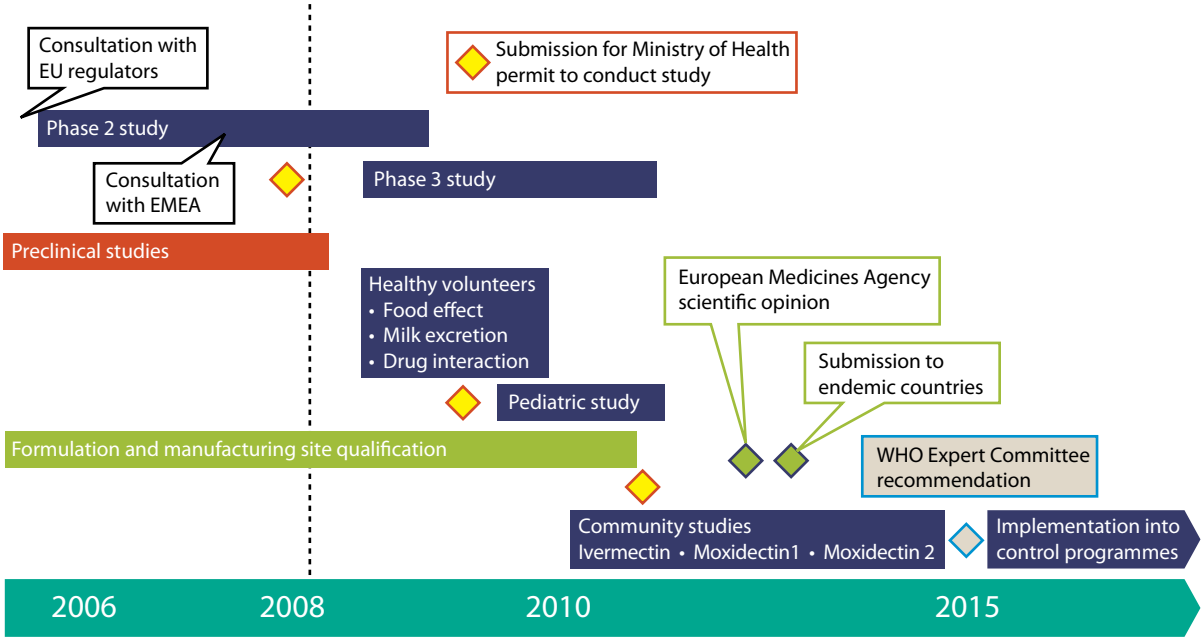

Fig. 1. Moxidectin development plan and status.

6.2. List of publications

Marin-Neto J et al. Rationale and design of a randomized placebo-controlled trial assessing the effects of etiologic treatment in Chagas' cardiomyopathy: the BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT). *American Heart Journal,* 2008, 156:37-43.

Danso-Appiah A, Utzinger J, Liu J, Olliaro P. Drugs for treating urinary schistosomiasis. *Cochrane Database of Systematic Reviews,* 2008, Jul 16;(3):CD000053.

Runge-Ranzinger S, Horstick O, Marx M, Kroeger A. What does dengue disease surveillance contribute to predicting and detecting outbreaks and describing trends? *Tropical Medicine and International Health,* 2008, 13:1022-1041.

Belizario Jr VY, Amarillo MLE, Martinez RM, Mallari AO, C. Tai CM. Efficacy and safety of 40 mg/kg and 60 mg/kg single doses of praziquantel in the treatment of schistosomiasis. *Journal of Pediatric Infectious Diseases,* 2008, 3:27-34.

Shenoy R. Clinical and pathological aspects of filarial lymphedema and its management. *Korean Journal of Parasitology*, 2008, 46: 119-125.

6.3. SAC membership

Dr Shally Awasthi, Department of Paediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India

Dr Jeremy Farrar, Oxford University Clinical Research Unit, Hospital for Tropical Disease, Ho Chi Minh City, Viet Nam

Dr Léon Kazumba, Centre Neuro-Psycho Pathologique, Departement de Neurolgie, Kinshasa, Democratic Republic of Congo

Dr Edward Greg Koski, Institute for Health Policy, Massachusetts General Hospital, Department of Anaesthesia and Critical Care, Boston, Massachusetts, USA

Dr Thomas B. Nutman, Helminth Immunology Section, Clinical Parasitology Unit, Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, MD, USA

Dr Ana Rabello (chair), René Rachou Research Center, Oswaldo Cruz Foundation, Laboratory of Clinical Research, Belo Horizonte, Minas Gerais, Brazil

Dr Mamadou Souncalo Traoré, DER de Santé Publique, Faculté de Médecine de Pharmacie et D'Odonto-Stomatolige (FMPOS), Bamako, Mali

Dr Nana Twum-Danso, Project Fives Alive! IHI/NCHS Partnership for Reducing Child Mortality in Ghana, National Catholic Secretariat, Department of Health, Accra, Ghana

Dr Juerg Utzinger, Department of Public Health and Epidemiology, Swiss Tropical Institute, Basel, Switzerland

Dr Taner VARDAR, Autoimmune Diseases and Emerging Therapies, Medical Saftey Group, Global Drug Safety, Merck Serono International SA, Geneva, Switzerland

6.4. Responses to specific STAC requests

- STAC recommends that transitional activities are operationally distinguished from new projects entering into the new strategy. This applies to allocation of human resources and budgets so that proper consideration is given to new projects. **ADDRESSED**
- BL6 will need to be fed with innovative and robust compounds for six different diseases. This business line will be very dependent on BL3 production efficiency. STAC recommends a thorough review of the relationship between BL3 and BL6 take place so that BL6 can organize itself to identify potential outside sources for drug candidates. STAC further recommends that BL6 concentrate on helminth infections. **ADDRESSED (see Annex 6.5)**
- No reference is made to research on efficacy biomarkers and interactions with pharmaceutical companies, specifically the European Union Innovative Medicines Initiative. STAC recommends that specific attention is given to biomarkers and to include this dimension into the BL6 research agenda (together with BL3 for early selection of lead compounds). **Partially ADDRESSED, on a per-project basis. No generic framework has been developed, but this will be addressed in the upcoming SAC meeting.**

6.5. Strategic consideration on BL3/BL6 interface

A meeting between the BL3 and BL6 leaders took place on 6 June 2008, concluding the following regarding strategic questions in product R&D and discovery/development interface:

- Under the current resource scenario, TDR cannot do candidate transition into drug development alone.
- Neither BL3 nor BL6 can undertake "interphase" activities (e.g. safety pharmacology, pre-formulation, formulation, animal toxicology, scale-up chemistry).
- Discovery/development interface is not simple; expecting a smooth interface without the necessary capacity to undertake further development is not realistic.
- While BL3, through the Helminths Drug Initiative (HDI), requires considerable funding for lead optimization which is currently not available, BL6 is not in a position to do pre-clinical development on its own without considerable resources. Possible scenarios to fill this gap are:
- BL3-identified development candidates belonging to pharmaceutical companies are promoted for a BL6/pharma joint development strategy, such as the moxidectin model;
- HDI gets significant funding support in the short term to cover preclinical development and then interface with BL6 as appropriate;
- Extensive promotion of developing country R&D innovation, such as the African Network for Drug and Diagnostic Initiative (ANDI) that covers discovery, pre-clinical and clinical development as well as regulatory capacity.
- The Helminth Drug Initiative has an encouraging drug discovery portfolio but it needs to go beyond discovery, and the only way this can be done is to aggressively seek external funding as an independent organization. In this context, HDI could be part of ANDI.
- Developing country R&D networks such as ANDI should be strongly supported by TDR as the model of the future. ANDI (including the Helminth Drug Initiative) may offer longer-term solutions; such efforts could potentially leverage external funding and identify industrial partners to support product R&D. The capacity to do clinical development in Africa, established through TDR and other organizations, should be used to promote the above R&D model. Several screening hits owned by TDR are now available and could benefit from this approach if successful.
- Regular BL3 and BL6 discussion is agreed for updates on candidate selection and TPP processes.

TDR For research on diseases of poverty

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